RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Baggrundsnotat med behandlingsvejledning vedrørende første linje behandling af nydiagnosticerede patienter med kronisk myeloid leukæmi (CML) i kronisk fase med tyrosinkinaseinhibitorer (TKI)

Fagudvalg under Rådet for Anvendelse af Dyr Sygehusmedicin, RADS, er rådgivende udvalg, som udarbejder udkast til behandlingsvejledning og baggrundsnotat for anvendelse af medicin inden for specifikke behandlingsområder. Dokumentet forelægges RADS, som herefter træffer beslutning om indholdet af den endelige behandlingsvejledning.

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Godkendt af RADS	30. oktober 2012

Resumé og behandlingsvejledning: *Behandlingen af kronisk myeloid leukæmi (CML) har siden år 2000 været en vedvarende tabletbehandling. Sygdommens prognose er herved bedret markant, og i mange år fremover vil antallet af patienter i kronisk behandling være stigende. Der opstår 80 – 110 nye tilfælde hvert år. Man antager, at der i Danmark lever mere end 600 mennesker med CML, og at antallet vil fordobles i løbet af nogle årtier.*

Der er registreret 3 lægemidler mod CML: Førstegenerationsstoffet imatinib og anden-generationsstofferne dasatinib og nilotinib. RADS fagudvalg har arbejdet med følgende kliniske problemstilling:

- *Hvilke lægemidler i hvilke doser er ækvi-effektive til at sikre sygdomskontrol (overlevelse, progressionsfri overlevelse, minimal sygdomsmængde) med færrest komplikationer og bivirkninger og med minimalt besvær for patienten ved første linje behandling af CML i kronisk fase?*

Fagudvalget har arbejdet efter GRADE metoden og i særdeleshed fokuseret på anvendelige definitioner af patientpopulationen og effektmål (outcome) Der er foretaget litteratursøgning og gennemgået relevante studier med særlig vægt på de foreliggende randomiserede, kontrollerede studier. Patientsikkerhedsmæssige forhold er gennemgået systematisk.

Fagudvalget bemærker at der både anvendes traditionelle effektmål i form af overlevelsesstatistik og surrogatmarkører af forskellig type. Surrogatmarkørerne udviser en hurtigere indtrædende effekt af anden-generationsstofferne, som dog endnu ikke afspejles i den samlede overlevelse. Anden linje behandlingerne er ikke undersøgt systematisk, men kan have kompenseret for en forskel i effekt. De patientsikkerhedsmæssige aspekter giver efter fagudvalgets opfattelse ikke grundlag for præference.

Fagudvalget konkluderer derfor at dasatinib, imatinib og nilotinib alle er egnede som første linje behandling af CML. Dog bemærkes at stoffernes individuelle egenskaber er lidt forskellige, og at enkelte nærmere beskrevne patienter bør undtages fra visse af behandlingerne. Samtidig kan man forudse større frafald fra en kohorte behandlet med imatinib i forhold til de to andre.

Fagudvalget har udarbejdet lægemiddelvejledninger, for hvert af de tre stoffer.

Den valgte første linje behandling gives kontinuerligt indtil én af følgende situationer foreligger:
1. Der foreligger intolerance
2. Behandlingsresultatet svarer ikke til veldefinerede krav for respons i relation til behandlingsvarighed
3. Tidligere opnået remission mistes

Der kan ikke gives faste retningslinjer for valg af anden linje behandling.
Seponering bør kun foregå i protokolleret sammenhæng.
Allerede iværksatte velfungerende behandlinger bør ikke ændres.

Fagudvalget gør opmærksom på, at livlig forskningsaktivitet vil kunne medføre målbare forskelle mellem reelt forbrug og fremskrevet forbrug i henhold til behandlingsvejledningen.

Fagudvalget skønner, at revurdering vil skulle foregå om cirka to år.

1 Formål

Formålet med RADS behandlingsvejledninger er at sikre national konsensus om behandling med lægemidler inden for sygehussektoren; herunder at definere hvilke lægemidler i hvilke doser, der anses for ækvieffektive.
Formålet med dette baggrundsnotat er at sikre transparens i forhold til beslutningsgrundlaget, der har ført frem til behandlingsvejledningen for første linje medicinsk behandling af CML ved debut af sygdommen i kronisk fase**.**

2 Baggrund

2.1 Introduktion

Kronisk myeloid leukæmi (CML) var tidligere en meget alvorlig sygdom med en middel overlevelse på kun ca. 4 år [1,2], undtagen for de få patienter der kunne knoglemarvstransplanteres. Gennem de seneste 12 år har patienter med CML kunnet behandles med TKI, hvilket for langt de flestes vedkommende har været effektivt og skånsomt. Bortset fra daglig medicinindtagelse og ambulante kontrolbesøg med blodprøver nogle få gange om året fører patienterne et normalt liv. Nogle patienter har ikke bivirkninger, mens andre har bivirkninger i moderat omfang [3].
Man antager, at langt de fleste patienter til gengæld er nødt til at være i medicinsk behandling altid. Der vil derfor i mange år fremover være en tilvækst i antallet af kronisk behandlingskrævende patienter med denne sygdom.

Det store gennembrud i behandlingen skete med stoffet imatinib, der blev registreret i Danmark i 2001. Til gavn for patienter, hos hvem effekten ikke er tilfredsstillende, eller hvor bivirkningerne er uacceptable, er der udviklet anden-generations medicin i samme klasse, dasatinib og nilotinib, som blev registreret i hhv. 2005 og 2006, og bosutinib, som forventes registreret i efteråret 2012. Efterfølgende er disse stoffer blevet sammenlignet med imatinib med henblik på anvendelighed som første linje behandling.

Nomenklatur: Sygdommen er næsten altid ved sin debut i *kronisk fase*. Uden effektiv behandling indtræder efter en kortere årrække *progression* til *blastkrise (BC)*, eventuelt med en kortere forudgående *accelerationsfase (AP)*. Progression er en meget alvorlig klinisk

begivenhed, selv med moderne behandlingsmuligheder, idet den leukæmirelaterede dødelighed inden for et år er over 50 % [4].

Effekten af kræftbehandling vurderes ofte ved *overlevelse*, enten total (*overall survival*) eller uden kliniske alvorlige begivenheder (*event free survival*). Ved dødsfald er det relevant at skelne mellem dødsfald relateret til den maligne sygdom versus dødsfald uden relation hertil. Ved CML er overlevelsen så høj, at man lige som ved andre kroniske sygdomme må støtte prognose estimater til prognostiske betydende biologiske variable, *surrogatmarkører*.
Effekten af TKI vurderes på 3 niveauer:
- *Hæmatologisk remission*
- *Cytogenetisk remission*
- *Molekylær remission (vurderes på forskellige niveauer, markeret ved en numerisk værdi)*

De to sidstnævnte surrogatmarkører er specifikt udviklet netop til denne sygdom. Vores viden om de tre effektmåls betydning for prognosen er fortsat under udvikling. Patienter kan ikke selv registrere cytogenetisk og molekylærbiologisk remission

2.2 Patientgrundlag
CML er en sjælden sygdom. Der opstår i Danmark 1,5 - 2 nye tilfælde per 100.000 eller 80 – 110 nye tilfælde hvert år [1]. Debutalderen i de nordiske lande er gennemsnitlig 60 år [2], og den typiske patient er således lidt mere end midaldrende, men i øvrigt rask og med mange års forventet restlevetid. Sygdommen er ekstremt sjælden hos børn (1 – 2 om året i Danmark). Der findes ikke præcise opgørelser over antallet af aktuelle patienter (prævalens), men man må antage, at der gennem de sidste 10 år er akkumuleret mange, idet den leukæmi-relaterede 5-års dødelighed har været under 10 % og samlet dødelighed mindre end 20 % i de tidligste kohorter af TKI-behandlede patienter [2,5-7]. Estimater fra USA tyder på mere end en fordobling af prævalensen de seneste 10 år og yderligere mere end en fordobling af den nuværende prævalens indtil et forventet plateau i ca. 2050 [8]. Et dansk estimat på disse præmisser vil være, at der aktuelt i Danmark lever 600 CML patienter.

I princippet skal alle nydiagnosticerede patienter med CML behandles med TKI vedvarende. Af medicinske årsager vil der a priori være et fåtal, hvor man vil finde relativ kontraindikation mod ét af stofferne, eller vægtige årsager til modificeret dosering. Patienter, der aktuelt er i effektiv og veltolereret behandling med et givet stof, bør forblive i behandling hermed. Behandlingsvejledningen omfatter derfor kun nydiagnosticerede patienter.

3 Lægemidler
Baggrundsnotatet omfatter behandling af patienter med følgende lægemidler i alfabetisk orden:
bosutinib L01XE14
dasatinib, L01XE06
imatinib, L01XE01
nilotinib, L01XE08
Ved gennemgang af data har fagudvalget vurderet, at dokumentationen for bosutinibs egnethed som første linje præparat endnu er for svag på grund af opfølgningens korte varighed. Se bilag B.

4 Metode
RADS Fagudvalg arbejder efter GRADE-metoden [9-12], som beskrevet i Rammenotat om GRADE i RADS Fagudvalg (www.regioner.dk).

5 Behandlingskriterier

Baggrundsnotatet indbefatter alle danske patienter debuterende fra behandlingsvejledningens ikrafttræden med CML i kronisk fase. Primær accelerationsfase, primær blastkrise, recidiv efter forudgående allogen stamcelletransplantation eller forudgående interferon-behandling samt progression efter forudgående pausering med TKI-behandling er ikke omfattet af vejledningen. Som ovenfor anført bør tidligere diagnosticerede patienter i effektiv og veltolereret behandling, hvad enten det måtte være første eller anden eller højere linje, fortsætte med det præparat de aktuelt får.

Som nærmere specificeret i pkt. 8 mener fagudvalget ikke at der er tilstrækkelig faglig dokumentation for en præference for ét af de registrerede præparater til den store gruppe af typiske CML patienter. Dette er også i overensstemmelse med international opinion. De individuelle farmakologiske og kliniske egenskaber for de tre præparater medfører, at der for visse mindre patientgrupper er individuelle hensyn, f.eks. forskellige relative kontraindikationer. Det har derfor været nødvendigt at udfærdige lægemiddelvejledninger for hvert enkelt præparat med disse mindre individuelle forskelle, hvorved der vil fremkomme lidt forskellige populationer alt efter hvilket der udvælges som første linje behandling.

6 Skiftekriterier

Første linje behandling gives kontinuerligt indtil én af følgende situationer foreligger:
1. Der foreligger intolerance
2. Behandlingsresultatet svarer ikke til veldefinerede krav for respons i relation til behandlingsvarighed
3. Tidligere opnået remission mistes

Ad 1. Absolut kontraindikation mod fortsat behandling er ekstremt sjælden. Da der er tale om vedvarende behandling, bør det også respekteres at én eller flere mere moderate bivirkninger kan udløse et skift til anden linje behandling. Selvom bivirkningsmønsteret for forskellige TKI er ret ensartet, er der sjældent kryds-intolerance. Fagudvalget anbefaler jf. lægemiddelvejledningerne, at der ved de ambulante kontroller udføres en systematisk bivirkningsregistrering med gradering med henblik på ensartethed i behandling.

Ad 2. Kravene til respons er bedst defineret for imatinib. Der er i Danmark tradition for anvendelse af European LeukemiaNet's reviderede kriterier [13], som i deres oprindelige form er validerede i en klinisk kontekst [5], og som Fagudvalget også vil støtte. Med hensyn til nilotinib og dasatinib findes ikke validerede rekommandationer [14]. Fagudvalget mener dog, at man bør anvende ELN kriterier, kombineret med individualiseret vurdering.

Ad 3. Der findes rimeligt validerede kriterier og anvisninger på nødvendig udredning, som kan vejlede med hensyn til behandlingsskift [15].

7 Seponeringskriterier

TKI bør aktuelt ikke seponeres uden for protokolleret sammenhæng. Systematisk seponering er kun undersøgt i et enkelt større studie med 100 inkluderede patienter, som er interessant og ofte citeret som "proof of concept", men som på ingen måde er populationsbaseret [16]. Seponering vil have meget stor klinisk interesse, men det er præmaturt at estimere den kvantitative betydning.

8 Sammenligning af lægemidler

8.1 Lægemidlernes effekter og bivirkninger

8.1.a Klinisk spørgsmål og valg af population, intervention, comparator og outcome (PICO)

Udarbejdelsen af kliniske behandlingsvejledninger bør altid tage udgangspunkt i et eller flere specifikke kliniske spørgsmål, som leder hen mod definition af den relevante population (*Population*), den undersøgte intervention (*Intervention*), det klinisk relevante sammenligningsgrundlag (*Comparator*) og kritiske effektmål (*Outcomes*).
I denne sammenhæng arbejder Fagudvalget med følgende kliniske spørgsmål:

- Hvilke lægemidler i hvilke doser er ækvi-effektive til at sikre sygdomskontrol (overlevelse, progressionsfri overlevelse, minimal sygdomsmængde) med færrest komplikationer og bivirkninger og med minimalt besvær for patienten ved første linje behandling af CML i kronisk fase

Lægemidlernes effekt vurderes ved brug af evidens, der omhandler følgende PICO-komponenter, jf. GRADE-metoden[11]:

P_1: Behandlingsnaive CML i kronisk fase
P_2: Behandlingsnaive CML i kronisk fase, som præsenterer sig med mindst et af nedenstående symptomer:

- Langt QT syndrom
- Hjerteinsufficiens
- Svær KOL
- Pleuraexudater
- Uregelmæssig levevis
- Vanskelig regulerbar diabetes
- Nylig pankreatitis

I_1: Tablet dasatinib 100 mg, 1 gang daglig
I_2: Tablet imatinib, 400 mg, 1 gang daglig
I_3: Kapsel nilotinib, 300 mg, 2 gange daglig

C_1: Tidligere anvendt behandling (IFN/ARA-C, imatinib standarddosering/højdosis)
C_2: Lav-intensiv kemoterapi

O_1: Cytogenetisk respons
O_2: Molekylært respons, forskellig dybde
O_3: Progression
O_4: Dødelighed (total og leukæmi-relateret)
O_5: Ophør med studier
O_6: Behandlingssvigt
O_7: Toksicitet

8.1.b Systematisk review

På baggrund af ovennævnte PICO'er er der foretaget en systematisk litteratursøgning i Entrez-PubMed 13/8 2012 ved brug af søgestrengen:

((((("Leukemia, Myeloid, Chronic-Phase/drug therapy"[Mesh])) OR ((("front line" OR "first line")) AND ("chronic phase")) AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR

Clinical Trial, Phase III[ptyp] OR Evaluation Studies[ptyp]))))) NOT ((("Case Reports"[Publication Type]) OR "Review"[Publication Type]) OR "Editorial"[Publication Type] AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Evaluation Studies[ptyp])))

Princippet i søgestrengen er at identificere CML, kronisk fase, første linje behandling og derefter indskrænke søgningen til randomiserede kliniske trials og evalueringsstudier, men udtrykkelig at udelade editorials, reviews og kasuistikker.

Den anførte søgning medfører 138 hits, som er gennemgået. Det viser sig, at der i materialet trods indexering er en hel del prækliniske studier, som er uden relevans. Yderligere søgestrategisk indsnævring medfører imidlertid tab af væsentlige publikationer, hvorfor det er besluttet at udvælge 41 relevante publikationer manuelt. Fagudvalgets medlemmer har gransket søgeresultatet og mener at nettoresultatet er retvisende. Det skal bemærkes at der ikke findes metaanalyser inden for området. De kliniske studier er gennemgået i de respektive specifikke afsnit. Under fagudvalgets arbejde er der online publiceret 3. års opfølgning af det randomiserede studium ENESTnd [4]. Da disse data er særdeles relevante, er publikationen medtaget.

8.1.c Placebo-kontrollerede sammenligninger
Som det er tilfældet for næsten al onkologisk medicinsk litteratur, er der ikke foretaget placebo-kontrollerede undersøgelser, væsentligst af etiske årsager. Der er heller ikke foretaget blindede undersøgelser. Blinding ville på grund af bivirkningsprofiler og forskelle i administration være illusorisk.

8.1.d Direkte sammenligninger
Dasatinib sammenlignet med imatinib

Kun ét fase 3-studie har direkte sammenlignet dasatinib med imatinib. Det drejer sig om DASISION [17,18], som er et stort multicenter, multinationalt, firmainitieret studie, hvor man for en målgruppe svarende til nærværende baggrundsnotats beskrevne patientpopulation sammenlignede standarddosis af imatinib (400 mg x 1) med dasatinib (100 mg x 1). Der blev i alt randomiseret 519 patienter 1:1.

Det primære endepunkt var fraktionen af patienter med bekræftet komplet cytogenetisk remission (cCCyR) opnået inden for 12 måneder efter påbegyndelse af behandling. Sekundære endepunkter var molekylær remission, defineret som MR3 til ethvert tidspunkt, og tiden til opnåelse af cCCyR og MR3. Andre vigtige endepunkter var fraktionen af komplet cytogenetisk remission (CCyR) og MR3 inden for 12 måneder samt antallet af progressioner, samlet overlevelse og toxicitet.

Studiet anerkendes bredt som veldesignet og velgennemført, og der er publiceret opfølgninger op til 24 måneder efter behandlingsstart [18].

Det primære endepunkt viste signifikant fordel for dasatinib (77% vs. 66%, p=0,007). Efter 24 måneders opfølgning fandtes dog ikke længere signifikant forskel i CCyR (85% vs. 82%) mellem de 2 lægemidler. Med hensyn til molekylær remission fandtes signifikant fordel for dasatinib både efter 12 og 24 måneder. Der blev desuden påvist et lavere antal progressioner til AP/BP ved dasatinib, idet det dog bemærkes at der er tale om små tal (6 vs. 13 patienter). Til gengæld er der endnu ikke forskel på den samlede overlevelse (16 vs. 14 dødsfald). Anden linjebehandlingen var ikke systematiseret, men der foreligger den mulighed, at den har været

tilstrækkelig til at kompensere en initial klinisk effektforskel. Toksiciteten var lav, dog bemærkes et signifikant øget antal patienter med pleuraeffusion (14%) i gruppen, som fik behandling med dasatinib. Resultaterne i kontrolarmen (imatinib) var i god overensstemmelse med andre beslægtede studier (IRIS, ENESTnd) [4,6] og med observationelle studier af imatinib behandling [5,19]

Eksperter inden for CML har indtil nu anerkendt resultaterne, men dog påpeget en vis usikkerhed ved resultaterne som følge af frafald. Desuden er der en vis usikkerhed når resultater angives som en fraktion inden for et tidsrum ("by") i stedet for på et bestemt tidspunkt ("at"), idet patienter som efterfølgende har mistet responset tælles med. Man har dog ikke været i tvivl om rimeligheden ved at godkende dasatinib som muligt førstevalgspræparat, jf. FDA og EMA godkendelsen.

Evidensniveau: Højt, idet det drejer sig om et prospektivt, randomiseret multicenter studie. Valget af primært endepunkt, cytogenetisk remission efter ét år, er et traditionelt valg af en surrogatmarkør med dokumenteret prognostisk betydning for progression og overlevelse. [5,6,19]. Den manglende forskel i overlevelse kan bero på relativt kort observationstid eller på behandlingsskift i kontrolarmen. Det bemærkes i øvrigt, at behandlingssvigt i løbet af de første 2 år, bedømt med ELN surrogatmarkører, var ens i begge arme.

Nilotinib sammenlignet med imatinib

Nilotinib har kun indgået i én fase 3-undersøgelse, hvor det blev sammenlignet med imatinib. Det drejer sig om studiet ENESTnd [4,20,21], som er et stort multicenter, multinationalt, firmainitieret studie, hvor man for en målgruppe svarende til nærværende baggrundsnotats beskrevne patientpopulation sammenlignede standard dosis af imatinib (400 mg x 1) med to doseringer af nilotinib (400 mg x 2, som var den hidtidig anvendte, og 300 mg x 2). Der blev i alt randomiseret 846 patienter i forholdet 1:1:1.

Det primære endepunkt var fraktionen af patienter i molekylær remission, specificeret som MR3, opnået efter 12 måneders behandling. Vigtige sekundære endepunkter var cytogenetisk remission, antallet af kliniske progressioner, samlet overlevelse og toksicitet.

Studiet anerkendes bredt som veldesignet og velgennemført, og der er publiceret opfølgninger op til 36 måneder efter behandlingsstart [4].

Det primære endepunkt viste signifikant fordel for begge nilotinib-doser over for imatinib (44 % versus 22%, $p<0,001$), mens der ikke var indbyrdes forskel. Også med hensyn til cytogenetisk remission efter 12 måneder var der fordel til nilotinib (93 % versus 76 %, $p<0,001$). Der blev desuden påvist et signifikant lavere antal tidlige progressioner ved nilotinib, idet det dog bemærkes, at der er tale om små tal (hhv. 2,1 og 11). Under den videre opfølgning øges fraktionen af patienter i MR3 i alle tre arme, men fortsat med signifikant forskel (85 % versus 64 %). Til gengæld er der endnu ikke efter 3 år forskel på den samlede overlevelse, og det bemærkes, at der fra andet til tredje år ikke er registreret nye progressioner, overensstemmende med erfaring fra IRIS studiet [6] og observationelle studier [19]. Anden linje behandlingen var ikke systematiseret, men der foreligger den mulighed, at den har været tilstrækkelig til at kompensere en initial klinisk effektforskel. Toxiciteten var lav, og som forventeligt lidt lavere ved den mindre af de to nilotinib-doser. Resultaterne i kontrolarmen (imatinib) var i god overensstemmelse med andre beslægtede studier (Dasision, IRIS) [6,18].

