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ORIGINAL ARTICLE

Dasatinib induces fast and deep responses in newly diagnosed chronic myeloid leukaemia patients in chronic phase: clinical results from a randomised phase-2 study (NordCML006)

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Abstract

We randomised 46 newly diagnosed patients with chronic myeloid leukaemia (median age 56) to receive dasatinib 100 mg QD or imatinib 400 mg QD and report outcome as an intention-to-treat analysis with 36 months follow-up. Early cytogenetic and molecular responses were superior in the dasatinib group, with a tendency that imatinib patients caught up with time. For instance, $MR^{3.0}$ was reached at 3 months in 36% vs. 8% ($P = 0.02$), at 12 months in 81% vs. 46% ($P = 0.02$) and at 18 months in 73% vs. 65% (n.s.) of the patients in the two groups. In contrast, $MR^{4.5}$ was consistently superior in the dasatinib group at all time points from 6 months onwards, reaching 61% vs. 21% ($P < 0.05$) at 36 months. Sixty-four vs. 71% of the patients in the dasatinib and imatinib arms, respectively, remained on assigned drug. Dasatinib dose was frequently reduced, but with maintained excellent effect. One imatinib patient progressed to blastic phase, but no CML-related deaths occurred. In conclusion, our data compare favourably with those of the dasatinib registration study, DASISION. The fast and deep molecular responses induced by dasatinib compared with imatinib may be exploited to increase the proportion of patients who can achieve a treatment-free remission after treatment discontinuation.

Key words dasatinib; imatinib; randomized controlled trial; deep response; toxicity

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Targeted therapy with tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, nilotinib and bosutinib efficiently induces rapid haematologic and cytogenetic responses in most newly diagnosed chronic-phase CML patients (1–7). In general, these studies demonstrate that the second-generation TKIs (2GTKIs) induce deeper and faster molecular and cytogenetic responses than imatinib when given in first line, but in spite of this, there is no clear improvement in overall survival. 2GTKIs prevent disease progression to advanced phase CML compared with imatinib, although disease progression is rare with any TKI. Side effects vary between these drugs. All have varying degrees of haematological toxicity, of which nilotinib and bosutinib have least and dasatinib most (1–7). Non-haematological toxicity is generally different between these drugs, and cross-intolerance is uncommon. Consequently, patients with side effects have excellent alternatives. Of interest, dasatinib treatment is associated with the appearance of clonal NK and cytotoxic T lymphocytes in peripheral blood, and this phenomenon is frequently accompanied by pleural or pericardial effusions dominated by lymphocytes (8, 9). Despite periods of discontinuations and dose reductions, patients with these phenomena have very good treatment responses compared with other patients, and it has been postulated that the clonal lymphocytosis is part of an anti-leukaemic immune response (10).

We conducted a randomised phase-2 trial (NordCML006) in which the proportion of Philadelphia chromosome positive leukaemic stem and progenitor cells ($CD34^+/CD38^-$, and $CD34^+/CD38^+$respectively) in bone marrow aspirates from 46 newly diagnosed patients with CML was analysed both at diagnosis and during dasatinib and imatinib therapy (11). Briefly, at diagnosis, the proportion of leukaemic stem cells varied markedly (1–100%) between individual patients but correlated with leukocyte count, spleen size, haemoglobin and blast percentage. A low leukaemic stem cell burden at diagnosis was associated with less therapy-related haematological toxicity and superior cytogenetic and molecular responses during the first year of therapy. Of interest, and in contrast to *in vitro* findings, TKI therapy very rapidly depleted most of leukaemic stem cells *in vivo* (11). We here provide a detailed report on the clinical data from this trial, with emphasis on deep molecular responses and adverse events with a minimum of 36 months of follow-up for all randomised patients.

Methods

Patients, randomisation and treatment

Newly diagnosed (not more than 3 months from diagnosis) chronic-phase (CP) CML patients at least 18 yr of age were eligible for the study. Pretreatment with hydroxyurea, but not TKI, was allowed for up to 60 d. Hydroxyurea treatment was given to 54% of included patients (mean 16 d in these 54%). Mean time from the diagnosis of CML to start of TKI was 33 d. The study was performed in accordance with the Declaration of Helsinki, and all patients provided written informed consent. The study was approved by the relevant ethics review boards and medicinal products agencies in Finland, Norway and Sweden and registered at ClinicalTrials.gov (NCT00852566). Imatinib was prescribed and reimbursed as commercial drug, while dasatinib was provided as study drug by Bristol-Myers Squibb. Patients were randomly assigned to treatment groups (1 : 1), starting with standard dose of imatinib 400 mg QD (daily) or dasatinib 100 mg QD. In the case of toxicity, two dose reduction steps were allowed: 70 and 50 mg for dasatinib and 300 and 200 mg for imatinib. In case of insufficient response, dose escalations were permitted, but not above 140 mg QD of dasatinib or 400 mg twice daily (BID) of imatinib. The primary endpoint of this study was the proportion of Philadelphia chromosome-positive (Ph+) CD34 + CD38− bone marrow cells after 6 months of treatment as reported previously (11). Cytogenetic responses at 3, 6, 12 and 18 months and molecular responses at 1, 3, 6, 12 and 18 months were secondary endpoints and are reported here. Later, an amendment to the protocol was made so that patients were followed at yearly intervals from month 24 with record of important medical events and response.