Eksperter inden for CML har indtil nu anerkendt resultaterne, men dog rejst tvivl om overholdelse af Intention-to-treat princippet og yderligere påpeget en vis usikkerhed ved resultaterne som følge af frafald [22]. Man har ikke været i tvivl om rimeligheden ved at godkende nilotinib som muligt første valgspræparat, jf. FDA og EMA godkendelsen.

Evidensniveau: Højt, idet det drejer sig om et prospektivt, randomiseret multicenter studie. Valget af primært endepunkt, MR3 efter 12 måneder, er foretaget ud fra ønsket om en moderne, mere dynamisk variabel, som suppleres med den traditionelle cytogenetiske undersøgelse, jf. beskrivelsen af dasatinib. Nilotinib udviser en fordel frem for imatinib med hensyn til surrogatmarkører, tidlige progressioner og CML relaterede dødsfald, men ikke i samlet overlevelse. Der er ikke observeret noget sikkert mønster med hensyn til ikke-CML relaterede dødsfald. En mulig fortolkning er, at en fordel med hensyn til anti-leukæmisk effekt balancerer med en ikke sikkert forklaret toksisk effekt. Dette forhold er vigtigt, da erfaringen med imatinib-behandling er, at progressioner efter 3. behandlingsår er ekstremt sjældne [6,19], hvorimod en uerkendt toksisk effekt af nilotinib med nogen sandsynlighed kan forventes at kumuleres.

Internationale guidelines er endnu ikke ændret til præference for 2. generations TKI. Man har endnu ikke turdet konkludere, at forskellen med hensyn til surrogatmarkør afspejler en regulær klinisk betydende forskel. Det skal bemærkes, at anvendelsen af TKI og molekylær monitorering er udviklet netop ved CML, og at langt størst erfaring kommer herfra. Der er således ikke præcedens fra andre sygdomme, og den samlede erfaring er genereret over en periode på kun godt 10 år.

8.1.e Indirekte sammenligninger
Der foreligger ikke direkte sammenligninger af 2. generations TKI ved CML. De randomiserede, kontrollerede studier udviser dog betydelige ligheder med hensyn til design og effektparametre. Fagudvalget finder det rimeligt at klassificere dasatinib og nilotinib som havende en i forhold til imatinib relativt ensartet bedre effekt på surrogatmarkører, men til gengæld ikke effekt på samlet overlevelse, bedømt på små tal og kort observationstid. Præference for den ene af de to 2. generations TKI er derimod ikke tilladelig på dette grundlag, da der utvivlsomt kan være forskelle i selektion og protokolprocedurer.

8.2 Værdier og præferencer vedr lægemiddelalternativerne
Fagudvalget finder det vigtigt, at der er langtidserfaring med brugen af de rekommanderede lægemidler.

8.3 Compliance/convenience
Ved systematisk gennemgang af compliance/convenience-relaterede aspekter ved behandling med de nuværende registrerede præparater af TKI´erne dasatinib, imatinib og nilotinib, vurderer fagudvalget, at der ikke er tilstrækkelige fagligt begrundede forskelle, der kan medføre præference for et af præparaterne som første valg i første linje.

De nuværende registrerede præparater er alle til peroral indgift (kapsel/tablet) med væsentlige, men efter fagudvalgets mening ikke diskvalificerende, forskelle indenfor dispenseringsform (+/- deles/åbnes) og doseringstidspunkt (1-2 gange dagligt, sammen med/forskudt fra mad).

Ved individuelle forhold med væsentlig indflydelse på adherence kan første valg af første linje behandling ud fra en samlet betragtning fraviges. Det kan være behovet for fleksibel dosering,

forventning om non-adherence med den rekommanderede farmakologiske behandling, problemer med indtagelse af den konkrete lægemiddelform (synkebesvær, sonde), m.m.

8.4 Patientsikkerhed

Ved systematisk gennemgang af patientsikkerhedsmæssige aspekter ved behandling med de nuværende registrerede præparater af TKI´erne dasatinib, imatinib og nilotinib, mener fagudvalget ikke, at der er tilstrækkelige fagligt dokumenterede forskelle, der kan begrunde præference for et af præparaterne som første valg i første linje.
Ved individuelle forhold med væsentlig indflydelse på patientsikkerheden kan første valg af første linje behandling ud fra en samlet betragtning fraviges. Det kan være præparaternes bivirkningsprofil og interaktionsmuligheder, nedsat organfunktion m.m.

Behandleren skal uanset valg af TKI sikre patientsikkerheden gennem en systematisk vurdering af alle patientsikkerhedsmæssige betydende aspekter, herunder:

1. Grundig medicinanamnese inkl. naturlægemidler på grund af risiko for interaktioner.
2. Grundig instruktion af patienten i korrekt administration (indgiftstidspunkt, fødevarer, glemt dosis, m.m.).
3. Monitorering af udvalgte parametre (blodtal, hjertefunktion, lever-/nyrepåvirkning) med de rigtige intervaller.
4. Information om bivirkninger, korrekt opbevaring, m.m.

I valget af behandling lægger fagudvalget størst vægt på effekten, da behandlingssvigt er forbundet med alvorlige risici. Bivirkninger og interaktioner vurderes som sekundære og afhjælpes gennem understøttende behandling og monitorering.

Ved skift fra et TKI til et andet TKI skal patienten instrueres grundigt på ny, bl.a. i forhold til ændrede administrationsrutiner, monitoreringsbehov, bivirkninger og opbevaringsforhold.

8.5 Konklusion vedr. ækvieffektive lægemidler

Fagudvalget bemærker ved en samlet vurdering af PICO, at de randomiserede studier bør tillægges størst vægt. Fagudvalget påpeger, at behandlingsresultaterne for alle tre registrerede TKI er overordentlig bemærkelsesværdige, men at udviklingen inden for området er sket meget hurtigt. De "hårde" endepunkter, som præger studier af andre maligne sygdomme, er fåtallige. Selvom surrogatmarkører således er nødvendige, finder fagudvalget det vanskeligt at vurdere de enkelte markørers samlede betydning over for traditionel overlevelsesstatistik. Det er et fælles træk for de randomiserede studier, at surrogatmarkørerne påpeger en tidligt opstående effektforskel, mens den samlede overlevelse ikke med sikkerhed er forskellig. For nilotinib er der desuden påvist et signifikant lavere antal tidlige progressioner uden signifikant forskel i overlevelse. De første observationer fra 3. års behandlinger synes at bekræfte den tidligere påviste meget lave forekomst af sene progressioner hos responderende patienter uanset behandling. Fagudvalget bemærker desuden, at flere behandlingsstrategier i tilfælde af svigt er mulige, men ikke vel dokumenterede med hensyn til effekt selvstændigt eller i relation til en patientkohorte.

Det er fagudvalgets holdning, at følgende lægemidler alle kan rekommanderes som første linje behandling til en stor majoritet af patienter med debuterende CML, kronisk fase:

- Tablet dasatinib, 100 mg, 1 gang daglig
- Tablet imatinib, 400 mg, 1 gang daglig
- Kapsel nilotinib, 300 mg, 2 gange daglig med 12 timers interval

Fagudvalget ønsker at pointere, at behandlingerne skal overvåges nøje i henhold til udarbejdede lægemiddelvejledninger.

8.6 Kaskade

Valget af anden linje behandling vil være stærkt individuelt, og generelle regler vil næppe være hensigtsmæssige.

8.7 Valg af lægemiddel

A. Til patienter som ikke er omfattet af mindst et af nedenstående kriterier • Langt QT syndrom • Hjerteinsufficiens • Svær KOL • Patient med pleuraexudater • Patient med uregelmæssig levevis • Vanskelig regulerbar diabetes • Nylig pankreatitis	B. Til patienter som præsenterer sig med mindst et af nedenstående kriterier • Langt QT syndrom[1] • Hjerteinsufficiens[2] • Svær KOL[2] • Patient med pleuraexudater[2] • Patient med uregelmæssig levevis[3] • Vanskelig regulerbar diabetes[3] • Nylig pankreatitis[3]
Vælges tablet dasatinib, 100 mg, 1 gang daglig eller tablet imatinib, 400 mg, 1 gang daglig eller kapsel nilotinib, 300 mg, 2 gange daglig med 12 timers interval	Vælges: **1** tablet imatinib, 400 mg, 1 gang daglig **2** tablet imatinib, 400 mg, 1 gang daglig eller kapsel nilotinib, 300 mg, 2 gange daglig med 12 timers interval **3** tablet imatinib, 400 mg, 1 gang daglig eller tablet dasatinib, 100 mg, 1 gang daglig
1.valg *Ved rekommandation anføres det eller de lægemidler, der ud fra de opnåede lægemiddelpriser giver billigste behandling.* 2.valg Vælges ved erkendt intolerance til 1. valg *Ved rekommandation anføres det eller de mulige alternativer til 1. valg i prioriteret rækkefølge ud fra de opnåede lægemiddelpriser.*	

9 Behandlingsmål

Overordnet forventes patienterne at fordele sig med 80 % af patienterne til gruppe A i skemaet "valg af lægemiddel" og 20 % til gruppe B.

Da der allerede er en stor pulje af behandlinger, som ikke på det foreliggende skal ændres, vil valget af ét præparat som første linje i en årelang periode kun have beskeden indflydelse på det samlede forbrug af TKI.

Fagudvalget ønsker at påpege, at der er livlig medicinsk forskningsaktivitet i området. Første linje protokoller, alternative anden linje og seponeringsprotokoller må forventes aktive, og de vil påvirke forbruget af TKI.

Fagudvalget ønsker at gøre opmærksom på, at imatinib som første linje behandling i uprotokolleret sammenhæng kun vil forblive opretholdt hos 50 – 70 % af patienterne efter få år, når man anvender kriterier for skift til anden linje som beskrevet [5,6,13,23].

For dasatinib og nilotinib kender man ikke de tilsvarende tal, hverken fra randomiserede studier eller observationelle studier, ligesom kriterierne for skift ikke er så alment accepterede [14]. Da disse præparater tåles lige så godt som imatinib og i færre tilfælde vil møde kriterierne for skift, er der grund til at formode, at puljen af første linje behandlede i højere grad vil forblive intakt med disse to præparater. Et indirekte mål herfor kan være frafaldet (alle årsager) i de randomiserede studier, som har været 20 – 25 %[18,20,21], svarende til en forventning om 75 – 80 % forblivende i første linje behandling.

10 Revurderingskriterier

Fagudvalget bemærker, at der med meget stor sandsynlighed ikke vil blive udført flere sammenlignende studier mellem imatinib versus dasatinib respektive nilotinib som første linje behandling, ligesom der ikke er forventning om direkte sammenligning mellem dasatinib og nilotinib. Ændringer af fagudvalgets konklusioner vil dermed formentlig kun kunne ske på basis af yderligere modning af foreliggende studiers resultater. Den forventelige videre udvikling vil være længere tids observation af progressionsfri overlevelse og udvikling i surrogatmarkører herfor. Endvidere foreligger den mulighed, at dele af de aktuelle kohorter videreføres i studier, hvor man undersøger mulighederne for ophør med behandling, og at der herved afsløres klinisk betydende forskelle. De randomiserede studier opdateres hvert halve år. Der vil dermed være basis for at revurdere situationen om ca. 2 år. Til den tid forventes også mere modne data vedrørende bosutinib.

Fagudvalgets sammensætning	Fagudvalgsformand Jesper Stentoft, Fagdidaktisk professor, overlæge, ph.d. (udpeget af Dansk Hæmatologisk Selskab) Ole Weis Bjerrum, overlæge, dr. med.(udpeget af Region Hovedstaden) Thomas Storkholm, farmaceut, souschef (udpeget af Dansk Selskab for Sygehusapoteksledelse) Lene Udby, afdelingslæge, ph.d. (udpeget af Region Sjælland) Marianne Tang Severinsen, overlæge, ph.d. (udpeget af Region Nord) Hanne Vestergaard, specialeansvarlig overlæge, ph.d. (udpeget af Region Syddanmark) Stanislaw Pulczynski, specialeansvarlig overlæge (udpeget af Region Midt) Eva Aggerholm Sædder, overlæge (Udpeget af Dansk Selskab for Klinisk Farmakologi)

11 Bilag

A. Skema over patientsikkerhedsforhold

B. Kompilation af ekstraherede effektvariable i skemaform

   a. Dasatinib, imatinib og nilotinib

   b. Specialnotat om bosutinib

C. Lægemiddelvejledninger for

   a. Dasatinib som første linie behandling

   b. Imatinib som første linie behandling

   c. Nilotinib som første linie behandling

D. Brutto referenceliste svarende til søgestreng

E. Sammenligningsgrundlag

12 Referencer

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Bilag A

RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Fagudvalgets holdning til patientsikkerheden

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Udarbejdet	Fagudvalget har udarbejdet dette bilag pr. september 2012

Patientsikkerhed og praktiske forhold, herunder compliance

Ud fra et patientsikkerhedsmæssigt perspektiv er det fagudvalgets opfattelse, at de nuværende markedsførte udgaver af TKI´erne imatinib, dasatinib og nilotinib ikke adskiller sig fra hinanden i en grad, der påvirker anbefalingen af et præparat frem for et andet som 1. valg i 1. linje.

Ved individuelle forhold med indflydelse på patientens sikkerhed og compliance kan behandlings-vejledningens rekommandationer fraviges. Det kan være præparaternes bivirkningsprofil og interaktionsmuligheder, behovet for fleksibel dosering, forventning om non-adherence med den rekommanderede farmakologiske behandling, nedsat organfunktion m.m.

Patientsikkerheden skal uanset valg af TKI´er sikres gennem bl.a.:

-grundig medicinanamnese inkl. naturlægemidler p.g.a. risiko for interaktioner.

-grundig instruktion af patienten i korrekt administration (indgiftstidspunkt, fødevarer, glemt dosis, m.m.).

-monitorering af udvalgte parametre (blodtal, hjertefunktion, lever-/nyrepåvirkning) med de rigtige intervaller.

-information om bivirkninger, korrekt opbevaring, m.m.

I valget af behandling lægger fagudvalget størst vægt på effekten, da behandlingssvigt er forbundet med alvorlige risici. Bivirkninger og interaktioner vurderes som sekundære og afhjælpes gennem understøttende behandling og monitorering.

Ved skift fra et TKI til et andet TKI skal patienten instrueres grundigt på ny, bl.a. i forhold til ændrede administrationsrutiner, monitoreringsbehov, bivirkninger og opbevaringsforhold.

Udvalgte betydningsfulde patientsikkerhedsmæssige forskelle med fagudvalgets kommentarer:

1. Ud fra en farmaceutisk vurdering er der tale om 3 veldokumenterede præparater fremstillet af seriøse producenter.

2. De 3 præparater er alle til oral indtagelse (kapsel/tablet), så på den vis er de nemme at administrere og skiller sig ikke ud fra hinanden, som havde det været oral kontra parenteral administration. Der er væsentlige, men efter fagudvalgets mening ikke diskvalificerende, forskelle indenfor doseringsform og doseringstidspunkt (med/uden mad, +/- deles/knuses).
3. Der er forskelle i interaktionsmuligheder, bivirkninger og monitoreringsbehov, men ingen af de 3 præparater skiller sig ud som værende afgørende nemmere.

Emne		Sammenfatning
Doserings-tidspunkt	Glivec (imatinib): med mad og stort glas vand Sprycel (dasatinib): uafhængig af mad, men fast klokkeslet Tasigna (nilotinib): 2 t. før eller 1 t. efter mad	Afgørende for effekt og bivirkninger at patient overholder indgiftstids-punkt(er) og +/- mad. **Kommentar:** Konsekvent indtagelse af Tasigna korrekt forskudt fra mad er svært pga. dosis hver 12. time. Glivec skal (for at minimere GI-gener) og Sprycel kan indtages ved måltid, hvilket gør det nemmere at huske, samtidig med at der er lagt op til dosering kun en gang dagligt.
Dosisjustering	Glivec (imatinib): skal justeres ved nedsat lever/nyre funktion. Sprycel (dasatinib): anvendes med forsigtighed ved leverinsufficiens. Tasigna (nilotinib): anvendes med forsigtighed ved leverinsufficiens.	Glivec skal dosisjusteres ved nedsat lever/nyre-funktion, mens der som minimum skal udvises forsigtighed ved Sprycel og Tasigna. **Kommentar:** Må betragtes som et praktisk problem som behandler kan løse ved grundig anamnese inden ordination og efter-følgende sufficient monitorering. Der skal også monitoreres andre værdier.
Lægemiddelform	Glivec (imatinib): tbl. kan opløses i vand eller æblejuice. Sprycel (dasatinib): tbl. skal synkes hele. Tasigna (nilotinib): kapsel kan åbnes og indhold drysses på en tsk. æblemos og ikke andet.	Sprycel skal synkes hele jf. produktresume, mens de to andre kan formindskes før indtagelse. **Kommentar:** Sprycel må ikke deles/knuses pga. risiko for optagelse gennem

		hud. Derfor skal sundhedspersonale bære handsker i dette tilfælde jf produktresume.
Børn, gravide, ammende	Glivec (imatinib): sparsomme erfaringer fra 3-18 år, til gravide under særlige forhold, ikke til ammende Sprycel (dasatinib): mangler erfaringer under 18 år, til gravide under særlige forhold, ikke til ammende Tasigna (nilotinib): mangler erfaringer under 18 år, til gravide under særlige forhold, ikke til ammende	Ens for de 3 præparater, bortset fra visse erfaringer med Glivec til 3-18 år.
Opbevaring	Glivec (imatinib): ikke over 30°C, beskyttet mod fugt og i originalemballage Sprycel (dasatinib): ingen særlige forholdsregler Tasigna (nilotinib): ikke over 30°C, beskyttet mod fugt og i originalemballage	Sprycel skiller sig ud ved ingen specielle regler til opbevaring. **Kommentar**: Selv om Sprycel ikke nævner specielle opbevaringsforhold, må opbevaring forventes at ligge inden for sund fornuft = original emballage, ikke for koldt/varmt/fugtigt.
Risiko ved overdosering	Glivec (imatinib): Enkelte tilfælde rapporteret, generelt med positiv udfald. Sprycel (dasatinib): Få tilfælde. Gav signifikant nedsat antal blodplader. Tasigna (nilotinib): Isolerede tilfælde opserveret med neutropeni, opkastning og døsighed, men patienter kom sig.	**Kommentar:** Produktresumeer oplyser om få rapporterede hændelser, generelt med positivt udfald. Risiko for overdosering og glemt dosis kan mindskes med ugedag-mærkede blisterpakninger frem for bøtter/glas med fx 100 stk.
Monitorering	Glivec (imatinib): diverse prøver/observationer Sprycel (dasatinib): diverse prøver/observationer	Der skal monitoreres på diverse (blodtal, hjerte-funktion m.m.). **Kommentar:** Ved skift af TKI´er skal

	Tasigna (nilotinib): diverse prøver/observationer	monitorering justeres.
Bivirkninger	Glivec (imatinib): diverse Sprycel (dasatinib): diverse Tasigna (nilotinib): diverse	**Kommentar:** Bivirkningsprofilen for imatinib, dasatinib og nilotinib varierer, men dog med langt overvejende fællestræk.
Interaktioner	Glivec (imatinib): bredt spekter primært inhibitorer og induktorer af CYP3A4 Sprycel (dasatinib): bredt spekter primært inhibitorer og induktorer af CYP3A4 Tasigna (nilotinib): bredt spekter primært inhibitorer og induktorer af CYP3A4	Der skal tages forholdsregler mod diverse interaktions-muligheder. **Kommentar:** Ingen skiller sig ud som væsentlig nemmere. Valg af præparat må afhænge af konkret overblik over samlet medicinering inkl. naturlægemidler.
Øvrig	Sprycel (dasatinib): Indeholder lactose Tasigna (nilotinib): Indeholder lactose	**Kommentar:** Sprycel og Tasigna, men ikke Glivec indeholder lactose, og bør ikke tages ved en række sjældne sygdomme (lactase-mangel, intolerans, mal-absorption).
Patientinformation	Glivec (imatinib): indlægsseddel Sprycel (dasatinib): indlægsseddel Tasigna (nilotinib): indlægsseddel	**Kommentar:** Der er indlægssedler i præparatæskerne, men de korrekte informationer og instrukser til patienten skal ske gennem samtale mellem behandler og patient, evt. suppleret af skriftlig patientinformation fra afdelingen.

Bilag B, a

RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Kompilation af ekstraherede effektvariable
Dasatinib, imatinib og nilotinib

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Udarbejdet	Fagudvalget har udarbejdet dette bilag pr. september 2012

ENESTnd[1-3]

Imatinib	**3**	**6**	**9**	**12**	**24**	**36**
CCyR (at) (%)				76		
CCyR (by) (%)				65	77	
MR 3 (at) (%)	1	12	18	22*		53
MR 3 (by) (%)				27	44	64
MR 4 (by) (%)						26
MR 4.5 (by) (%)						15
Progression (%)				4	6	6
Overall survival (%)				100	96,3	94
Antal døde/ heraf leukæmirelateret				0	11/10	17/14
Ophørt (%)				21	33	38
Svigt (ELN) (%)				6	10	

Nilotinib 300 mg x 2	3	6	9	12	24	36
CCyR (at) (%)				93		
CCyR (by) (%)				80	87	
MR 3 (at) (%)	9	33	43	44*		73
MR 3 (by) (%)				51	71	85
MR 4 (by) (%)						50
MR 4.5 (by) (%)						32
Progression (%)				<1	0,7	0,7
Overall survival (%)				100	97,4	95,1
Antal døde/ heraf leukæmirelateret				0	9/5	13/5
Ophørt (%)				16	26	29
Svigt (ELN) (%)				4	7	

Nilotinib 400 mg x 2	3	6	9	12	24	36
				93		
CCyR (by) (%)				78	85	
MR 3 (at) (%)	5	30	38	43*		70
MR 3 (by) (%)				50	67	79
MR 4 (by) (%)						44
MR 4.5 (by) (%)						28
Progression (%)				<1	1,8	1,8
Overall survival (%)				100	97,8	97
Antal døde/ heraf leukæmirelateret				0	6/3	8/4
Ophørt (%)				18	22	26
Svigt (ELN) (%)				2	<1	

By = Intention to treat
Gul = Saglio (12 måneders data)
Rosa = Kantarjian (24 måneders data)
Blå = Larson (36 måneders data)
* = Primary endpoint, p < 0,001

DASISION [4,5]

Imatinib	**3**	**6**	**9**	**12**	**24**	**36**
CCyR (at) (%)						
CCyR / cCCyR (by) (%)	31	59	67	72/66*	82	
MR 3 (at) (%)						
MR 3 (by) (%)	0,4	8	18	26	46	
MR 4 (by) (%)						
MR 4.5 (by) (%)					8	
Progression (%)				3,5	5,0	
Overall survival (%)				99,6	95	
Antal døde/heraf leukæmirelateret				1/?	14/10	
Ophørt (%)				18,6	25	
Svigt (ELN) (%)				3,9	4	

Dasatinib	**3**	**6**	**9**	**12**	**24**	**36**
CCyR (at) (%)						
CCyR / cCCyR (by) (%)	54	73	78	83/77*	86	
MR 3 (at) (%)						
MR 3 (by) (%)	8	27	39	46	64	
MR 4 (by) (%)						
MR 4.5 (%)					17	
Progression (%)				1,9	2,3	
Overall survival (%)				98,5	94	
Antal døde/heraf leukæmirelateret				4/?	16/8	
Ophørt (%)				15,5	23	
Svigt (ELN) (%)				2,3	3	

Blå = 12 måneders data

Grå = 24 måneders data

* = Primary end point, $p < 0,007$

Referencer: (NB! Ikke samme nummerering som i Baggrundsnotatet)

(1) Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010; 362: 2251-9.

(2) Kantarjian HM, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol 2011; 12: 841-51.

(3) Larson RA, Hochhaus A, Hughes TP, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia 2012.

(4) Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010; 362: 2260-70.

(5) Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood 2012; 119: 1123-9.

Bilag B, b

RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Kompilation af ekstraherede effektvariable
Specialnotat om bosutinib

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Udarbejdet	Fagudvalget har udarbejdet dette bilag pr. september 2012

BOSUTINIB
Effekt (komplet cytogenetisk remission og molekylær remission (med specifikation af niveau)) i absolutte tal fra fase 3 studier i forhold til definerede tidslinjer:

Bosutinib *versus* Imatinib

Abstr ASH 2011	3 mdr	6 mdr	9 mdr	12 mdr	18 mdr
CCyR % I T T	**50 vs 25**	**59 vs 49**	**63 vs 55**	**70 vs 68 175 vs 171**	**62 vs 67**
MR 3 ? %	**7 vs 3**	**28 vs 11**	**35 vs 19**	**41 vs 27**	**46 vs 38**
MR 4.5					
MR andre					
Antal pt	**248 vs 250**				

Mødte ikke primære end-point for CCygR ved 12 måneder gr frafald. Absolutte antal pt kan ikke gives ud fra dette abstract. Fremgår i nogen grad af data fra ppt ved oral præsentation. I EHA abstract 2012 (#587) angives CMR til 4 log.

Bosutinib *versus* Imatinib

ORAL ppt	3 mdr	6 mdr	9 mdr	12 mdr	
CCyR % evaluable				**78 vs 68 219 vs 241**	**p < 0.026**
MR 3 ? % evaluable				**43 vs 27 219 vs 241**	**P < 0.001**
MR 4.5					
MR andre					
Antal pt					

Kliniske referencer

Jorge E. Cortes, Hagop M. Kantarjian, Tim H. Brümmendorf, et al.: Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome–positive chronic myeloid leukemia patients with resistance or intolerance to imatinib *Blood*. 2011;118(17): 4567 – 4576.
FASE 1-2 Studie. Imatinib-intolerante (88) eller resistente (200) pt. Dosis 500 mg x 1 dgl.

Peter C. Traska, David Cellac, Nadine Bessond et al: Health-related quality of life of bosutinib (SKI-606) in imatinib-resistant or imatinib-intolerant chronic phase chronic myeloid leukemia. *Leukemia Res* 2012; 36: 438 – 442. QoL studie på materiale fra Cortes et al. Studie 2011.

H. Jean Khoury, Jorge E. Cortes, Hagop M. Kantarjian et al: Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood* 2012; 2012; 119(15): 3403 – 3412.
Fase 1-2 studie, imatinib up-front med intolerans - resistens, siden nilotinib / dasatinib (118 pt). Dosis 500 mg bosutinib / dag.

Carlo Gambacorti-Passerini, Jorge E. Cortes,Patricia Harris et al. : Safety and Management of Toxicities in the BELA Trial of Bosutinib Versus Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia. Abstract ASH 2011. Om bivirkninger, safety I FASE 3 studie (BELA) ….og yderligere opfølgning ASCO 2012 mht bivirkning, safety med **30 mdr responsdata.** Hyppigere diarre / ALAT m bosutinib vs imatinib, og SAE (31 vs 19%).

Dong-Wook Kim, Jorge E. Cortes, Zvenyslava Maslyak et al.: The Incidence of Bcr-Abl Mutations and Their Impact on Clinical Outcome in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia Patients Treated With Bosutinib Versus Imatinib in the BELA Trial. ASH 2011 abstract.
Flere punktmutationer ved udgang af studiet hos pt I imatinib arm, og udvikling af flere resistente.

Bilag C, a

RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Lægemiddelvejledning

Dasatinib til voksne patienter med nydiagnosticeret CML i kronisk fase.

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Udarbejdet	Fagudvalget har udarbejdet dette bilag pr. september 2012

Dosering og administration

Dosis er 100 mg dasatinib per os indtaget en gang daglig. Bør indtages på samme tidspunkt hver dag, indtages med eller uden samtidig fødeindtagelse.

Dispenseringsform: Tabletter

Findes pr. september 2012 i styrkerne 20, 50, 70, 80, 100 og 140 mg

Forsigtighedsregler

Behandling med dasatinib gives sammen med allopurinol indtil leukocyttal er under 50 x 10^9/l. Forbehandling med hydroxyurea kan anbefales ved leukocyttal væsentligt over 100 x 10^9/l.

Blodprøver før behandlings start: blodbillede, nyrefunktion og elektrolytter, leverfunktion. EKG: personer > 60 år eller anamnese for hjertesygdom mhp rytmestatus og QT. Rtg af thorax. Ved mistanke til kardiopulmonal sygdom foretages ekkokardiografi og anden relevant udredning.

Ved moderat nedsat leverfunktion indledes behandling med 70 mg x 1 dgl, individuel vurdering og leverfunktion monitoreres, men dosis øges til 100 mg x 1 hvis ikke yderligere leverpåvirkning
Komorbiditet og medicin liste vurderes.

Kontraindikationer, absolutte

- Graviditet. Individuel håndtering af nydiagnosticeret, gravid CML patient
- Amning frarådes samtidigt med behandling

Antikonception er påkrævet hos mænd og kvinder der er i behandling med dasatinib. Graviditet kan gennemføres under behandlingspause, men forudsætter individuel vurdering. Sæddeponering anbefales, hvis der foreligger ønske om familieforøgelse.

Kontraindikationer, relative

- Hjerteinsufficiens
- Kronisk obstruktiv lungesygdom
- Forud eksisterende pleuraexudater

Behandling med dasatinib kan gennemføres under skærpet opmærksomhed, men vil være vanskeliggjort af differentialdiagnostiske overvejelser ved dyspnø.

Bivirkninger

For fuldstændig redegørelse henvises til SPC for Sprycel® og til pro.medicin.dk

Meget almindelige (over 10%)	Temperaturstigning. Kvalme, opkastning, abdominalsmerter, diarré. Perifere ødemer, pleuraekssudat, dyspnø. Blødningstendens. Smerter i ekstremiteter. Hovedpine. Hududslæt. Infektioner.
Almindelige (1-10%)	Nedsat appetit, vægtændring, feber, kulderystelser, kraftesløshed. Smagsforstyrrelser, dyspepsi, gastro-intestinal blødning, enterocolitis. Hypertension, hjerteinsufficiens, perikardieansamling, arytmier, palpitationer, pneumoni, lungeødem, hoste. Neutropeni, pancytopeni. Forhøjet serum-urat. Artralgi, myalgi, muskelsvaghed, muskelkramper. Svimmelhed, neuropati, depression, søvnløshed, døsighed. Hudkløe, alopeci, acne, tør hud, urticaria, øget svedtendens. Sepsis, infektion i øvre luftveje. Synsforstyrrelser, tørre øjne, tinnitus.

Dosisjustering ved bivirkninger

Fagudvalget anbefaler at bivirkninger registreres og graderes systematisk, f.eks. NCI kriterier **Bemærk**. Det har høj prioritet at der overholdes adherence større end 90 %, idet lavere adherence er korreleret til dårligere behandlingsresultat. Lægeinitierede behandlingspauser som konsekvens af SPC kan komme i konflikt med dette overordnede princip, og i så fald må man individualisere.

Hvis der opstår uacceptable bivirkninger til dasatinib behandling, afbrydes behandlingen indtil bivirkningen er forsvundet eller minimal, afhængigt af en individuel vurdering og symptomets karakter. Behandlingen genoptages med 100 mg daglig. Ved recidiv af bivirkning anbefales igen pause, og når bivirkningen er forsvundet genoptages behandlingen i reduceret dosis (80 mg daglig) med yderligere reduktion fra 80 til 50 mg dagligt hvis bivirkningen atter recidiverer.

Hæmatologiske bivirkninger

Myelosuppresion er almindelig. Anvendelse af hæmatopoetiske vækstfaktorer kan anvendes med henblik på at tilsikre høj adherence. Der findes i SPC detaljerede regelsæt for dosismodifikation, men dosisintensitet vil af de fleste blive prioriteret under ekstensive forsigtighedsregler.

Blødning ses ved trombocytopeni. Derfor bør der udvises forsigtighed ved samtidig behandling med trombocythæmmere, som alle bør pauseres ved trombocyttal < 50 x 10^9/l. Evt warfarin behandling skal kontrolleres ved hver blodprøve og pauseres efter indikation og trombocyttal, men generelt også ved trombocyttal < 50. Heparinisering kan evt overvejes ved ustabilt forløb koagulationsmæssigt.

Ikke-hæmatologiske bivirkninger

Væskeretention er meget almindelig. Specielt forekommer pleuraeffusion (PE) ofte. PE kan vise sig sent i behandlingsforløbet og forekommer således ikke sjældent efter 1 års behandling. Symptomer som giver mistanke om PE (hoste/dyspnoe) bør afklares med relevante undersøgelser. Ved symtomgivende PE behandles afhængig af sværhedsgrad. I milde tilfælde gøres behandlingspause indtil symptomfrihed, ved manglende bedring efter 1 uge eller i svære tilfælde tilføjes behandling med diuretika og/eller kortikosteroider, eventuelt pleuradrænage.
Pulmonal arteriel hypertension (PAH) er rapporteret. Hvis PAH bekræftes skal behandlingen med dasatinib seponeres permanent.
QT-forlængelse ses ved behandling med dasatinib. Hos pt der i forvejen har forlænget QT bør dasatinib administreres med forsigtighed og under kontrol.
Hjertebivirkninger er almindelige hos patienter i behandling med dasatinib. Forværring/Incompensatio cordis ses specielt hos pt med risikofaktorer (hypertension, hyperlipidæmi, diabetes tidl hjertesygdom) hos hvem særlig forsigtighed anbefales.

Interaktioner med andre medikamenter

Midler der kan **øge plasmakoncentrationen af dasatinib**: hæmmere af CYP3a4 øger eksponeringen af dasatinib hvorfor det anbefales at undgå samtidig administration af CYP3a4 hæmmere (ex. ketoconazol, itraconazol, erytromycin, claritromycin m.m.)

Midler der **mindsker plasmakoncentrationen af dasatinib**: induktorer af CYP3a4 øger metabolismen af dasatinib og reducerer plasmakoncentrationen. Samtidig brug af CYP3a4 induktorer bør undgås (ex. dexamethazon, phenytoin, carbamazepin, phenobarbital og naturlægemidler som perikon m.fl.). Studier har desuden vist reduceret plasmakoncentration af dasatinib ved samtidig indtagelse af protonpumpe hæmmere (omeprazol) samt H_2-antagonister.
Samtidig behandling med dasatinib øger eksponering af simvastatin betydelig, formentligt grundet en hæmning af CYP3A4-medieret metabolisme af simvastatin. Dosisreduktion af simvastatin f.eks. fra 40 til 20 mg dagligt under monitorering af kolesterolprofil foreslås. Alternativt anvendelse af pravastatin eller rosuvastatin, der har en anden metabolisme.

Behandlingsforslag ved udvalgte bivirkninger

Træthed: udeluk andre årsager (mangeltilstande, DM, myxoedem, komorbiditet)
Øjenlåg / periorbitalt ødem: evt øjendråber metaoxidrin 0.25 % (magistrel) x 1-3.
Conjunctivale blødninger ufarlige, kan ikke behandles specifikt.
Ødemer: diuretika individuelt, evt kontrol kardiel status og interaktioner
Øvre gastrointestinale gener: antiemetika. Bemærk interaktion med protonpumpe-inhibitor og h2 blokkere.
Diarre: obstiperende midler, evt opiumsdråber, hvis infektion er udelukket
Muskelkramper: kontroller elektrolytter, chlordiazepoxid, peroral calcium kan forsøges
Udslæt: pausere, genoptag i reduceret dosis, men tilstræbe standard dosis. Kortvarig systemisk glukokortikoid kur / salve, evt samtidigt med genoptaget dasatinib. Overveje andre årsager til udslæt (anden behandling, hudsygdom)
Svedtendens: kontroller thyreoidea parametre og PCR status for Ph.

Monitorering af effekt

1. Det er vigtigt at indskærpe betydningen af regelmæssig medicinindtagelse
2. Initialt ses patienten ambulant ca. dag 14, 28, 56 og 84 med henblik på kontrol af miltstørrelse, hæmatologiske blodprøver, lever og nyrefunktion samt til imødegåelse af bivirkninger
3. Knoglemarvsundersøgelse med cytogenetiske undersøgelse foretages med 3 måneders interval indtil opnået komplet cytogenetisk remission. Herefter kun ved mistanke om progression
4. Blodprøve med molekylærbiologisk undersøgelse foretages hver 3. måned i de første 3 år. Herefter efter skøn med 3 – 6 måneders interval, forudsat der er opnået MR3
5. Stigning i fusionstranskript med faktor 3 eller mere, som ikke tvangfrit kan forklares ved svigtende adherence, motiverer udredning for sekundær resistens

Behandlingsskift

1. Intolerance: Non-hæmatologiske grad 3 bivirkninger, gentagne grad 2 bivirkninger trods energisk symptomatisk behandling, multiple grad 1 bivirkninger trods energisk symptombehanding

2. Primære resistens, vurderet efter ELN rekommandationer som manglende opnåelse af defineret respons til adækvat tid (”failure”). Der kan ikke udstedes generel vejledning for håndtering af ”suboptimalt repons”

3. Sekundær resistens, der ikke skyldes mangelfuld adherence. Sekundært præparatvalg skal vejledes af abl-mutationsundersøgelse

Bilag C, b

RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Lægemiddelvejledning

Imatinib til voksne patienter med nydiagnosticeret CML i kronisk fase.

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Udarbejdet	Fagudvalget har udarbejdet dette bilag pr. september 2012

Dosering og administration

Dosis er 400 mg imatinib per os indtaget en gang daglig. Bør indtages på samme tidspunkt hver dag, indtages gerne med samtidig fødeindtagelse og væske, gerne svarende til min 200 ml. Grapefrugt og grapejuice, stjernefrugt og Sevilla orange frugt frarådes samtidigt med imatinib behandling.

Administrationsform: Tabletter

Findes pr. september 2012 i styrkerne 100 og 400 mg (med delekærv)

Forsigtighedsregler

Behandling med imatinib gives sammen med allopurinol indtil leukocyttal er under 50 x 10^9/l.
Forbehandling med hydroxyurea kan anbefales ved leukocyttal væsentligt over 100 x 10^9/l.

Blodprøver før behandlings start: blodbillede, nyrefunktion og elektrolytter, leverfunktion.
EKG: personer > 60 år eller anamnese for hjertesygdom mhp rytmestatus og QT. Rtg af thorax. Ved mistanke til kardiopulmonal sygdom foretages ekkokardiografi og anden relevant udredning.
Ved nyrefunktionspåvirkning < 20 ml/min skal indledes i reduceret dosis, og fortsættes efter vurdering af nyrefunktionen. Dosis bør ikke øges ved forværring i clearance.
Ved moderat nedsat leverfunktion indledes behandling med 300 mg x 1 dgl, individuel vurdering og leverfunktion monitoreres, men dosis øges til 400 mg x 1 hvis ikke yderligere leverpåvirkning
Komorbiditet og medicin liste vurderes.

Kontraindikationer

- Graviditet. Individuel håndtering af nydiagnosticeret, gravid CML patient
- Amning frarådes samtidigt med behandling

  Antikonception er ikke påkrævet hos mænd, men kvinder i behandling med imatinib bør anvende sikker prævention i fertil alder. Graviditet kan gennemføres under behandlingspause, men forudsætter individuel vurdering. Sæddeponering overvejes.

Bivirkninger

For fuldstændig redegørelse henvises til SPC for Glivec® og til pro.medicin.dk

Meget almindelige, (> 10 %) iht lmk
Træthed, vægtstigning.
Dyspepsi, kvalme, opkastning, abdominalsmerter, diarré.
Væskeretention, ødemer.
Neutropeni, trombocytopeni, anæmi.
Muskelkramper, myalgi, artralgi, knoglesmerter.
Hovedpine. Dermatitis, hududslæt. Periorbitalt ødem.

Almindelige (1 – 10 %)iht lmk
Nedsat appetit, vægttab, feber, kulderystelser.
Smagsforstyrrelser, mundtørhed, obstipation, flatulens, forhøjede leverenzymer.
Dyspnø, hoste, epistaxis. Pancytopeni.
Ledstivhed. Svimmelhed, søvnløshed, paræstesier.
Alopeci, hudkløe, øget svedtendens.
Infektioner. Øjenlågsødem, conjunctivitis, tåreflåd, synsforstyrrelser.

P-koncentrationsbestemmelse

Ikke tilgængeligt rutinemæssigt, anvendes ikke i nogen standard scenarier. Udføres KUN på speciallaboratorium (September 2012)**.**

Dosisjustering ved bivirkninger

Fagudvalget anbefaler at bivirkninger registreres og graderes systematisk, f.eks med NCI kriterier
Bemærk. Det har høj prioritet at der overholdes adherence større end 90 %, idet lavere adherence er korreleret til dårligere behandlingsresultat. Lægeinitierede behandlingspauser som konsekvens af SPC kan komme i konflikt med dette overordnede princip, og i så fald må man individualisere.

Hvis der opstår uacceptable bivirkninger til imatinib behandling, afbrydes behandlingen indtil bivirkningen er forsvundet eller minimal, afhængigt af en individuel vurdering og symptomets karakter. Behandlingen genoptages med 400 mg daglig. Ved recidiv af bivirkning anbefales igen pause, og når bivirkningen er forsvundet genoptages behandlingen i reduceret dosis (300 mg daglig) med yderligere reduktion fra 300 til 200 mg dagligt hvis bivirkningen atter recidiverer.

Hæmatologiske bivirkninger

Myelosuppresion er almindelig. Anvendelse af hæmatopoetiske vækstfaktorer kan anvendes med henblik på at tilsikre høj adherence. Der findes i SPC detaljerede regelsæt for dosismodifikation, men dosisintensitet er relateret til prognose og vil af de fleste blive prioriteret under ekstensive forsigtighedsregler

Blødning ses ved trombocytopeni derfor forsigtighed ved samtidig behandling med trombocythæmmere som alle bør pauseres ved trombocyttal < 50 x 10^9/l. Evt warfarin behandling skal kontrolleres ved hver blodprøve og pauseres efter indikation og trombocyttal, men generelt også ved trombocyttal < 50. Heparinisering kan evt overvejes ved ustabilt forløb koagulationsmæssigt.

Behandlingsforslag ved udvalgte bivirkninger

Træthed: udeluk andre årsager (mangeltilstande, DM, myxoedem, komorbiditet)
Øjenlåg / periorbitalt ødem: evt øjendråber metaoxidrin 0.25 % (magistrel) x 1-3.
Conjunctivale blødninger ufarlige, kan ikke behandles specifikt.
Ødemer: diuretika individuelt, evt kontrol kardiel status og interaktioner
Øvre gastrointestinale gener: antiemetika, protonpumpe-inhibitor
Diarre: obstiperende midler, evt opiumsdråber, hvis infektion er udelukket
Muskelkramper: kontroller elektrolytter, chlordiazepoxid, peroral calcium kan forsøges
Udslæt: pausere, genoptag i reduceret dosis, men tilstræbe standard dosis. Kortvarig systemisk glukokortikoid kur / salve, evt samtidigt med genoptaget imatinib. Overveje andre årsager til udslæt (anden behandling, hudsygdom)
Kløe: principielt tilsvarende, men evt forsøge antihistamin. Overveje andre årsager
Svedtendens: kontroller thyreoidea parametre og PCR status for Ph.

Udvalgte interaktioner med andre medikamenter

Se også interaktionsdatabasen

Midler der kan **øge plasmakoncentrationen af imatinib**: hæmmere af CYP3A4 øger eksponeringen af imatinib hvorfor det anbefales at undgå samtidig administration af CYP3A4 hæmmere (ex. ketoconazol, itraconazol, erytromycin, claritromycin m.m.)

Midler der **mindsker plasmakoncentrationen af imatinib**: induktorer af CYP3A4 øger metabolismen af imatinib og reducerer plasmakoncentrationen. Samtidig brug af CYP3A4 induktorer bør undgås (ex. dexamethazon, phenytoin, carbamazepin, phenobarbital og naturlægemidler som perikon m.fl.). Studier har ikke vist væsentlig reduceret plasmakoncentration af imatinib ved samtidig indtagelse af protonpumpe hæmmere (omeprazol).

Samtidig behandling med imatinib øger eksponering af simvastatin betydelig, formentligt grundet en hæmning af CYP3A4-medieret metabolisme af simvastatin. Dosisreduktion af simvastatin f.eks. fra 40 til 20 mg dagligt under monitorering af kolesterolprofil foreslås. Alternativt anvendelse af pravastatin eller rosuvastatin, der har en anden metabolisme.

Monitorering af effekt

1. Det er vigtigt at indskærpe betydningen af regelmæssig medicinindtagelse
2. Initialt ses patienten ambulant ca. dag 14, 28, 56 og 84 med henblik på kontrol af miltstørrelse, hæmatologiske blodprøver, lever og nyrefunktion samt til imødegåelse af bivirkninger

3. Knoglemarvsundersøgelse med cytogenetiske undersøgelse foretages med 3 måneders interval indtil opnået komplet cytogenetisk remission. Herefter kun ved mistanke om progression
4. Blodprøve med molekylærbiologisk undersøgelse foretages hver 3. måned i de første 3 år. Herefter efter skøn med 3 – 6 måneders interval, forudsat der er opnået MR3
5. Stigning i fusionstranskript med faktor 3 eller mere, som ikke tvangfrit kan forklares ved svigtende adherence, motiverer udredning for sekundær resistens

Behandlingsskift

1. Intolerance: Non-hæmatologiske grad 3 bivirkninger, gentagne grad 2 bivirkninger trods energisk symptomatisk behandling, multiple grad 1 bivirkninger trods energisk symptombehanding

2. Primære resistens, vurderet efter ELN rekommandationer som manglende opnåelse af defineret respons til adækvat tid (”failure”). Der kan ikke udstedes generel vejledning for håndtering af ”suboptimalt repons”

3. Sekundær resistens, der ikke skyldes mangelfuld adherence. Sekundært præparatvalg skal vejledes af abl-mutationsundersøgelse

Bilag C, c

RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Lægemiddelvejledning

Nilotinib til voksne patienter med nydiagnosticeret CML i kronisk fase.

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Udarbejdet	Fagudvalget har udarbejdet dette bilag pr. september 2012

Dosering og administration

Dosis er 300 mg nilotinib per os indtaget to gang daglig med 10 – 14 timers interval. Bør indtages på samme tidspunkt hver dag, og patienten bør faste 2 timer før og én time efter medicinindtagelse.. Grapefrugt og grapejuice, stjernefrugt og Sevilla orange frugt frarådes samtidigt med nilotinib behandling.

Administrationsform: Kapsler

Findes pr. september 2012 i styrkerne 150 og 200 mg

Forsigtighedsregler

Behandling med nilotinib gives sammen med allopurinol indtil leukocyttal er under 50 x 10^9/l. Forbehandling med hydroxyurea kan anbefales ved leukocyttal væsentligt over 100 x 10^9/l.

Blodprøver før behandlings start: blodbillede, nyrefunktion og elektrolytter, leverfunktion. EKG: personer > 60 år eller anamnese for hjertesygdom mhp rytmestatus og QT. Ved mistanke til kardiopulmonal sygdom foretages ekkokardiografi og anden relevant udredning.

Ved svær nedsat leverfunktion indledes behandling med 300 mg x 1 dgl, individuel vurdering og leverfunktion monitoreres, men dosis øges til 300 mg x 2 hvis ikke yderligere leverpåvirkning.

Ved nyrefunktionspåvirkning < 20 ml/min skal indledes i reduceret dosis, og fortsættes efter vurdering af nyrefunktionen. Dosis bør ikke øges ved forværring i clearance.
Komorbiditet og medicin liste vurderes, især mht risiko for interaktion og kompliance.

Kontraindikationer, absolutte

- Graviditet. Individuel håndtering af nydiagnosticeret, gravid CML patient
- Amning frarådes samtidigt med behandling.
  Antikonception er påkrævet hos mænd og kvinder der er i behandling med dasatinib. Graviditet kan gennemføres under behandlingspause, men forudsætter individuel vurdering. Sæddeponering anbefales, hvis der foreligger ønske om familieforøgelse.
- Langt QT syndrom

Kontraindikationer, relative

- Aktuel, nylig eller hyppigt recidiverende pankreatitis
- Svært regulérbar diabetes mellitus
- Uregelmæssig levevis, medførende problemer med doseringsskema

Bivirkninger

For fuldstændig redegørelse henvises til SPC for Tasigna® og pro.medicin.dk

Organklasse	Hyppighed	Bivirkning	Alle grader %	Grad 3-4 %
Nervesystemet	Meget almindelig	Hovedpine	14	1
Mave-tarm-kanalen	Meget almindelig	Kvalme	14	<1
	Almindelig	Obstipation	9	0
	Almindelig	Diarré	8	<1
	Almindelig	Opkastning	5	0
	Almindelig	Øvre abdominalsmerter	9	<1
	Almindelig	Abdominalsmerter	6	0
	Almindelig	Dyspepsi	5	0
Hud og subkutane væv	Meget almindelig	Udslæt	32	<1
	Meget almindelig	Pruritus	16	<1
	Almindelig	Alopeci	9	0
	Almindelig	Tør hud	8	0
Knogler, led, muskler og bindevæv	Meget almindelig	Myalgi	10	<1
	Almindelig	Artralgi	7	<1
	Almindelig	Muskelkramper	8	0
	Almindelig	Ekstremitetssmerter	5	<1
Almene symptomer og reaktioner på administrationsstedet	Meget almindelig	Træthed	11	0
	Almindelig	Asteni	9	<1
	Almindelig	Perifert ødem	5	0

P-koncentrationsbestemmelse

Ikke tilgængeligt rutinemæssigt, anvendes ikke i nogen standard scenarier. Udføres kun på speciallaboratorium (SEPT 12).

Dosisjustering ved bivirkninger

Fagudvalget anbefaler at bivirkninger registreres og graderes systematisk f.eks med NCI kriterier
Bemærk. Det har høj prioritet at der overholdes adherence større end 90 %, idet lavere adherence er korreleret til dårligere behandlingsresultat. Lægeinitierede behandlingspauser som konsekvens af SPC kan komme i konflikt med dette overordnede princip, og i så fald må man individualisere.
Hvis der opstår uacceptable bivirkninger til nilotinib behandling, afbrydes behandlingen indtil bivirkningen er forsvundet eller minimal, afhængigt af en individuel vurdering og symptomets

karakter. Behandlingen genoptages med 300 mg x 2 daglig. Ved recidiv af bivirkning anbefales igen pause, og når bivirkningen er forsvundet genoptages behandlingen i reduceret dosis (eks 200 mg x 2 daglig).

Hæmatologiske bivirkninger

Myelosuppresion er almindelig. Anvendelse af hæmatopoetiske vækstfaktorer kan anvendes med henblik på at tilsikre høj adherence. Der findes i SPC detaljerede regelsæt for dosismodifikation, men dosisintensitet er relateret til prognose og vil af de fleste blive prioriteret under ekstensive forsigtighedsregler

Blødning ses ved trombocytopeni. Derfor udvises forsigtighed ved samtidig behandling med trombocythæmmere som alle bør pauseres ved trombocyttal < 50 x 10^9/l. Evt warfarin behandling skal kontrolleres ved hver blodprøve og pauseres efter indikation og trombocyttal, men generelt også ved trombocyttal < 50. Heparinisering kan evt overvejes ved ustabilt forløb koagulationsmæssigt.

Behandlingsforslag ved udvalgte bivirkninger

Træthed: udeluk andre årsager (mangeltilstande, DM, myxoedem, komorbiditet)
Øjenlåg / periorbitalt ødem: evt øjendråber metaoxidrin 0.25 % (magistrel) x 1-3.
Conjunctivale blødninger ufarlige, kan ikke behandles specifikt.
Ødemer: diuretika individuelt, evt kontrol kardiel status og interaktioner
Øvre gastrointestinale gener: antiemetika, protonpumpe-inhibitor
Diarre: obstiperende midler, evt opiumsdråber, hvis infektion er udelukket
Muskelkramper: kontroller elektrolytter, chlordiazepoxid, peroral calcium kan forsøges
Udslæt: pausere, genoptag i reduceret dosis, men tilstræbe standard dosis. Kortvarig systemisk glukokortikoid kur / salve, evt samtidigt med genoptaget nilotinib. Overveje andre årsager til udslæt (anden behandling, hudsygdom)
Kløe: principielt tilsvarende, men evt forsøge antihistamin. Overveje andre årsager
Svedtendens: kontroller thyreoidea parametre og PCR status for Ph.

Udvalgte interaktioner med andre medikamenter

Se også interaktionsdatabasen

Midler der kan **øge plasmakoncentrationen af nilotinib**: hæmmere af CYP3A4 øger eksponeringen af nilotinib hvorfor det anbefales at undgå samtidig administration af CYP3A4 hæmmere (ex. ketoconazol, itraconazol, erytromycin, claritromycin m.m.)

Midler der **mindsker plasmakoncentrationen af nilotinib**: induktorer af CYP3A4 øger metabolismen af nilotinib og reducerer plasmakoncentrationen. Samtidig brug af CYP3A4 induktorer bør undgås (ex. dexamethazon, phenytoin, carbamazepin, phenobarbital og naturlægemidler som perikon m.fl.). Studier har ikke vist væsentlig reduceret plasmakoncentration af nilotinib ved samtidig indtagelse af protonpumpe hæmmere (omeprazol).

Samtidig behandling med nilotinib øger eksponering af simvastatin betydelig, formentligt grundet en hæmning af CYP3A4-medieret metabolisme af simvastatin. Dosisreduktion af

simvastatin f.eks. fra 40 til 20 mg dagligt under monitorering af kolesterolprofil foreslås. Alternativt anvendelse af pravastatin eller rosuvastatin, der har en anden metabolisme.

Monitorering af effekt

1. Det er vigtigt at indskærpe betydningen af regelmæssig medicinindtagelse
2. Initialt ses patienten ambulant ca. dag 14, 28, 56 og 84 med henblik på kontrol af miltstørrelse, hæmatologiske blodprøver, lever og nyrefunktion samt til imødegåelse af bivirkninger
3. Knoglemarvsundersøgelse med cytogenetiske undersøgelse foretages med 3 måneders interval indtil opnået komplet cytogenetisk remission. Herefter kun ved mistanke om progression
4. Blodprøve med molekylærbiologisk undersøgelse foretages hver 3. måned i de første 3 år. Herefter efter skøn med 3 – 6 måneders interval, forudsat der er opnået MR3
5. Stigning i fusionstranskript med faktor 3 eller mere, som ikke tvangfrit kan forklares ved svigtende adherence, motiverer udredning for sekundær resistens

Behandlingsskift

1. Intolerance: Non-hæmatologiske grad 3 bivirkninger, gentagne grad 2 bivirkninger trods energisk symptomatisk behandling, multiple grad 1 bivirkninger trods energisk symptombehanding

2. Primære resistens, vurderet efter ELN rekommandationer som manglende opnåelse af defineret respons til adækvat tid (”failure”). Der kan ikke udstedes generel vejledning for håndtering af ”suboptimalt repons”

3. Sekundær resistens, der ikke skyldes mangelfuld adherence. Sekundært præparatvalg skal vejledes af abl-mutationsundersøgelse

Bilag D

RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Bruttoreferenceliste

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Udarbejdet	Fagudvalget har udarbejdet dette bilag pr. september 2012

1. Blood. 2012 May 10;119(19):4524-6. Epub 2012 Mar 19.

EUTOS score is not predictive for survival and outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors: a single institution experience.

Jabbour E, Cortes J, Nazha A, O'Brien S, Quintas-Cardama A, Pierce S, Garcia-Manero G, Kantarjian H.

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To validate the recently reported European Treatment and Outcomes Study (EUTOS) score, we applied it to 465 patients with early chronic phase chronic myeloid leukemia treated with standard-dose imatinib (n=71), high-dose imatinib (n=208),
or second-generation tyrosine kinase inhibitors (n=186), and assessed its ability to predict event-free survival (EFS), transformation-free survival (TFS), and overall survival (OS). The median follow-up was 69 months. The overall complete
cytogenetic response and major molecular response rates were 92% and 85%, respectively. The 3-year EFS, TFS, and OS rates were 86%, 95%, and 97%, respectively. Of the 465 patients, 427 (92%) were in low EUTOS score category. There was no difference in the major molecular response, TFS, EFS, and OS rates between patients with low and high EUTOS score, overall and within specific therapies. In conclusion, 8% of patients with chronic phase chronic myeloid leukemia treated at our institution are in the high EUTOS score; in this population, the EUTOS score was not predictive for outcome.

PMCID: PMC3362365 [Available on 2013/5/10]
PMID: 22431574 [PubMed - indexed for MEDLINE]

2. Blood. 2012 Apr 12;119(15):3403-12. Epub 2012 Feb 27.

Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure.

Khoury HJ, Cortes JE, Kantarjian HM, Gambacorti-Passerini C, Baccarani M, Kim DW, Zaritskey A, Countouriotis A, Besson N, Leip E, Kelly V, Brümmendorf TH.

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Bosutinib, a dual Src/Abl tyrosine kinase inhibitor (TKI), has shown potent activity against chronic myeloid leukemia (CML). This phase 1/2 study evaluated the efficacy and safety of once-daily bosutinib 500 mg in leukemia patients after resistance/intolerance to imatinib. The current analysis included 118 patients with chronic-phase CML who had been pretreated with imatinib followed by dasatinib and/or nilotinib, with a median follow-up of 28.5 months. In this subpopulation, major cytogenetic response was attained by 32% of patients; complete cytogenetic response was attained by 24%, including in one of 3 patients treated with 3 prior TKIs. Complete hematologic response was achieved/maintained in 73% of patients. On-treatment transformation to accelerated/blast phase occurred in 5 patients. At 2 years, Kaplan-Meier-estimated progression-free

survival was 73% and estimated overall survival was 83%. Responses were seen across Bcr-Abl mutations, including those associated with dasatinib and nilotinib resistance, except T315I. Bosutinib had an acceptable safety profile; treatment-emergent adverse events were primarily manageable grade ½ gastrointestinal events and rash. Grade 3/4 nonhematologic adverse events (> 2%of patients) included diarrhea (8%) and rash (4%). Bosutinib may offer a new treatment option for patients with chronic-phase CML after treatment with multiple TKIs. This trial was registered at www.clinicaltrials.gov as NCT00261846.

PMID: 22371878 [PubMed - indexed for MEDLINE]

3. Blood. 2012 Feb 2;119(5):1123-9. Epub 2011 Dec 9.

Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION).

Kantarjian HM, Shah NP, Cortes JE, Baccarani M, Agarwal MB, Undurraga MS, Wang J, Ipiña JJ, Kim DW, Ogura M, Pavlovsky C, Junghanss C, Milone JH, Nicolini FE, Robak T, Van Droogenbroeck J, Vellenga E, Bradley-Garelik MB, Zhu C, Hochhaus A.

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Dasatinib is a highly potent BCR-ABL inhibitor with established efficacy and safety in imatinib-resistant/-intolerant patients with chronic myeloid leukemia (CML). In the phase 3 DASISION trial, patients with newly diagnosed chronic-phase (CP) CML were randomized to receive dasatinib 100 mg (n = 259) or imatinib 400 mg (n = 260) once daily. Primary data showed superior efficacy for dasatinib compared with imatinib after 12 months, including significantly higher rates of complete cytogenetic response (CCyR), confirmed CCyR (primary end point), and major molecular response (MMR). Here, 24-month data are presented. Cumulative response rates by 24 months in dasatinib and imatinib arms were: CCyR in 86% versus 82%, MMR in 64% versus 46%, and BCR-ABL reduction to ≤ 0.0032% (4.5-log reduction) in 17% versus 8%. Transformation to accelerated-/ blast-phase CML on study occurred in 2.3% with dasatinib versus 5.0% with imatinib. BCR-ABL mutations, assessed after discontinuation, were detected in 10 patients in each arm. In safety analyses, fluid retention, superficial edema, myalgia, vomiting, and rash were less frequent with dasatinib compared with imatinib, whereas pleural effusion and grade 3/4 thrombocytopenia were more frequent with dasatinib. Overall, dasatinib continues to show faster and deeper responses
compared with imatinib, supporting first-line use of dasatinib in patients with newly diagnosed CML-CP. This study was registered at ClinicalTrials.gov: NCT00481247.

PMID: 22160483 [PubMed - indexed for MEDLINE]

4. Leukemia. 2012 Jun;26(6):1189-94. doi: 10.1038/leu.2011.323. Epub 2011 Nov 11.

Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results.

le Coutre PD, Giles FJ, Hochhaus A, Apperley JF, Ossenkoppele GJ, Blakesley R, Shou Y, Gallagher NJ, Baccarani M, Cortes J, Kantarjian HM.

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Nilotinib (Tasigna) is a potent and selective BCR-ABL inhibitor approved for use in patients with newly diagnosed chronic myeloid leukemia (CML) in chronic phase (CML-CP) and in patients with CML-CP and accelerated phase (CML-AP) who are resistant to or intolerant of imatinib. Patients with CML-AP (N = 137) with at least 24 months of follow-up or who discontinued early were evaluated to determine the efficacy and tolerability of nilotinib. The majority (55%) of patients achieved a confirmed hematologic response, and 31% attained a confirmed complete hematologic response on nilotinib treatment. Overall, 32% of patients
achieved major cytogenetic responses (MCyR), with most being complete cytogenetic responses. Responses were durable, with 66% of patients maintaining MCyR at 24 months. The estimated overall and progression-free survival rates at 24 months
were 70% and 33%, respectively. Grade 3/4 neutropenia and thrombocytopenia were each observed in 42% of patients. Non-hematologic adverse events were mostly mild to moderate; the safety profile of nilotinib has not changed with longer follow-up. In all, 20 (15%) patients remained on study at data cutoff. In summary, nilotinib has a manageable safety profile, and can provide favorable long-term outcomes in the pretreated CML-AP patient population for whom treatment options are limited.

PMID: 22076466 [PubMed - indexed for MEDLINE]

5. J Clin Oncol. 2011 Nov 10;29(32):4260-5. Epub 2011 Oct 11.

Front-line therapy with second-generation tyrosine kinase inhibitors in patients with early chronic phase chronic myeloid leukemia: what is the optimal response?

Jabbour E, Kantarjian HM, O'Brien S, Shan J, Quintás-Cardama A, Garcia-Manero G, Rios MB, Cortes JE.

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PURPOSE: The response definitions proposed by the European LeukemiaNet (ELN) are defined on the basis of imatinib front-line therapy. It is unknown whether these definitions apply to patients treated with second-generation tyrosine kinase inhibitors (TKIs).
PATIENTS AND METHODS: One hundred sixty-seven patients with newly diagnosed chronic myelogenous leukemia (CML) in chronic phase were treated with second-generation TKIs in phase II trials (nilotinib, 81; dasatinib, 86). Median follow-up was 33 months. Event-free survival (EFS) was measured from the start of treatment to the date of loss of complete hematologic response, loss of complete or major cytogenetic response, discontinuation of therapy for toxicity or lack of efficacy, progression to accelerated or blastic phases, or death at any time.
RESULTS: Overall, 155 patients (93%) achieved complete cytogenetic response (CCyR), including 146 (87%) with major molecular response (MMR; complete in 46 patients [28%]). According to the ELN definitions, the rates of suboptimal
response were 0%, 2%, 1%, and 12% at 3, 6, 12, and 18 months of therapy, respectively. There was no difference in EFS and CCyR duration between patients who achieved CCyR with and without MMR across all the landmark times of 3, 6, 12,
and 18 months.
CONCLUSION: The use of second-generation TKIs as initial therapy in CML induces high rates of CCyR at early time points. The ELN definitions of response proposed for imatinib therapy are not applicable in this setting. We propose that achievement of CCyR and partial cytogenetic response at 3 months should be considered optimal and suboptimal responses, respectively. The achievement of MMR offered no advantage over CCyR in defining long-term outcome in patients with newly diagnosed CML treated with second-generation TKIs.

PMCID: PMC3221527 [Available on 2012/11/10]
PMID: 21990394 [PubMed - indexed for MEDLINE]

6. Int J Hematol. 2011 Oct;94(4):361-71. Epub 2011 Sep 8.

Long-term pattern of pleural effusion from chronic myeloid leukemia patients in second-line dasatinib therapy.

Kim D, Goh HG, Kim SH, Cho BS, Kim DW.

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Dasatinib is a potent second-generation tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukemia after imatinib failure. However, some patients treated with dasatinib experience pleural effusions (PEs). The determinants of pleural effusion in long-term dasatinib treatment (median 35 months, range 1-55) were investigated in single-center data of 65 patients
enrolled in global phase 2 and phase 3 trials. Of the 65 patients, 35 (54%) developed dasatinib-induced pleural effusion (a median onset time, 20 months; range 0.2-54). The first pleural effusion developed in 15 (43%) patients within
12 months of dasatinib therapy. Disease phase (P = 0.02), dose schedule (P = 0.002) and actual daily mean dose (P = 0.0002) were significantly associated with an increased risk of pleural effusion. Twice-daily administration of dasatinib resulted in significantly more patients developing pleural effusions compared with the once-daily dosing schedule, particularly in advanced disease.
In addition, a strong correlation was found between actual daily mean dose and time to onset of pleural effusions in patients treated with a daily mean dose >100 mg/day of dasatinib (P = 0.01). These data emphasize the need for dasatinib dose and schedule optimization and long-term monitoring of dasatinib-treated patients to prevent the negative clinical implications of pleural effusion.

PMID: 21901399 [PubMed - indexed for MEDLINE]

7. Haematologica. 2011 Dec;96(12):1779-82. Epub 2011 Aug 22.

Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed.

Ibrahim AR, Clark RE, Holyoake TL, Byrne J, Shepherd P, Apperley JF, Milojkovic, D, Szydlo R, Goldman J, Marin D.

Department of Haematology, Imperial College London, London, UK.

Comment in
Haematologica. 2012 May;97(5):e14-5.

BACKGROUND: It has not been clearly established whether second-generation tyrosine kinase inhibitors actually improve the survival of patients with chronic myeloid leukemia in chronic phase who are given nilotinib or dasatinib therapy
after treatment failure with imatinib.
DESIGN AND METHODS: To address this issue we compared the survival of 104 patients in whom first-line therapy with imatinib failed and who were then treated with second-generation tyrosine kinase inhibitors with the outcome of 246
patients in whom interferon-α therapy failed and who did not receive tyrosine kinase inhibitor therapy.
RESULTS: Patients treated with second-generation tyrosine kinase inhibitors had longer overall survival than the interferon controls (adjusted relative risk= 0.28, P=0.0001). However this survival advantage was limited to the 64.4% of patients in whom imatinib failed but who achieved complete cytogenetic response with the subsequent tyrosine kinase inhibitor (adjusted relative risk =0.05, P=0.003), whereas the 35.6% of patients who failed to achieve complete cytogenetic response on the second or third inhibitor had similar overall survival to that of the controls (adjusted relative risk=0.76, P=0.65).
CONCLUSIONS: Patients in whom imatinib treatment fails who receive sequential therapy with second-generation tyrosine kinase inhibitors have an enormous advantage in survival over controls (palliative therapy); this advantage is, however, limited to the majority of the patients who achieve a complete cytogenetic response.

PMCID: PMC3232259
PMID: 21859733 [PubMed - indexed for MEDLINE]

8. Lancet Oncol. 2011 Sep;12(9):841-51. Epub 2011 Aug 17.

Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial.

Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L, Goh YT, Rosti G, Nakamae H, Gallagher NJ, Hoenekopp A, Blakesley RE, Larson RA, Hughes TP.

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Erratum in
Lancet Oncol. 2011 Oct;12(11):989.

Comment in
Lancet Oncol. 2011 Sep;12(9):826-7.

BACKGROUND: Nilotinib has shown greater efficacy than imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia (CML) in chronic phase after a minimum follow-up of 12 months. We present data from the
Evaluating Nilotinib Efficacy and Safety in clinical Trials-newly diagnosed patients (ENESTnd) study after a minimum follow-up of 24 months.
METHODS: ENESTnd was a phase 3, multicentre, open-label, randomised study. Adult patients were eligible if they had been diagnosed with chronic phase,Philadelphia chromosome-positive CML within the previous 6 months. Patients were randomly assigned (1:1:1) to receive nilotinib 300 mg twice a day, nilotinib 400 mg twice a day, or imatinib 400 mg once a day, all administered orally, by use of a computer-generated randomisation schedule, using permuted blocks, and stratified according to Sokal score. Efficacy results are reported for the intention-to-treat population. The primary endpoint was major molecular response at 12 months, defined as BCR-ABL transcript levels on the

International Scale (BCR-ABL(IS)) of 0·1% or less by real-time quantitative PCR in peripheral blood. This study is registered with ClinicalTrials.gov, number NCT00471497.
FINDINGS: 282 patients were randomly assigned to receive nilotinib 300 mg twice daily, 281 to receive nilotinib 400 mg twice daily, and 283 to receive imatinib. By 24 months, significantly more patients had a major molecular response with nilotinib than with imatinib (201 [71%] with nilotinib 300 mg twice daily, 187 [67%] with nilotinib 400 mg twice daily, and 124 [44%] with imatinib; p<0·0001 for both comparisons). Significantly more patients in the nilotinib groups achieved a complete molecular response (defined as a reduction of BCR-ABL(IS) levels to ≤0·0032%) at any time than did those in the imatinib group (74 [26%] with nilotinib 300 mg twice daily, 59 [21%] with nilotinib 400 mg twice daily, and 29 [10%] with imatinib; p<0·0001 for nilotinib 300 mg twice daily vs imatinib, p=0·0004 for nilotinib 400 mg twice daily vs imatinib). There were fewer progressions to accelerated or blast phase on treatment, including clonal evolution, in the nilotinib groups than in the imatinib group (two with nilotinib 300 mg twice daily, five with nilotinib 400 mg twice daily, and 17 with imatinib; p=0·0003 for nilotinib 300 mg twice daily vs imatinib, p=0·0089 for nilotinib 400 mg twice daily vs imatinib). At 24 months, survival was comparable in all
treatment groups, but fewer CML-related deaths had occurred in both the nilotinib groups than in the imatinib group (five with nilotinib 300 mg twice daily, three with nilotinib 400 mg twice daily, and ten with imatinib). Overall, the only grade 3 or 4 non-haematological adverse events that occurred in at least 2·5% of patients were headache (eight [3%] with nilotinib 300 mg twice daily, four [1%] with nilotinib 400 mg twice daily, and two [<1%] with imatinib) and rash (two [<1%], seven [3%], and five [2%], respectively). Grade 3 or 4 neutropenia was more common with imatinib than with either dose of nilotinib (33 [12%] with
nilotinib 300 mg twice daily, 30 [11%] with nilotinib 400 mg twice daily, and 59 [21%] with imatinib). Serious adverse events were reported in eight additional patients in the second year of the study (four with nilotinib 300 mg twice daily, three with nilotinib 400 mg twice daily, and one with imatinib).
INTERPRETATION: Nilotinib continues to show better efficacy than imatinib for the treatment of patients with newly diagnosed CML in chronic phase. These results support nilotinib as a first-line treatment option for patients with newly diagnosed disease.
FUNDING: Novartis.

PMID: 21856226 [PubMed - indexed for MEDLINE]

9. Blood. 2011 Oct 27;118(17):4541-6; quiz 4759. Epub 2011 Jul 29.

The achievement of an early complete cytogenetic response is a major determinant for outcome in patients with early chronic phase chronic myeloid leukemia treatedwith tyrosine kinase inhibitors.

Jabbour E, Kantarjian H, O'Brien S, Shan J, Quintas-Cardama A, Faderl S, Garcia-Manero G, Ravandi F, Rios MB, Cortes J.

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We analyzed the association between achievement of early complete cytogenetic response (CCyR) and event-free survival (EFS) and overall survival (OS) in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with imatinib 400 mg (n = 73), or imatinib 800 mg daily (n = 208), or second-generation tyrosine kinase inhibitors (n = 154). The overall CCyR rates were 87%, 91%, and 96%, respectively (P = .06); and major molecular response (MMR) rates were 77%, 87%, and 89%, respectively (P = .05). Their 3-year EFS rates were 85%, 92%, and 97% (P = .01), and OS rates were 93%, 97%, and 100% (P = .18), respectively. By landmark analysis, patients with 3-, 6-, and 12-month CCyR had significantly better outcome: 3-year EFS rates of 98%, 97%, and 98% and OS rates of 99%, 99%, and 99%, respectively, compared with 83%, 72%, and 67% and 95%, 90%,and 94%, in patients who did not achieve a CCyR. Among patients achieving CCyR at 12 months, the depth of molecular response was not associated with differences in OS or EFS. In conclusion, second tyrosine kinase inhibitors induced higher rates of CCyR and MMR than imatinib. The achievement of early CCyR remains a major determinant of chronic myeloid leukemia outcome regardless of whether MMR is achieved or not.

PMCID: PMC3291489 [Available on 2012/10/27]
PMID: 21803854 [PubMed - indexed for MEDLINE]

10. Eur J Haematol. 2011 Aug;87(2):157-68. doi: 10.1111/j.1600-0609.2011.01637.x.

Treatment of consecutive patients with chronic myeloid leukaemia in the cooperating centres from the Czech Republic and the whole of Slovakia after 2000--a report from the population-based CAMELIA Registry.

Faber E, Mužík J, Koza V, Demečková E, Voglová J, Demitrovičová L, Chudej J, Markuljak I, Cmunt E, Kozák T, Tóthová E, Jarošová M, Dušek L, Indrák K.

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BACKGROUND: Most results on the treatment of chronic myeloid leukaemia (CML) with imatinib were obtained from clinical trials that may differ from the routine
practice. We report the results of treatment of consecutive patients with CML at
ten major centres during 2000-2008.
PATIENTS AND METHODS: Data reporting was retrospective in 2000-2004 and
prospective from 2005 on. A total of 661 patients [301 women and 360 men; median age 51 (range, 15-83)] with Ph+CML were registered. The median follow-up was 46.1months (0-122.2).
RESULTS: Most patients were treated with first- (379; 57.3%) or second-line (193; 29.2%) imatinib; some of the patients underwent allogeneic hematopoietic stem cell transplantation (AHSCT) (83; 12.6%), but 6.1% were treated with other
modalities [40 patients; median age 66 (range, 32-83)]. The probability of overall survival (OS) at 5 years, according to Kaplan and Meier, was 88.9%, 77.5% and 68.7% for chronic-phase patients treated with first-line imatinib, second-line imatinib and first-line AHSCT, respectively, but only 25.2% for patients receiving other modalities. The OS was dependent on the disease phase and Sokal, Hasford and European group for blood and marrow transplantation (EBMT) risk scores (P<0.001; each). Only 46.2% of deaths in patients treated with other modalities were attributable to CML. Elderly patients over 65 years achieved
similar response rates and progression-free survival to the younger ones. Therewas a trend for inferior results of AHSCT performed after the failure of imatinib (P=0.075), probably as a result of differences in EBMT risk scores (P<0.001).
CONCLUSIONS: The ability to achieve results comparable to those of previous clinical studies in our CML cohort was influenced by centralised care. Decisions not to initiate imatinib or to delay AHSCT may have a negative impact on OS, but comorbidities may limit the treatment potential of imatinib in the elderly.

PMID: 21535160 [PubMed - indexed for MEDLINE]

11. Int J Hematol. 2011 May;93(5):624-32. Epub 2011 Apr 27.

Nilotinib as frontline therapy for patients with newly diagnosed Ph+ chronic myeloid leukemia in chronic phase: results from the Japanese subgroup of ENESTnd.

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Recent results from the phase 3 ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients) study have demonstrated superiority of nilotinib over imatinib for the treatment of newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (CML-CP). Here, we report results from the Japanese subset of patients in ENESTnd, and assesswhether results in this subpopulation are consistent with the overall study population. Seventy-nine Japanese patients with CML-CP were randomized to receive nilotinib 300 mg twice daily (BID) (n = 30), nilotinib 400 mg BID (n = 24) or imatinib 400 mg once daily (QD) (n = 25). Major molecular response rates at 12 months, the primary endpoint, were at least twice as high for nilotinib 300 mg BID (57%) and nilotinib 400 mg BID (50%) compared with imatinib 400 mg QD (24%).
No patient on nilotinib progressed, while one patient progressed on imatinib. Both drugs were generally well tolerated and discontinuations due to adverse events were comparable among treatment arms. The results in the subpopulation of Japanese patients from ENESTnd closely mirror the results of the overall population, and support the use of nilotinib at 300 mg BID in Japanese patients with newly diagnosed CML-CP.

PMID: 21523338 [PubMed - indexed for MEDLINE]

12. Blood. 2011 May 26;117(21):5600-6. Epub 2011 Apr 5.

Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib.

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Nilotinib has significant efficacy in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) and in patients with CML-CP or CML in accelerated phase (CML-AP) after imatinib failure. We investigated the occurrence of cross-intolerance to nilotinib in imatinib-intolerant patients with CML. Only 1/75 (1%) patients with nonhematologic imatinib intolerance experienced a similar grade 3/4 adverse event (AE), and 3/75 (4%) experienced a similar persistent grade 2 nonhematologic AE on nilotinib. Only 7/40 (18%) patients with hematologic imatinib intolerance discontinued nilotinib, all because of grade 3/4 thrombocytopenia. Ninety percent of imatinib-intolerant patients with CML-CP who did not have complete hematologic response (CHR) at baseline (n = 52) achieved CHR on nilotinib. Nilotinib induced a major cytogenetic response in 66% and 41% of patients with imatinib-intolerant CML-CP and CML-AP (complete cytogenetic response in 51% and 30%), respectively. Minimal cross-intolerance was confirmed in patients with imatinib-intolerant CML. The favorable tolerability of nilotinib in patients with imatinib intolerance leads to alleviation of AE-related symptoms and significant and durable responses. In addition to its established clinical benefit in patients with newly diagnosed CML and those resistant to imatinib, nilotinib is effective and well-tolerated for long-term use in patients with imatinib intolerance. This study is registered at http://www.clinicaltrials.gov as NCT00471497.

PMID: 21467546 [PubMed - indexed for MEDLINE]

13. Leuk Res. 2011 Sep;35(9):1184-7. Epub 2011 Feb 12.

Evaluation of tolerability and efficacy of imatinib mesylate in elderly patients with chronic phase CML: ELDERGLI study.

Sánchez-Guijo FM, Durán S, Galende J, Boqué C, Nieto JB, Balanzat J, Gracia A, García I, Avellaneda-Molina C, Moreno MV, Luño-Fernandez E, Hermosilla M, Sanchez-Varela JM, Dios A, López-Garrido P, Giraldo P, Bargay J, Domingo JM, Soler A, Salinas R, del Cañizo MC.

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Imatinib mesylate (IM) is the treatment of choice in patients with newly diagnosed chronic myeloid leukemia (CML), irrespectively of their age. Nevertheless, information regarding tolerability and responses in advanced-age patients, a subgroup in which co-morbidities and other factors may influence outcome, is scarce, since they were excluded from most clinical trials. In this observational study (ELDERGLI), information regarding demographics, concomitant medication, physical examination, performance status, hemogram, biochemistry, hematologic, cytogenetic and molecular responses, time to progression, adverse
events (AE) and severe adverse events (SAE) were prospectively recorded in a series of 36 elderly patients with CML, with a median age of 76.6 years. Most patients had cardiovascular co-morbidities, especially hypertension. Regarding IM toxicity, round one third of patients required treatment interruptions because of adverse events, especially hematologic toxicity (66% of cases that needed dose interruptions). When analyzing non hematologic adverse events, the most frequent ones were superficial edemas and GI symptoms. Of note, 9 of patients experienced an infection episode during the follow-up, and 4 were diagnosed during the study period of another type of cancer. Finally, cardiovascular events were reported in 7 patients, most of them with prior cardiovascular risk factors. Regarding responses, after 12 months of imatinib therapy, the rate of complete hematologic
response (CHR), complete cytogenetic response (CCyR) and major molecular response (MMolR) were 89%, 72% and 55% respectively. In summary, IM display, in advanced-age patients with chronic phase CML, an efficacy and safety profile comparable to younger patients.

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14. N Engl J Med. 2010 Dec 23;363(26):2511-21.

Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia.

Preudhomme C, Guilhot J, Nicolini FE, Guerci-Bresler A, Rigal-Huguet F, Maloisel F, Coiteux V, Gardembas M, Berthou C, Vekhoff A, Rea D, Jourdan E, Allard C, Delmer A, Rousselot P, Legros L, Berger M, Corm S, Etienne G, Roche-

Lestienne C, Eclache V, Mahon FX, Guilhot F; SPIRIT Investigators; France Intergroupe des Leucémies Myéloïdes Chroniques (Fi-LMC).

Collaborators: Roy L, Fleck E, Saulnier PJ, Marit G, Bouabdallah K, Leguay T, Schmitt A, Giovanelli HB, Kiladjian JJ, Facon T, Jouet JP, Noel MP, Ifrah N, Dib M, François S, Ame S, Lioure B, Fohrer C, Attal M, Laurent G, Recher C, Nouvel C,
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Maisonneuve H, Chatellier T, Priou F, Tiab M, Bonnevie F, Pignon JM, Zerazhi H, Lepeu G, Boulat O, Azzedine A, Slama B, Turlure P, Bordessoule D, Jaccard A, Remenieras L, Touati M, Moreau S, Chaury MP, Girault S, Ojeda-Uribe M, Eisenmann JC, Arkam Y, Drenou B, Blanc M, Besson C, Raphael M, Tertian G, Courby S, Bulabois CE, Gressin R, Richard B, Lavabre bertrand T, Castaigne S, Taksin AL, Fahrat H, Sohn C, Fezoui H, de Jaureguiberry JP, Gisserot O, Jardel H, Godmer P, Dutel JL, Ghomari K, Charbonnier A, Blaise D, Bouabdallah R, Vey N, Aurran-Schleinitz T, Prebet T, Vernant JP, Tona A, Choufi B, Pollet B, Reman O, Leporrier M, Macro M, Cheze S, Launay V, Jonhson-ansah H, Audhuy B, Himberlin C, Kolb B, Thyss A, Peyrade F, Plantier I, Fawaz A, Rossi JF, Quittet P, Fegueux N, Cellabos P, Navarro R, Autrand C, Morel P, Stalnikiewicz L, Dupriez B, Desablens B, Royer B, Damaj GL, Garidi R, Rodon P, Boulet JM, Berger M, Tournilhac O, Chaleteix C, DeRenzis B, Bay O, Hermet E, Aljassem-Abdelkader L, Maigre M, Etienne G, Reiffers J, Eghbali H, Joly B, Devidas A, Bouledroua S, Petitdidier C, Salanoubat C, Fouillard L, Benramdane R, Gonzales H, Vanhaeke D, Guyotat D, Mounier C, Jaubert J, Levaltier X, Giraudeau B, Salles G, Solal-Celigny P.

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BACKGROUND: Imatinib (400 mg daily) is considered the best initial therapy for patients with newly diagnosed chronic myeloid leukemia (CML) in the chronic phase. However, only a minority of patients treated with imatinib have a complete molecular remission.
METHODS: We randomly assigned 636 patients with untreated chronic-phase CML to receive imatinib alone at a dose of 400 mg daily, imatinib (400 mg daily) plus cytarabine (20 mg per square meter of body-surface area per day on days 15 through 28 of each 28-day cycle) or pegylated interferon (peginterferon) alfa-2a (90 μg weekly), or imatinib alone at a dose of 600 mg daily. Molecular and cytogenetic responses, time to treatment failure, overall and event-free survival, and adverse events were assessed. An analysis of molecular response at 12 months was planned. A superior molecular response was defined as a decrease in the ratio of transcripts of the tyrosine kinase gene BCR-ABL to transcripts of ABL of 0.01% or less, corresponding to a reduction of 4 log(10) units or more from the baseline level, as assessed by means of a real-time quantitativepolymerase-chain-reaction assay.
RESULTS: At 12 months, the rates of cytogenetic response were similar among the four groups. The rate of a superior molecular response was significantly higher among patients receiving imatinib and peginterferon alfa-2a (30%) than among patients receiving 400 mg of imatinib alone (14%) (P=0.001). The rate was significantly higher among patients treated for more than 12 months than among those treated for 12 months or less. Gastrointestinal events were more frequent among patients receiving cytarabine, whereas rash and depression were more frequent among patients receiving peginterferon alfa-2a.
CONCLUSIONS: As compared with other treatments, the addition of peginterferon alfa-2a to imatinib therapy resulted in significantly higher rates of molecular response in patients with chronic-phase CML. (Funded by the French Ministry of
Health and others; ClinicalTrials.gov number, NCT00219739.).

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15. Leuk Res. 2011 May;35(5):585-90. Epub 2010 Dec 10.

15. Leuk Res. 2011 May;35(5):585-90. Epub 2010 Dec 10.

Seven-year follow-up of patients receiving imatinib for the treatment of newly diagnosed chronic myelogenous leukemia by the TARGET system.

Tauchi T, Kizaki M, Okamoto S, Tanaka H, Tanimoto M, Inokuchi K, Murayama T, Saburi Y, Hino M, Tsudo M, Shimomura T, Isobe Y, Oshimi K, Dan K, Ohyashiki K, Ikeda Y; TARGET Investigators.

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Comment in
Leuk Res. 2011 May;35(5):575-6.

The TARGET system is an online database that can be easily accessed by physicians. The registration of one's own chronic myeloid leukemia (CML) patients in the TARGET system makes it possible to share experiences among physicians, and, thus, may facilitate appropriate treatment for patients. Patients were registered in the TARGET system from October 2003 to March 2010 in Japan. A total of 1236 patients from 176 hospitals were registered in

Japan. We analyzed data from 639 CML chronic phase patients not receiving prior therapy registered in this system. After 90 months follow-up, high survival rates were demonstrated for imatinib-treated newly diagnosed CML patients, with event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) rates of 79.1, 94.8, and 95.1%, respectively. A landmark analysis of 296 patients who showed a
complete cytogenetic response (CCyR) at 12 months after the initiation of imatinib treatment revealed that, at 90 months, 99% of patients (95% CI, 98-100) had not progressed to accelerated phase (AP) or blastic crisis (BC). The patients showing a CCyR and a reduction of at least 3log levels of BCR-ABL transcripts after 18 months of treatment had an estimated survival rate without CML progression of 100% at 84 months. The probability of achieving undetectable BCR-ABL in patients by 72 months with an major molecular response (MMR) at 12 months was 86.5%, compared with 64.7% for those without an MMR ($p < 0.0001$).
There were no new safety issues. In summary, based on this 7-year TARGET analysis, imatinib showed a continual clinical benefit as first-line therapy for newly diagnosed CML. The TARGET system may represent a more practical and general feature compared with the IRIS study.

PMID: 21145591 [PubMed - indexed for MEDLINE]

16. Blood. 2011 Jan 27;117(4):1141-5. Epub 2010 Nov 22.

Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results.

Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, Gattermann N, Ottmann OG, Hochhaus A, Radich JP, Saglio G, Hughes TP, Martinelli G, Kim DW, Shou Y, Gallagher NJ, Blakesley R, Baccarani M, Cortes J, le Coutre PD.

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Nilotinib is a potent selective inhibitor of the BCR-ABL tyrosine kinase approved for use in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP), and in CML-CP and CML-accelerated phase after imatinib failure.
Nilotinib (400 mg twice daily) was approved on the basis of the initial results of this phase 2 open-label study. The primary study endpoint was the proportion of patients achieving major cytogenetic response (CyR). All patients were followed for ≥ 24 months or discontinued early. Of 321 patients, 124 (39%) continue on nilotinib treatment. Overall, 59% of patients achieved major CyR;
this was complete CyR (CCyR) in 44%. Of patients achieving CCyR, 56% achieved major molecular response. CyRs were durable, with 84% of patients who achieved CCyR maintaining response at 24 months. The overall survival at 24 months was
87%. Adverse events were mostly mild to moderate, generally transient, and easily managed. This study indicates that nilotinib is effective, with a manageable safety profile, and can provide favorable long-term benefits for patients with CML-CP after imatinib failure.

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17. Blood. 2011 Feb 10;117(6):1822-7. Epub 2010 Oct 28.

Predictive factors for outcome and response in patients treated with second-generation tyrosine kinase inhibitors for chronic myeloid leukemia in chronic phase after imatinib failure.

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Comment in
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We assessed the predictive factors for outcome and response in 123 patients with chronic myeloid leukemia in chronic phase treated with second-generation tyrosine kinase inhibitors (TKIs) after imatinib failure. Better event-free survival rates
with second-generation TKI therapy were associated with a previous cytogenetic response to imatinib ($P < .001$) and a performance status of 0 ($P = .001$).

Patients with 0, 1, or 2 adverse factors had 2-year event-free survival rates of 78%, 49%, and 20% (P < .001), respectively; 2-year overall survival rates of 95%, 85%, and 40%, (P = .002), respectively; and a 12-month probability of achieving a
major cytogenetic response of 64%, 36%, and 20% (P = .007), respectively. In conclusion, patients with poor performance status and no previous cytogenetic response to imatinib therapy have a low likelihood of responding to second-generation TKI with poor event-free survival and therefore should be offered additional treatment options. This scoring system could serve to advise patients of their prognosis and treatment options, as well as to evaluate the benefit of newer alternate options.

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18. Cancer. 2011 Feb 1;117(3):572-80. doi: 10.1002/cncr.25438. Epub 2010 Sep 30.

Immune modulation of minimal residual disease in early chronic phase chronic myelogenous leukemia: a randomized trial of frontline high-dose imatinib mesylate with or without pegylated interferon alpha-2b and granulocyte-macrophage
colony-stimulating factor.

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BACKGROUND: Most patients with chronic myelogenous leukemia (CML) harbor residual disease, as evidenced by molecular techniques even after treatment with high-dose imatinib (ie, 800 mg/d). Interferon alpha (IFN α) is efficacious in CML likely
due to its immunomodulatory properties, and is synergistic in vitro with imatinib and granulocyte macrophage-colony stimulating factor (GM-CSF).
METHODS: A study was undertaken to determine whether adding pegylated (PEG) IFN α-2b and GM-CSF to high-dose imatinib may improve the complete molecular response rate in patients with CML in chronic phase. Ninety-four patients were treated
with imatinib 800 mg/d for the first 6 months, then randomly assigned to continue high-dose imatinib alone (n = 49) or in combination with PEG IFN α-2b 0.5 μg/kg/wk and GM-CSF 125 mg/m² 3× weekly (n = 45).
RESULTS: The median follow-up for all patients was 54 months (range, 7-70 months). There were no differences in the rates of complete cytogenetic response (87% vs 90%; P = 1.0), or of major (77% vs 77%; P = 1.0) or complete (11% vs 13%;
P = 1.0) molecular response (on the international scale) at 12 months between the 2 arms, or at any time during the study. Adverse events led to PEG IFN α-2b discontinuation in all patients.
CONCLUSIONS: The addition of PEG IFN α-2b and GM-CSF to high-dose imatinib therapy does not improve significantly the cytogenetic or molecular response rates compared with high-dose imatinib alone. The high dropout rate in the PEG IFN α-2b arm may have compromised its potential immunomodulatory benefit.

PMID: 20886606 [PubMed - indexed for MEDLINE]

19. Blood. 2010 Dec 16;116(25):5497-500. Epub 2010 Sep 10.

Efficacy of tyrosine kinase inhibitors (TKIs) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy.

Ibrahim AR, Paliompeis C, Bua M, Milojkovic D, Szydlo R, Khorashad JS, Foroni L, Reid A, de Lavallade H, Rezvani K, Dazzi F, Apperley JF, Goldman JM, Marin D.

Department of Haematology, Imperial College London, London, UK.

We analyzed a cohort of 26 patients with chronic myeloid leukemia who had failed imatinib and a second tyrosine kinase inhibitor but were still in first chronic phase and identified prognostic factors for response and outcomes. The achievement of a prior cytogenetic response on imatinib or on second-line therapy were the only independent predictors for the achievement of complete cytogenetic responses on third-line therapy. Younger age and the achievement of a cytogenetic response on second line were the only independent predictors for overall survival (OS).

At 3 months, the 9 patients who had achieved a cytogenetic response had better 30-month probabilities of complete cytogenetic responses and OS than the patients who had failed to do so. Factors measurable before starting treatment with third line therapy and cytogenetic responses at 3 months can accurately
predict subsequent outcome and thus guide clinical decisions.

PMID: 20833982 [PubMed - indexed for MEDLINE]

20. Cancer. 2010 Jul 1;116(13):3152-9.

Imatinib front-line therapy is safe and effective in patients with chronic myelogenous leukemia with pre-existing liver and/or renal dysfunction.

Tong WG, Kantarjian H, O'Brien S, Faderl S, Ravandi F, Borthakur G, Shan J, Pierce S, Rios MB, Cortes J.

Department of Leukemia, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.

BACKGROUND: Imatinib 400 mg daily is the standard treatment for patients with chronic myelogenous leukemia (CML). The safety and efficacy of imatinib in CML patients with pre-existing liver and/or renal dysfunction has not been analyzed.
METHODS: The authors analyzed the outcome of 259 patients with early chronic phase CML treated with imatinib (starting dose 400 mg in 50, 800 mg in 209). Pre-existing liver and/or renal dysfunction was seen in 38 (15%) and 11 (4%)
patients, respectively.
RESULTS: Dose reductions were required in 91 (43%) of 210 patients with normal organ function, compared with 8 (73%) of 11 (P = .065) with renal dysfunction, and 19 (50%) of 38 (P = .271) with liver dysfunction. Grade 3-4 hematologic toxicities including anemia (29%, 10%, and 7% of patients with renal dysfunction, liver dysfunction, and normal organ function, respectively), neutropenia (57%, 30%, and 30%), and thrombocytopenia (43%, 30%, and 26%) were more frequent in patients with pre-existing renal dysfunction treated with high-dose imatinib. Grade 3-4 nonhematologic toxicities were observed at similar frequencies. Complete cytogenetic response rates, event-free survival, and overall survival were similar in all groups.
CONCLUSIONS: Although patients with pre-existing liver and/or renal dysfunction might have a higher rate of hematologic toxicity and require more frequent dose reductions, most patients can be adequately managed, resulting in response rates
and survival similar to those without pre-existing organ dysfunction.

PMID: 20564631 [PubMed - indexed for MEDLINE]

21. N Engl J Med. 2010 Jun 17;362(24):2260-70. Epub 2010 Jun 5.

Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.

Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, Moiraghi B, Shen Z, Mayer J, Pasquini R, Nakamae H, Huguet F, Boqué C, Chuah C, Bleickardt E, Bradley-Garelik MB, Zhu C, Szatrowski T, Shapiro D, Baccarani M.

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Comment in
N Engl J Med. 2010 Jun 17;362(24):2314-5.
N Engl J Med. 2010 Oct 21;363(17):1672-3; author reply 1673-5.
Expert Opin Pharmacother. 2011 Jan;12(1):157-63.
N Engl J Med. 2010 Oct 21;363(17):1673; author reply 1673-5.
N Engl J Med. 2010 Oct 21;363(17):1672; author reply 1673-5.
N Engl J Med. 2010 Oct 21;363(17):1673; author reply 1673-5.

BACKGROUND: Treatment with dasatinib, a highly potent BCR-ABL kinase inhibitor, has resulted in high rates of complete cytogenetic response and progression-free survival among patients with chronic myeloid leukemia (CML) in the chronic phase,
after failure of imatinib treatment. We assessed the efficacy and safety of dasatinib, as compared with imatinib, for the first-line treatment of chronic-phase CML.
METHODS: In a multinational study, 519 patients with newly diagnosed chronic-phase CML were randomly assigned to receive dasatinib at a dose of 100 mg once daily (259 patients) or imatinib at a dose of 400 mg once daily (260

patients). The primary end point was complete cytogenetic response by 12 months, confirmed on two consecutive assessments at least 28 days apart. Secondary end points, including major molecular response, were tested at a significance level of 0.0001 to adjust for multiple comparisons.
RESULTS: After a minimum follow-up of 12 months, the rate of confirmed complete cytogenetic response was higher with dasatinib than with imatinib (77% vs. 66%, P=0.007), as was the rate of complete cytogenetic response observed on at least
one assessment (83% vs. 72%, P=0.001). The rate of major molecular response was higher with dasatinib than with imatinib (46% vs. 28%, P<0.0001), and responses were achieved in a shorter time with dasatinib (P<0.0001). Progression to the
accelerated or blastic phase of CML occurred in 5 patients who were receiving dasatinib (1.9%) and in 9 patients who were receiving imatinib (3.5%). The safety profiles of the two treatments were similar.
CONCLUSIONS: Dasatinib, administered once daily, as compared with imatinib, administered once daily, induced significantly higher and faster rates of complete cytogenetic response and major molecular response. Since achieving complete cytogenetic response within 12 months has been associated with better long-term, progression-free survival, dasatinib may improve the long-term outcomes among patients with newly diagnosed chronic-phase CML. (ClinicalTrials.gov number, NCT00481247.)

PMID: 20525995 [PubMed - indexed for MEDLINE]

22. N Engl J Med. 2010 Jun 17;362(24):2251-9. Epub 2010 Jun 5.

Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia.

Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM; ENESTnd Investigators.

Collaborators: Moiraghi B, Perez M, Greil R, Valent P, Bosly A, Martiat P, Noens L, André M, Verhoef G, Conchon M, Souza C, Nonino A, Hungria V, Zanichelli MA, Colturato V, Forrest D, Lipton JH, Savoie ML, Delage R, Lalancette M, Quintero G, Gomez M, Klamova H, Faber E, Bjerrum OW, Fredriksen H, Vestergaard H, Marcher C, Kamel H, Elzawam H, Porkka K, Remes K, Reiffers J, Guilhot F, Facon T, Tulliez M,Guerci-Bresler AP, Nicolini FE, Charbonnier A, Rea D, Johnson-Ansah A, Legros L, Harousseau JL, Rigal-Huguet F, Escoffre M, Gardembas M, Guyotat D, Cahn JY, Gattermann N, Ottmann O, Niederwieser D, Stegelmann F, Schafhausen P, Brümmendorf T, Duyster J, Blumenstengel K, Scheid C, Kneba M, Kwong YL, Masszi T, Petrini M, Alimena G, Di Raimondo F, Rosti G, Rotoli B, Pane F, Pungolino E, Amadori S, Abruzzese E, Fioritoni G, Lauria F, Bosi A, Martelli M, Rambaldi A, Ferrara F, Nobile F, Gobbi M, Carella AM, Orlandi EM, Leoni P, Tiribelli M, Levis A, Imamura M, Takahashi N, Tsukamoto N, Chiba S, Nagai T, Okamoto S, Miura O, Kurokawa M, Ohnishi K, Toba K, Nakao S, Tomita A, Miyamura K, Hino M, Maeda Y, Kimura A, Kawaguchi T, Miyazaki Y, Nakaseko C, Jinnai I, Matsuda A, Matsumura I, Ishikawa J, Ohyashiki K, Okada M, Usuki K, Kobayashi Y, Ohishi K, Imai K, Miyawaki S, Kanda Y, Park SY, Kim HJ, Sohn SK, Lee KH, Jung CW, Ong TC, Gómez Almaguer D, Kassack J, Ossenkoppele GJ, Gedde-Dahl T, Hjorth-Hansen H, Jedrzejczak W, Dmoszynska A, Starzak-Dwozdz J, Holowiecki J, Kyrcz-Krzemieñ S, Kuliczkowski K, Zaritsky A, Turkina A, Pospelova T, Goh YT, Koh LP, Demitrovicova L, Mistrik M, Ruff P, Louw V, Dreosti LM, Novitzky N, Cohen G, Cervantes F, Cañizo C, de Paz R, del Castillo S, Perez Encinas M, Sanz Alonso M, Marin F, Pérez-López R, Hernandez Boluda J, Echeveste Gutierrez MA, Odriozola J, Herrera P, Steegman JL, Conde E, Lopez P, Giraldo P, Boque C, Heredia B, Font AJ, Rodriguez RF, Rodriguez MJ, Batlle J, Stenke L, Lehmann S, Wadenvik H, Simonsson B, Markevärn B, Själander A, Richter J, Bjoreman M, Eriksson KM, Chalandon Y, Shih LY, Yao M, Wang MC, Jootar S, Bunworasate U, Ulkü B, Haznedar R, Undar B, Sahin B, Marin D, Smith G, Byrne J, Holyoake T, Kalaycio M, Akard L, Heaney M, Al-Janadi A, Goldberg S, Powell B, Harker WG, Shea T, Gingrich R, Glass J, Paquette R, Siegrist C, Woodson M, Fehrenbacher L, Koh H, Flinn I, Arrowsmith E, Ervin T, Guerra M, Wallach H, Berry W, Burke J, Edenfield W, Guzley G, Davis J, Richards D, Schlossman D, Kolibaba K, Alemany C, Savin M, Robbins G, Lopez J, Goldman JM, Camm J, Schiffer CA, Sargent DJ.

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Comment in
N Engl J Med. 2010 Jun 17;362(24):2314-5.
N Engl J Med. 2010 Oct 21;363(17):1672; author reply 1673-5.
Expert Opin Pharmacother. 2011 Jan;12(1):157-63.
N Engl J Med. 2010 Oct 21;363(17):1673; author reply 1673-5.
N Engl J Med. 2010 Oct 21;363(17):1673; author reply 1673-5.
N Engl J Med. 2010 Oct 21;363(17):1672-3; author reply 1673-5.

BACKGROUND: Nilotinib has been shown to be a more potent inhibitor of BCR-ABL than imatinib. We evaluated the efficacy and safety of nilotinib, as compared with imatinib, in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (CML) in the chronic phase.
METHODS: In this phase 3, randomized, open-label, multicenter study, we assigned 846 patients with chronic-phase Philadelphia chromosome-positive CML in a 1:1:1 ratio to receive nilotinib (at a dose of either 300 mg or 400 mg twice daily) or
imatinib (at a dose of 400 mg once daily). The primary end point was the rate of major molecular response at 12 months.
RESULTS: At 12 months, the rates of major molecular response for nilotinib (44% for the 300-mg dose and 43% for the 400-mg dose) were nearly twice that forimatinib (22%) (P<0.001 for both comparisons). The rates of complete cytogenetic response by 12 months were significantly higher for nilotinib (80% for the 300-mg dose and 78% for the 400-mg dose) than for imatinib (65%) (P<0.001 for both comparisons). Patients receiving either the 300-mg dose or the 400-mg dose of nilotinib twice daily had a significant improvement in the time to progression to the accelerated phase or blast crisis, as compared with those receiving imatinib (P=0.01 and P=0.004, respectively). No patient with progression to the accelerated phase or blast crisis had a major molecular response. Gastrointestinal and fluid-retention events were more frequent among patients receiving imatinib, whereas dermatologic events and headache were more frequent in those receiving nilotinib. Discontinuations due to aminotransferase and bilirubin elevations were low in all three study groups.
CONCLUSIONS: Nilotinib at a dose of either 300 mg or 400 mg twice daily was superior to imatinib in patients with newly diagnosed chronic-phase Philadelphia chromosome-positive CML. (ClinicalTrials.gov number, NCT00471497.)

PMID: 20525993 [PubMed - indexed for MEDLINE]

23. Leukemia. 2010 Jul;24(7):1299-301. Epub 2010 Jun 3.

Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy.

Giles FJ, Abruzzese E, Rosti G, Kim DW, Bhatia R, Bosly A, Goldberg S, Kam GL, Jagasia M, Mendrek W, Fischer T, Facon T, Dünzinger U, Marin D, Mueller MC, Shou Y, Gallagher NJ, Larson RA, Mahon FX, Baccarani M, Cortes J, Kantarjian HM.

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Nilotinib is a highly selective Bcr-Abl inhibitor approved for imatinib-resistant chronic myeloid leukemia (CML). Nilotinib and dasatinib, a multi-targeted kinase inhibitor also approved for second-line therapy in CML, have different patterns of kinase selectivity, pharmacokinetics, and cell uptake and efflux properties, and thus patients may respond to one following failure of the other. An international phase II study of nilotinib was conducted in CML patients (39 chronic phase (CP), 21 accelerated phase (AP)) after failure of both imatinib and dasatinib. Median times from diagnosis of CP or AP to nilotinib therapy were 89
and 83 months, respectively. Complete hematological response and major cytogenetic response (MCyR) rates in CP were 79% and 43%, respectively. Of 17 evaluable patients with CML-AP, 5 (29%) had a confirmed hematological response and 2 (12%) a MCyR. The median time to progression has not yet been reached in CP patients. At 18 months 59% of patients were progression-free. Median overall survival for both populations has not been reached, and the estimated 18-month survival rate in CML-CP was 86% and that at 12 months for CML-AP was 80%. Nilotinib is an effective therapy in CML-CP and -AP following failure of both imatinib and dasatinib therapy.

PMCID: PMC3078756
PMID: 20520639 [PubMed - indexed for MEDLINE]

24. Neoplasma. 2010;57(4):355-9.

Dasatinib in imatinib-resistant or -intolerant CML patients: data from the clinical practice of 6 hematological centers in the Czech Republic.

Klamova H, Faber E, Zackova D, Markova M, Voglova J, Cmunt E, Novakova L, Machova-Polakova K, Moravcova J, Dvorakova D, Michalova K, Brezinova J, Oltova A, Jarosova M, Cetkovsky P, Indrak K, Mayer J.

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Dasatinib is effective second line treatment for patients with chronic myeloid leukemia (CML) resistant or intolerant to imatinib. We report here the first experiences with dasatinib therapy in 71 CML patients resistant or intolerant to imatinib from the real clinical practice of 6 hematological centers in the Czech Republic. Dose 100 mg daily and 70 mg twice daily was administered to patients with chronic phase (CP) and advanced phases (AP) CML. In chronic phase (n=46), complete hematological reponse (CHR) was achieved in 97%, major cytogenetic reponse (MCgR) in 77% and complete cytogenetic response (CCgR) in 67%. Major molecular reponse (MMR) was achieved in 19/31 patients in median of 10 months. In advanced phase (n=25), CHR was attained in 77%, MCgR in 39%, CCgR in 33% and MMR in 2/18 patients. Eleven different baseline mutations were followed up in 15 patients. Dasatinib eliminated mutations in most of the patients, but 3 patients acquired a new one. Novel mutations were detected under dasatinib therapy in 2 patients. Dasatinib was well tolerated, cytopenias were common and was managed by
dose modification. The estimated progression free survival (PFS) at 12 months was 97+/-3% in CP and 62+/-21% in AP. The median time to treatment failure was 605 days in AP while it was not reached in CP patients. Our clinical experiences,
described here, confirmed that dasatinib is associated with high response rates especially in imatinib resistant or intolerant CML patients in chronic phase.

PMID: 20429627 [PubMed - indexed for MEDLINE]

25. Haematologica. 2010 Aug;95(8):1317-24. Epub 2010 Mar 10.

Early intervention during imatinib therapy in patients with newly diagnosed chronic-phase chronic myeloid leukemia: a study of the Spanish PETHEMA group.

Cervantes F, López-Garrido P, Montero MI, Jonte F, Martínez J, Hernández-Boluda JC, Calbacho M, Sureda A, Pérez-Rus G, Nieto JB, Pérez-López C, Román-Gómez J, González M, Pereira A, Colomer D.

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BACKGROUND: Despite the favorable results of imatinib front line in chronic-phase chronic myeloid leukemia there is room for improvement.
DESIGN AND METHODS: Early intervention during imatinib therapy was undertaken in 210 adults with chronic-phase chronic myeloid leukemia less than three monthsfrom diagnosis (Sokal high risk: 16%). Patients received imatinib 400 mg/day. At
three months, dose was increased if complete hematologic response was not achieved. At six months, patients in complete cytogenetic response were kept on 400 mg and the remainder randomized to higher imatinib dose or 400 mg plus interferon-alfa. At 18 months, randomized patients were switched to a 2(nd) generation tyrosine kinase inhibitor if not in complete cytogenetic response and imatinib dose increased in non-randomized patients not in major molecular response.
RESULTS: Seventy-two percent of patients started imatinib within one month from diagnosis. Median follow-up is 50.5 (range: 1.2-78) months. At three months 4 patients did not have complete hematologic response; at six months 73.8% were in
complete cytogenetic response; among the remainder, 9 could not be randomized (toxicity or consent withdrawal), 17 were assigned to high imatinib dose, and 15 to 400 mg + interferon-alpha. The low number of randomized patients precluded
comparison between the two arms. Cumulative response at three years was: complete hematologic response 98.6%, complete cytogenetic response 90% and major molecular response 82%. On an intention-to-treat basis, complete cytogenetic response was 78.8% at 18 months. At five years, survival was 97.5%, survival free from accelerated/blastic phase 94.3%, failure free survival 82.5%, and event free survival (including permanent imatinib discontinuation) 71.5%.
CONCLUSIONS: These results indicate the benefit of early intervention during imatinib therapy (ClinicalTrials.gov Identifier: NCT00390897).

PMCID: PMC2913080
PMID: 20220063 [PubMed - indexed for MEDLINE]

26. Haematologica. 2010 Feb;95(2):232-40.

Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance,suboptimal response or intolerance to imatinib.

Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PE, Enrico A, Vela-Ojeda J, Silver RT, Khoury HJ, Müller MC, Lambert A, Matloub Y, Hochhaus A.

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BACKGROUND: Dasatinib 100 mg once daily achieves intermittent BCR-ABL kinase inhibition and is approved for chronic-phase chronic myeloid leukemia patients resistant or intolerant to imatinib. To better assess durability of response to and tolerability of dasatinib, data from a 2-year minimum follow-up for a dose-optimization study in chronic-phase chronic myeloid leukemia are reported here.
DESIGN AND METHODS: In a phase 3 study, 670 chronic-phase chronic myeloid leukemia patients with resistance, intolerance, or suboptimal response to imatinib were randomized to dasatinib 100 mg once-daily, 50 mg twice-daily, 140 mg once-daily, or 70 mg twice-daily.
RESULTS: Data from a 2-year minimum follow-up demonstrate that dasatinib 100 mg once daily achieves major cytogenetic response and complete cytogenetic response rates comparable to those in the other treatment arms, and reduces the frequency
of key side effects. Comparable 2-year progression-free survival and overall survival rates were observed (80% and 91%, respectively, for 100 mg once daily, and 75%-76% and 88%-94%, respectively, in other arms). Complete cytogenetic
responses were achieved rapidly, typically by 6 months. In patients treated with dasatinib 100 mg once daily for 6 months without complete cytogenetic response, the likelihood of achieving such a response by 2 years was 50% for patients who
had achieved a partial cytogenetic response, and only 8% or less for patients with minor, minimal, or no cytogenetic response. Less than 3% of patients suffered disease transformation to accelerated or blast phase.
CONCLUSIONS: Intermittent kinase inhibition can achieve rapid and durable responses, indistinguishable from those achieved with more continuous inhibition.

PMCID: PMC2817025
PMID: 20139391 [PubMed - indexed for MEDLINE]

27. J Clin Oncol. 2010 Jan 20;28(3):424-30. Epub 2009 Dec 14.

Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloidleukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study.

Cortes JE, Baccarani M, Guilhot F, Druker BJ, Branford S, Kim DW, Pane F, Pasquini R, Goldberg SL, Kalaycio M, Moiraghi B, Rowe JM, Tothova E, De Souza C, Rudoltz M, Yu R, Krahnke T, Kantarjian HM, Radich JP, Hughes TP.

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Erratum in
J Clin Oncol. 2010 May 1;28(13):2314.

PURPOSE: To evaluate the safety and efficacy of initial treatment with imatinib mesylate 800 mg/d (400 mg twice daily) versus 400 mg/d in patients with newly diagnosed chronic myeloid leukemia in chronic phase.
PATIENTS AND METHODS: A total of 476 patients were randomly assigned 2:1 to imatinib 800 mg (n = 319) or 400 mg (n = 157) daily. The primary end point was the major molecular response (MMR) rate at 12 months.
RESULTS: At 12 months, differences in MMR and complete cytogenetic response (CCyR) rates were not statistically significant (MMR, 46% v 40%; P = .2035; CCyR, 70% v 66%; P = .3470). However, MMR occurred faster among patients randomly
assigned to imatinib 800 mg/d, who had higher rates of MMR at 3 and 6 months compared with those in the imatinib 400-mg/d arm (P = .0035 by log-rank test). CCyR also occurred faster in the 800-mg/d arm (CCyR at 6 months, 57% v 45%; P = .0146). The most common adverse events were edema, gastrointestinal problems, and rash, and all were more common in patients in the 800-mg/d arm. Grades 3 to 4 hematologic toxicity also occurred more frequently in patients receiving imatinib
800 mg/d.
CONCLUSION: MMR rates at 1 year were similar with imatinib 800 mg/d and 400 mg/d, but MMR and CCyR occurred earlier in patients treated with 800 mg/d. Continued follow-up is needed to determine the clinical significance of earlier responses
on high-dose imatinib.

PMID: 20008622 [PubMed - indexed for MEDLINE]

28. J Clin Oncol. 2010 Jan 20;28(3):398-404. Epub 2009 Dec 14.

Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia.

Cortes JE, Jones D, O'Brien S, Jabbour E, Ravandi F, Koller C, Borthakur G, Walker B, Zhao W, Shan J, Kantarjian H.

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Comment in
J Clin Oncol. 2010 Jan 20;28(3):363-5.

PURPOSE: Dasatinib is effective therapy for chronic myeloid leukemia (CML) after imatinib failure. In this study, we investigate the efficacy of dasatinib as initial therapy for patients with CML in early chronic phase.
PATIENTS AND METHODS: Patients with newly diagnosed CML in early chronic phase were randomly assigned to receive dasatinib 100 mg once daily or 50 mg twice daily as initial therapy.
RESULTS: Among 50 patients observed for at least 3 months, 49 patients (98%) achieved a complete cytogenetic response (CCyR), and 41 patients (82%) achieved a major molecular response (MMR). Responses occurred rapidly, with 94% of patients
achieving CCyR by 6 months. There was no difference in response rate by treatment arm. The projected event-free survival rate at 24 months is 88%, and all patients are alive after a median follow-up time of 24 months. Grade >or= 3 neutropenia
and thrombocytopenia occurred in 21% and 10% of patients, respectively. Nonhematologic toxicity was usually grade 1 to 2. There was no significant difference in toxicity between the two arms, and the actual median dose at 12 months was 100 mg (range, 20 to 100 mg).
CONCLUSION: Dasatinib is an effective agent for the initial management of CML in early chronic phase, producing high rates of CCyR and MMR.

PMCID: PMC2815702
PMID: 20008620 [PubMed - indexed for MEDLINE]

29. Blood. 2010 Mar 11;115(10):1880-5. Epub 2009 Nov 18.

Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV.

Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, Kolb HJ, Ho AD, Falge C, Holler E, Schlimok G, Zander AR, Arnold R, Kanz L, Dengler R, Haferlach C, Schlegelberger B, Pfirrmann M, Müller MC, Schnittger S, Leitner A,
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Comment in
Nat Rev Clin Oncol. 2010 Jun;7(6):298.
Blood. 2010 Mar 11;115(10):1860-1.

The role of allogeneic stem cell transplantation in chronic myeloid leukemia is being reevaluated. Whereas drug treatment has been shown to be superior in first-line treatment, data on allogeneic hematopoietic stem cell transplantation (allo SCT) as second-line therapy after imatinib failure are scarce. Using an interim safety analysis of the randomized German CML Study IV designed to optimize imatinib therapy by combination, dose escalation, and transplantation, we here report on 84 patients who underwent consecutive transplantation according to predefined criteria (low European Group for Blood and Marrow transplantation [EBMT] score, imatinib failure, and advanced disease). Three-year survival after transplantation of 56 patients in chronic phase was 91% (median follow-up: 30months). Transplantation-related mortality was 8%. In a matched pair comparison
of patients who received a transplant and those who did not, survival was not different. Three-year survival after transplantation of 28 patients in advanced phase was 59%. Eighty-eight percent of patients who received a transplant achieved complete molecular remissions. We conclude that allo SCT could become the preferred second-line option after imatinib failure for suitable patients with a donor. The study is registered at the National Institutes of Health, http://clinicaltrials.gov: NCT00055874.

PMID: 19965667 [PubMed - indexed for MEDLINE]

30. Cancer. 2009 Sep 15;115(18):4136-47.

Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R).

Kantarjian H, Pasquini R, Lévy V, Jootar S, Holowiecki J, Hamerschlak N, Hughes T, Bleickardt E, Dejardin D, Cortes J, Shah NP.

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BACKGROUND: In patients with chronic-phase chronic myeloid leukemia (CP-CML), imatinib resistance is of increasing importance. Imatinib dose escalation was the main treatment option before dasatinib, which has 325-fold more potent inhibition
than imatinib against unmutated Bcr-Abl in vitro. Data with a minimum of 2 years of follow-up were available for the current study of dasatinib and high-dose imatinib in CP-CML resistant to imatinib at daily doses from 400 mg to 600 mg.
METHODS: A phase 2, open-label study was initiated of 150 patients with imatinib-resistant CP-CML who were randomized (2:1) to receive either dasatinib 70 mg twice daily (n=101) or high-dose imatinib 800 mg (400 mg twice daily; n=49).
RESULTS: At a minimum follow-up of 2 years, dasatinib demonstrated higher rates of complete hematologic response (93% vs 82%; P=.034), major cytogenetic response (MCyR) (53% vs 33%; P=.017), and complete cytogenetic response (44% vs 18%;
P=.0025). At 18 months, the MCyR was maintained in 90% of patients on the dasatinib arm and in 74% of patients on the high-dose imatinib arm. Major molecular response rates also were more frequent with dasatinib than with high-dose imatinib (29% vs 12%; P=.028). The estimated progression-free survival also favored dasatinib (unstratified log-rank test; P=.0012).
CONCLUSIONS: After 2 years of follow-up, dasatinib demonstrated durable responses and improved response and progression-free survival rates relative to high-dose imatinib.

PMID: 19536906 [PubMed - indexed for MEDLINE]

31. Leukemia. 2009 Jun;23(6):1054-61. Epub 2009 Mar 12.

Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia.

Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L, Goldman JM, Müller MC, Radich JP, Rudoltz M, Mone M, Gathmann I, Hughes TP, Larson RA; IRIS Investigators.

Collaborators: Hughes T, Taylor K, Durant S, Schwarer A, Joske D, Seymour J, Grigg A, Ma D, Arthur C, Bradstock K, Joshua D, Agis H, Verhoef G, Louwagie A, Martiat P, Bosly A, Shepherd J, Shistok C, Lipton J, Forrest D, Walker I, Roy DC, Rubinger M, Bence-Bruckler I, Stewart D, Kovacs M, Turner AR, Nielsen J, Birgens H, Bjerrum O, Rousselot P, Reiffers J, Facon T, Harousseau JL, Tulliez M, Guerci A, Blaise D, Maloisel F, Michallet M, Fischer T, Hochhaus A, Andreesen R, Nerl C, Freund M, Gattermann N, Ehninger G, Niederwieser D, Ottmann OG, Peschel C, Ho AD, Neubauer A, le Coutre P, Aulitzky W, Saglio G, Baccarani M, Fanin R, Rosti G, Mandelli F, Lazzarino M, Morra E, Carella A, Petrini M, Nobile F, Liso V, Ferrara F, Rizzoli V, Fiortoni G, Martinelli G, Cornelissen J, Ossenkoppele G, Browett P, Gedde-Dahl T, Tangen JM, Dahl I, Cervantes F, Odrizoala J, Hernandez Boulda JC,
Steegmann JL, Canizo C, Diaz J, Grenena A, Fernandez M, Simonsson B, Stenke L, Paul C, Bjoreman M, Malm C, Wadenvik H, Nilsson PG, Turesson I, Gratwohl A, Hess U, Solenthaler M, Goldman JM, Clark RE, Green A, Holyoake T, Lucas G, Smith G,
Milligan D, Rule S, Burnett A, Kantarjian H, Silver R, Stone R, Powell B, Gabrilove J, Moroose R, Wetzler M, Bearden J, Cataland S, Rabinowitz I, Meisenberg B, Thompson K, Graziano S, Emanuel P, Gross H, Cobb P, Bhatia R, Dakhil S, Irwin AD, Issell B, Pavletic S, Kuebler P, Layhe E, Butra P, Glass J, Moore J, Grant B, Neill H, Herzig R, Burris H, Petersen B, Kalaycio M, Stirewalt
D, Samlowski W, Berman E, Limentani S, Seay T, Shea T, Akard L, Smith G, Becker P, Devine S, Hart R, Veith R, Wade J, Brunvad M, Kalman L, Strickland D, Shurafa M, Bashey A, Shadduck R, Safah H, Rubenstein M, Collins R, Keller A, Tallman M,

Pecora A, Agha M, Homes H, Guidice R, Druker BJ, Guilhot F, Larson RA, O'Brien S, Rowe J, Schiffer CA, Buyse M, Baccarani M, Cervantes F, Cornelissen J, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Reiffers J, Rousselot P, Saglio G,
Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Talpaz M, Taylor K, Verhoef G, Santini V.

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Erratum in
Leukemia. 2010 May;24(5):1102.

Imatinib mesylate is considered standard of care for first-line treatment of chronic phase chronic myeloid leukemia (CML-CP). In the phase III, randomized, open-label International Randomized Study of Interferon vs STI571 (IRIS) trial, previously untreated CML-CP patients were randomized to imatinib (n=553) or interferon-alpha (IFN) plus cytarabine (n=553). This 6-year update focuses on patients randomized to receive imatinib as first-line therapy for newly diagnosed CML-CP. During the sixth year of study treatment, there were no reports of disease progression to accelerated phase (AP) or blast crisis (BC). The toxicity
profile was unchanged. The cumulative best complete cytogenetic response (CCyR) rate was 82%; 63% of all patients randomized to receive imatinib and still on study treatment showed CCyR at last assessment. The estimated event-free survival
at 6 years was 83%, and the estimated rate of freedom from progression to AP and BC was 93%. The estimated overall survival was 88% -- or 95% when only CML-related deaths were considered. This 6-year update of IRIS underscores the efficacy and safety of imatinib as first-line therapy for patients with CML.

PMID: 19282833 [PubMed - indexed for MEDLINE]

32. Clin Cancer Res. 2009 Feb 1;15(3):1059-63.

Treatment of Philadelphia-positive chronic myeloid leukemia with imatinib: importance of a stable molecular response.

Palandri F, Iacobucci I, Soverini S, Castagnetti F, Poerio A, Testoni N, Alimena G, Breccia M, Rege-Cambrin G, Tiribelli M, Varaldo R, Abruzzese E, Martino B, Luciano L, Pane F, Saglio G, Martinelli G, Baccarani M, Rosti G.

Department of Hematology/Oncology L. and A. Seràgnoli, St. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

PURPOSE: The achievement of a major molecular response (MMolR) at 12 months is a surrogate marker of progression-free survival in chronic myeloid leukemia patients treated with imatinib.
EXPERIMENTAL DESIGN: We evaluated the prognostic value of the long-term evolution of the molecular response based on a retrospective analysis of 130 late chronic phase chronic myeloid leukemia patients who achieved a complete cytogenetic
response (CCgR) with 400 mg/d imatinib and have now a median follow-up of 72 months (range, 48-77).
RESULTS: In 71 (55%) patients, molecular response was consistently major (stable MMolR); in 19 (15%) patients, molecular response was occasionally less than major (unstable MMolR); in 40 (30%) patients, MMolR was never achieved (never MMolR)
during all the course of CCgR. Patients with stable MMolR had a longer CCgR duration and a significantly better progression-free survival compared with patients with absent or unstable MMolR. The achievement of a MMolR, if maintained continuously, conferred a marked long-term stability to the CCgR: patients with a stable MMolR have a significantly lower risk of losing the CCgR than patients with unstable and never MMolR (4% versus 21%, P = 0.03, and 4% versus 33%, P < 0.0001, respectively). Finally, if a MMolR is not maintained consistently, the risk of losing the CCgR is higher but not significantly than if it is never
achieved (33% versus 21%, P = 0.5).
CONCLUSIONS: These data confirm that achieving a MMolR is prognostically important but point out that the prognostic value of achieving a MMolR is greater if the response is confirmed and stable.

PMID: 19188180 [PubMed - indexed for MEDLINE]

33. Haematologica. 2008 May;93(5):770-4. Epub 2008 Mar 26.

Front-line treatment of Philadelphia positive chronic myeloid leukemia with imatinib and interferon-alpha: 5-year outcome.

Palandri F, Iacobucci I, Castagnetti F, Testoni N, Poerio A, Amabile M, Breccia M, Intermesoli T, Iuliano F, Rege-Cambrin G, Tiribelli M, Miglino M, Pane F, Saglio G, Martinelli G, Rosti G, Baccarani M; GIMEMA Working Party on CML.

Department of Hematology and Oncology "L. and A. Seràgnoli", St. Orsola-Malpighi University Hospital, via Massarenti 9, 40138 Bologna, Italy. francesca.palandri@libero.it.

In 2004, we reported the short-term results of a multicentric, phase 2 study of imatinib 400 mg daily and pegylated interferon-alpha in the treatment of 76 early chronic phase Philadelphia-positive chronic myeloid leukemia patients. In this report, we update the results with an observation time of five years. After two years of treatment, all but 10 patients (13%) had discontinued pegylated interferon-alpha. The complete cytogenetic response rate at five years was 87%, and 94% of complete cytogenetic responders maintained the complete cytogenetic response after five years. All but one complete cytogenetic response also achieved a major molecular response. These data confirm the excellent response to imatinib front-line and the stability of the complete cytogenetic response. Any possible additional benefit of the combination with interferon-alpha remains
uncertain, due to low patient compliance.

PMID: 18367490 [PubMed - indexed for MEDLINE]

34. Blood. 2008 Apr 15;111(8):4022-8. Epub 2008 Feb 6.

Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study.

Larson RA, Druker BJ, Guilhot F, O'Brien SG, Riviere GJ, Krahnke T, Gathmann I, Wang Y; IRIS (International Randomized Interferon vs STI571) Study Group.

Collaborators: Durant S, Schwarer A, Joske D, Seymour J, Grigg A, Ma D, Arthur C, Bradstock K, Joshua D, Louwagie A, Martiat P, Bosly A, Shistok C, Lipton J, Forrest D, Walker I, Roy DC, Rubinger M, Bence-Bruckler I, Stewart D, Kovacs M, Turner AR, Birgens H, Bjerrum O, Facon T, Harousseau JL, Tulliez M, Guerci A, Maloisel F, Michallet M, Andreesen R, Ner C, Freund M, Gautterman N, Ehninger G, Deininger M, Ottman O, Peschel C, Fruehauf S, Neubauer A, Le Coutre P, Aulitzky W, Fanin R, Rosti G, Mandelli F, Lazzarino M, Morra E, Carella A, Petrini M, Nobile F, Liso V, Ferrara F, Rizzoli V, Fiortoni G, Martinelli G, Ossenkoppele G, Browett P, Gedde-Dahl T, Tangen JM, Dahl I, Odrizoala J, Hernandez Boulda JC, Steegman JL, Canizo C, Diaz J, Grenena A, Fernandez MN, Stenke L, Paul C, Bjoreman M, Malm C, Wadenvik H, Nilsson PG, Turesson I, Hess U, Solenthaler M,
Clark RE, Green AR, Holyoake TL, Lucas GS, Smith G, Milligan DW, Rule SJ, Burnett AK, Moroose R, Wetzler M, Bearden J, Cataland S, Rabinowitz I, Meisenberg B, Thompson K, Graziano S, Emanuel P, Gross H, Cobb P, Bhatia R, Dakhil S, Irwin D,
Issell B, Pavletic S, Kuebler P, Layhe E, Butra P, Glass J, Moore J, Grant B, Neill H, Herzig R, Burris H, Petersen B, Kalaycio M, Stirewalt D, Samlowski W, Berman E, Limentani S, Seay T, Shea T, Akard L, Smith G, Becker P, Devine S, Hart R, Veith R, Wade J, Brunvad M, Kalman L, Strickland D, Shurafa M, Bashey A, Shadduck R, Safah H, Rubenstein M, Collins R, Keller A, Tallman M, Pecora A, Agha M, Homes H, Guidice R, Druker BJ, Guilhot F, Larson RA, O'Brien SG, Rowe J, Schiffer CA, Buyse M, Baccarani M, Cervantes F, Cornelissen J, Fischer T, Hochaus A, Hughes T, Lechner K, Nielsen JL, Reiffers J, Rousselot P, Saglio G, Shepherd
J, Simonsson B, Gratwohl A, Goldman JM, Talpaz M, Taylor K, Verhoef G.

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Imatinib at 400 mg daily is standard treatment for chronic myeloid leukemia in chronic phase. We here describe the correlation of imatinib trough plasma concentrations (C(mins)) with clinical responses, event-free survival (EFS), and adverse events (AEs). Trough level plasma samples were obtained on day 29 (steady state, n = 351). Plasma concentrations of imatinib and its metabolite CGP74588 were determined by liquid chromatography/mass spectrometry. The overall mean (+/- SD, CV%) steady-state C(min) for imatinib and CGP74588 were 979 ng/mL (+/- 530 ng/mL, 54.1%) and 242 ng/mL (+/- 106 ng/mL, 43.6%), respectively. Cumulative estimated complete cytogenetic response (CCyR) and major molecular response (MMR) rates differed among the quartiles of imatinib trough levels (P = .01 for CCyR, P = .02 for MMR). C(min) of imatinib was significantly higher in patients who achieved CCyR (1009 +/- 544 ng/mL vs 812 +/- 409 ng/mL, P = .01). Patients with high imatinib exposure had better rates of CCyR and MMR and EFS. An exploratory analysis demonstrated that imatinib trough levels were predictive of higher CCyR independently of Sokal risk group. AE rates were similar among the imatinib quartile categories except fluid retention, rash, myalgia, and anemia, which were more common at higher imatinib concentrations. These results suggest that an
adequate plasma concentration of imatinib is important for a good clinical response. This study is registered at http://clinicaltrials.gov as NCT00333840.

PMID: 18256322 [PubMed - indexed for MEDLINE]

35. Clin Cancer Res. 2007 Dec 1;13(23):7080-5.

BCR-ABL messenger RNA levels continue to decline in patients with chronic phase chronic myeloid leukemia treated with imatinib for more than 5 years and approximately half of all first-line treated patients have stable undetectable BCR-ABL using strict sensitivity criteria.

Branford S, Seymour JF, Grigg A, Arthur C, Rudzki Z, Lynch K, Hughes T.

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PURPOSE: In the first years of imatinib treatment, BCR-ABL remained detectable in all but a small minority of patients with chronic myeloid leukemia. We determined whether BCR-ABL continues to decline with longer imatinib exposure and the
incidence and consequence of undetectable BCR-ABL.
EXPERIMENTAL DESIGN: BCR-ABL levels were measured in a subset of 53 imatinib-treated IRIS trial patients for up to 7 years (29 first-line, 24second-line). Levels were deemed undetectable using strict PCR sensitivity criteria.
RESULTS: By 18 months, the majority achieved a 3-log reduction [major molecular response (MMR)]. BCR-ABL continued to decline but at a slower rate (median time to 4-log reduction and undetectable BCR-ABL of 45 and 66 months for first-line).
The probability of undetectable BCR-ABL increased considerably from 36 to 81 months of first-line imatinib {7% [95% confidence interval (95% CI), 0-17%] versus 52% (95% CI, 32-72%)}. Undetectable BCR-ABL was achieved in 18 of 53 patients and none of these 18 lost MMR after a median follow-up of 33 months. Conversely, MMR was lost in 6 of 22 (27%) patients with sustained detectable BCR-ABL and was associated with BCR-ABL mutations in 3 of 6. Loss of MMR was recently defined as suboptimal imatinib response. There was no difference in the probability of achieving molecular responses between first- and second-line patients but first-line had a significantly higher probability of maintaining MMR [P = 0.03; 96% (95% CI, 88-100%) versus 71% (95% CI, 48-93%)].
CONCLUSIONS: With prolonged therapy, BCR-ABL continued to decline in most patients and undetectable BCR-ABL was no longer a rare event. Loss of MMR was only observed in patients with sustained detectable BCR-ABL.

PMID: 18056186 [PubMed - indexed for MEDLINE]

36. Haematologica. 2007 Nov;92(11):1579-80.

Long-term molecular responses to imatinib in patients with chronic myeloid leukemia: comparison between complete cytogenetic responders treated in early and in late chronic phase.

Palandri F, Iacobucci I, Quarantelli F, Castagnetti F, Cilloni D, Baccarani M; GIMEMA Working Party on CML.

CML patients who obtain a complete cytogenetic response (CCgR) may harbor different degrees of molecular disease, which are associated with different progression-free survival. We have compared the pattern and the magnitude of the molecular response (MolR) of 54 early chronic phase (ECP) and of 115 late CP patients who achieved a stable CCgR with IM 400 mg/daily. ECP patients obtained earlier, higher and more sustained MMolR.

PMID: 18024412 [PubMed - indexed for MEDLINE]

37. Blood. 2008 Feb 1;111(3):1039-43. Epub 2007 Oct 11.

Favorable long-term follow-up results over 6 years for response, survival, and safety with imatinib mesylate therapy in chronic-phase chronic myeloid leukemia after failure of interferon-alpha treatment.

Hochhaus A, Druker B, Sawyers C, Guilhot F, Schiffer CA, Cortes J, Niederwieser DW, Gambacorti-Passerini C, Stone RM, Goldman J, Fischer T, O'Brien SG, Reiffers JJ, Mone M, Krahnke T, Talpaz M, Kantarjian HM.

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Erratum in
Blood. 2008 Jul 15;112(2):452. Gambacorti, Carlo [corrected to Gambacorti-Passerini, Carlo].

Imatinib mesylate, a targeted inhibitor of BCR-ABL tyrosine kinase, is the standard of care for chronic myeloid leukemia (CML). A phase 2 trial of imatinib in late chronic-phase (CP) CML after interferon-alpha (IFNalpha) failure enrolled 532 patients, 454 with a confirmed diagnosis of CP CML. Median time from diagnosis was 34 months; median duration of imatinib treatment was 65 months.
Cumulative best rates of major cytogenetic response (MCyR) and complete cytogenetic response (CCyR) were 67% and 57%, respectively. At the 5-year landmark, 184 (41%) of the 454 patients are in CCyR. At more than 6 years, 199 (44%) of the 454 patients remain on imatinib. Most responses occurred within 12 months of starting imatinib; however, some patients achieved initial MCyR and CCyR more than 5 years after imatinib initiation. Estimated rates of freedom from progression to accelerated phase (AP) and blastic phase (BP) and overall survival at 6 years were 61% and 76%, respectively. Both freedom from progression to AP/BP and overall survival (OS) were associated with cytogenetic response level at 12 months. No increase in rates of serious adverse events was observed with continuous use of imatinib for up to 6.5 years, compared with earlier time
points. Imatinib continues to be an effective and safe therapy for patients with CP CML after failure of IFN.

PMID: 17932248 [PubMed - indexed for MEDLINE]

38. Cancer. 2004 Jun 15;100(12):2592-7.

Granulocyte-colony-stimulating factor (filgrastim) may overcome imatinib-induced neutropenia in patients with chronic-phase chronic myelogenous leukemia.

Quintas-Cardama A, Kantarjian H, O'Brien S, Garcia-Manero G, Rios MB, Talpaz M, Cortes J.

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Comment in
Cancer. 2005 Jan 1;103(1):210-11.

BACKGROUND: Imatinib mesylate administration has become standard treatment for patients with chronic myelogenous leukemia (CML). Although the safety profile of imatinib is favorable, Grade > or = 3 neutropenia (according to the National
Cancer Institute Common Toxicity Criteria) occurs in 35-45% of patients with CML in chronic phase who receive standard-dose imatinib. Myelosuppression results in treatment interruptions, which may compromise responses to imatinib. The authors
investigated the ability of granulocyte-colony-stimulating factor (filgrastim) to reverse imatinib-associated neutropenia, thereby allowing for more continuousimatinib administration.
METHODS: Thirteen patients with chronic-phase CML and Grade > or = 3, imatinib-induced neutropenia were treated with filgrastim. Treatment with filgrastim was initiated after a median of 22 months from the start of imatinib. Eleven patients received filgrastim 5 microg/kg 1-3 times weekly, and 2 patients received filgrastim 5 microg/kg daily; doses were titrated to maintain anabsolute neutrophil count (ANC) > or = 10(9)/L.
RESULTS: Seven of 11 patients (64%) who began treatment with an ANC < 1.5 x 10(9)/L had responses (i.e., their ANC improved to > or = 2 x 10(9)/L within 21 days); the other 4 patients experienced slower recovery but were able to continue
receiving imatinib uninterrupted. Before filgrastim administration was initiated, patients did not receive imatinib (due to neutropenia-related treatment interruptions) for an average of 21% of the total time since the start of imatinib. This figure decreased to 6% after the start of filgrastim treatment (P = 0.0008). Before filgrastim treatment was initiated, only one patient had achieved a major (partial) cytogenetic response. After the start of filgrastim treatment, five patients had major cytogenetic responses (including two complete responses).
CONCLUSIONS: The authors concluded that filgrastim may overcome imatinib-associated neutropenia and allow improved delivery of imatinib. Some patients may experience improvements in their responses to therapy as a result.

PMID: 15197801 [PubMed - indexed for MEDLINE]

39. Ann Hematol. 2004 Apr;83(4):258-64. Epub 2003 Nov 29.

Imatinib and beyond--the new CML study IV. A randomized controlled comparison of imatinib vs imatinib/interferon-alpha vs imatinib/low-dose AraC vs imatinib after interferon-alpha failure in newly diagnosed chronic phase chronic myeloid leukemia.

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PMID: 14648019 [PubMed - indexed for MEDLINE]

40. Leukemia. 2003 Dec;17(12):2392-400.

Dynamics of BCR-ABL mRNA expression in first-line therapy of chronic myelogenous leukemia patients with imatinib or interferon alpha/ara-C.

Müller MC, Gattermann N, Lahaye T, Deininger MW, Berndt A, Fruehauf S, Neubauer A, Fischer T, Hossfeld DK, Schneller F, Krause SW, Nerl C, Sayer HG, Ottmann OG, Waller C, Aulitzky W, le Coutre P, Freund M, Merx K, Paschka P, König H, Kreil S,
Berger U, Gschaidmeier H, Hehlmann R, Hochhaus A.

III. Medizinische Universitätsklinik, Fakultät für Klinische Medizin Mannheim der Universität Heidelberg, Mannheim, Germany.

We sought to determine dynamics of BCR-ABL mRNA expression levels in 139 patients with chronic myelogenous leukemia (CML) in early chronic phase, randomized to receive imatinib (n=69) or interferon (IFN)/Ara-C (n=70). The response was sequentially monitored by cytogenetics from bone marrow metaphases (n=803) and qualitative and quantitative RT-PCR from peripheral blood samples (n=1117). Complete cytogenetic response (CCR) was achieved in 60 (imatinib, 87%) vs 10 patients (IFN/Ara-C, 14%) after a median observation time of 24 months. Within the first year after CCR, best median ratio BCR-ABL/ABL was 0.087%, (imatinib, n=48) vs 0.27% (IFN/Ara-C, n=9, P=0.025). BCR-ABL was undetectable in 25 cases by real-time PCR, but in only four patients by nested PCR. Median best response in patients with relapse after CCR was 0.24% (n=3) as compared to 0.029% in patients with continuous remission (n=52, P=0.029). We conclude that (i) treatment with imatinib in newly diagnosed CML patients is associated with a rapid decrease of BCR-ABL transcript levels; (ii) nested PCR may reveal residual BCR-ABL transcripts in samples that are negative by real-time PCR; (iii) BCR-ABL transcript levels parallel cytogenetic response, and (iv) imatinib is superior to IFN/Ara-C in terms of the speed and degree of molecular responses, but residual disease is rarely eliminated.

PMID: 14523462 [PubMed - indexed for MEDLINE]

41. N Engl J Med. 2003 Mar 13;348(11):994-1004.

Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia.

O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ; IRIS Investigators.

University of Newcastle, Newcastle, United Kingdom.

Comment in
N Engl J Med. 2003 Mar 13;348(11):1048-50.
Clin Lab Haematol. 2005 Dec;27(6):416-7.
Curr Hematol Rep. 2004 Jan;3(1):37-8.

BACKGROUND: Imatinib, a selective inhibitor of the BCR-ABL tyrosine kinase, produces high response rates in patients with chronic-phase chronic myeloid leukemia (CML) who have had no response to interferon alfa. We compared the efficacy of imatinib with that of interferon alfa combined with low-dose cytarabine in newly diagnosed chronic-phase CML.
METHODS: We randomly assigned 1106 patients to receive imatinib (553 patients) or interferon alfa plus low-dose cytarabine (553 patients). Crossover to the alternative group was allowed if stringent criteria defining treatment failure or intolerance were met. Patients were evaluated for hematologic and cytogenetic responses, toxic effects, and rates of progression.
RESULTS: After a median follow-up of 19 months, the estimated rate of a major cytogenetic response (0 to 35 percent of cells in metaphase positive for the Philadelphia chromosome) at 18 months was 87.1 percent (95 percent confidence interval, 84.1 to 90.0) in the imatinib group and 34.7 percent (95 percent confidence interval, 29.3 to

40.0) in the group given interferon alfa plus cytarabine (P<0.001). The estimated rates of complete cytogenetic response were 76.2 percent (95 percent confidence interval, 72.5 to 79.9) and 14.5 percent (95 percent confidence interval, 10.5 to 18.5), respectively (P<0.001). At 18 months,
the estimated rate of freedom from progression to accelerated-phase or blast-crisis CML was 96.7 percent in the imatinib group and 91.5 percent in the combination-therapy group (P<0.001). Imatinib was better tolerated than combination therapy.
CONCLUSIONS: In terms of hematologic and cytogenetic responses, tolerability, and the likelihood of progression to accelerated-phase or blast-crisis CML, imatinib was superior to interferon alfa plus low-dose cytarabine as first-line therapy in newly diagnosed chronic-phase CML.

PMID: 12637609 [PubMed - indexed for MEDLINE]

Bilag E

RADS Fagudvalg
Rådet for Anvendelse af Dyr Sygehusmedicin

Sammenligningsgrundlag

Målgruppe	Relevante afdelinger Lægemiddelkomitéer Sygehusapoteker
Udarbejdet af	Fagudvalg for Medicinsk Behandling af Kronisk Myeloid Leukæmi under Rådet for Anvendelse af Dyr Sygehusmedicin
Godkendt af RADS	[dato]

Sammenligningsgrundlaget er udarbejdet på basis af Baggrundsnotatet for terapiområdet. Baggrundsnotatet med referencer, behandlingsvejledning samt dette sammenligningsgrundlag kan downloades fra Danske Regioners hjemmeside, www.regioner.dk.

Formål
Formålet med dette sammenligningsgrundlag er at sikre korrekt fastlæggelse af ækvipotente behandlinger i henhold til den godkendte behandlingsvejledning for terapiområdet. Baggrundsnotatet omfatter nye patienter.

Doseringstabel (daglig dosering	**Lægemiddeladministration ved indledende- og vedligeholdelsesbehandling i 1. linje**
Dasatinib (ATC L01XE06) 100 mg	1 tablet 1 gang daglig
Imatinib (ATC L01XE01) 400 mg	1 tablet 1 gang daglig
Nilotinib (ATC L01XE08) 600 mg	2 kapsler 2 gange daglig med 12 timers interval

Estimeret patientantal (nye patienter per år)	
A. Patienter som ikke er omfattet af mindst et af nedenstående kriterier • Langt QT syndrom • Hjerteinsufficiens • Svær KOL • Patient med pleuraexudater • Patient med uregelmæssig levevis • Vanskelig regulerbar diabetes • Nylig pankreatitis	64
B. Patienter som præsenterer sig med mindst et af nedenstående kriterier • Langt QT syndrom[1] • Hjerteinsufficiens[2] • Svær KOL[2] • Patient med pleuraexudater[2] • Patient med uregelmæssig levevis[3] • Vanskelig regulerbar diabetes[3] • Nylig pankreatitis[3]	16

Valg af behandling 1. linje

Patientgruppe A	**Patienter som <u>ikke</u> er omfattet af mindst et af nedenstående kriterier** • **Langt QT syndrom** • **Hjerteinsufficiens** • **Svær KOL** • **Patient med pleuraexudater** • **Patient med uregelmæssig levevis** • **Vanskelig regulerbar diabetes** • **Nylig pankreatitis**	
	1. valg *Ved rekommandation anføres et af de anførte lægemidler ud fra den opnåede lægemiddelpris jvf. sammenligningsgrundlag*	Dasatinib eller imatinib eller nilotinib
	2. valg *Ved rekommandation anføres et af de anførte lægemiddel som ikke er 1. valg ud fra den opnåede lægemiddelpris jvf. sammenligningsgrundlag*	Dasatinib eller imatinib eller nilotinib
Patientgruppe B	**Patienter med langt QT syndrom**	
	1.valg *Ved rekommandation anføres det lægemiddel ud fra den opnåede lægemiddelpris jvf. sammenligningsgrundlag*	imatinib
	Patienter med hjerteinsufficeins, svær KOL eller pleuraexudater	
	2. valg *Ved rekommandation anføres et af de anførte lægemidler ud fra den opnåede lægemiddelpris*	imatinib eller nilotinib

	jvf. sammenligningsgrundlag	
	2. valg *Ved rekommandation anføres det lægemiddel som ikke er1.valg*	imatinib eller nilotinib
	Patienter med uregelmæssig levevis eller vanskelig regulerbar diabetes eller nylig pankreatitis	
	1. valg *Ved rekommandation anføres et af de anførte lægemidler ud fra den opnåede lægemiddelpris jvf. sammenligningsgrundlag*	imatinib eller dasatinib
	2. valg *Ved rekommandation anføres det lægemiddel som ikke er 1. valg*	imatinib eller dasatinib