Procedures

Bone marrow (BM) samples for cytogenetic analysis were taken at 0, 1, 3, 6, 12 and 18 months after therapy start. Complete cytogenetic response (CCgR) was defined as 0 Ph+ metaphases out of at least 20 analysed. *BCR-ABL1* transcript levels were assessed by real-time quantitative PCR (RQ-PCR) on peripheral blood samples at 0, 1, 3, 6, 12, 18, 24 and 36 months and performed in eight university molecular laboratories in Finland, Sweden and Norway. Results were reported using the International Scale (IS) and according to the ELN/EUTOS definitions (12, 13). One laboratory was not standardised to IS (Tromsø, Norway, five patients assessed), but this laboratory performed on par with others in previous Nordic validation rounds of *BCR-ABL1* RQ-PCR and data were included in the analysis.

Statistical analysis

Two-sided tests for differences in distributions, repeated measures and correlations were performed with non-parametric methods (Wilcoxon, Mann–Whitney, Fisher's exact test, Kruskal–Wallis, Spearman's rank tests), as appropriate. *P*-values <0.05 were considered statistically significant and calculated using IBM SPSS Statistics version 18.0 (Armonk, NY, USA) .

All patients ($n = 46$) were followed for 36 months after the start of the study drug. Unless specifically stated, all analyses were performed by randomisation arm, that is, according to the intention-to-treat principle (ITT). Missing values were omitted from analysis.

Funding, sponsorship and publication

The Norwegian University of Science and Technology (NTNU, Trondheim Norway) sponsored the study on behalf of the Nordic CML Study Group (NCMLSG). The trial was supported by a grant to NTNU by Bristol-Myers Squibb. Neither sponsor nor BMS had any role in study design, collection, analysis or interpretation of data or preparation of the manuscripts.

Results

Patient characteristics and treatments

Between March 2009 and October 2010 46 patients with newly diagnosed CP-CML (24 women and 22 men) were recruited at 10 academic centres in Finland (Helsinki), Norway (Bergen, Oslo, Trondheim), and Sweden (Linköping, Lund, Stockholm, Umeå and Uppsala). The mean age of the patients was 56 yr (range 29–78 yr). Twenty-four patients were randomly assigned to treatment with imatinib and 22 to dasatinib. Baseline characteristics by treatment group are reported in Table 1. High-risk patients constituted 19 % (Sokal), 9% (Euro/Hasford) and 15% (EUTOS) of the cohort.

Early cytogenetic and molecular responses

Early cytogenetic responses were superior in the dasatinib arm as compared to the imatinib arm (Table 2). The median percentage of Ph+ metaphases in the bone marrow at 1 month was 81% (imatinib) vs. 70% (dasatinib) and 5% vs. 0% at 3 months. At 3 months 82% of dasatinib treated, but just 42 % of imatinib-treated patients were in CCgR (Table 2).

The achievement of ≤10% *BCR-ABL1* after 3 months of therapy has recently been highlighted as an important milestone (14). All but one of the dasatinib-treated patients (95%), in contrast to 71% of those on imatinib, attained this early goal of therapy (Fig. 1). At the same 3-month milestone, more than one-third of dasatinib patients were already in $MR^{3.0}$ (previously denoted major molecular response or MMR) but <10% of imatinib patients had reached this level (Fig. 2A).

Table 1 Patient characteristics

	Dasatinib	Imatinib
Number of patients	22	24
Female/Male	15/7	9/15
Mean age (range) in years	53 (29–71)	58 (38–78)
Sokal risk score median (range)	0.88 (0.61–4.20)	0.80 (0.57–13.22)
LR/IR/HR	7/10/5	12/8/4
Euro risk score median (range)	912 (41–1839)	901 (182–2049)
LR/IR/HR	9/12/1	7/14/3
EUTOS score median (range)	55 (7–119)	33 (0–105)
LR/HR	19/3	20/4

LR/IR/HR is number of patients with low, intermediate and high risk, respectively, for progression according to Sokal, Euro or EUTOS scoring systems.

Table 2 Complete cytogenetic response (CCgR) during TKI therapy

	Rate of CCgR		
Month	Dasatinib	Imatinib	*P*-value
1	0/17[1] (0%)	0/24 (0%)	1
3	14/17 (82%)	8/18 (42%)	0.02
6	17/19 (89%)	15/17(88%)	0.91
12	20/20 (100%)	21/22 (95%)	0.33

[1]Number of patients with CCgR divided by number of evaluable samples (percentage).
TKI, Tyrosine kinase inhibitor.

Cytogenetic and molecular responses from month 6 and onwards

Rates of CCgR were high at both 6 and 12 months (Table 2). Missing data are due to insufficient metaphases for evaluation. At 6 months, all but two patients in each treatment group had achieved this landmark, and at 12 months, all patients but one in the imatinib arm was in CCgR.

$MR^{3.0}$ (major molecular response) is a standard treatment goal and regarded as a 'safe haven' in CML treatment.

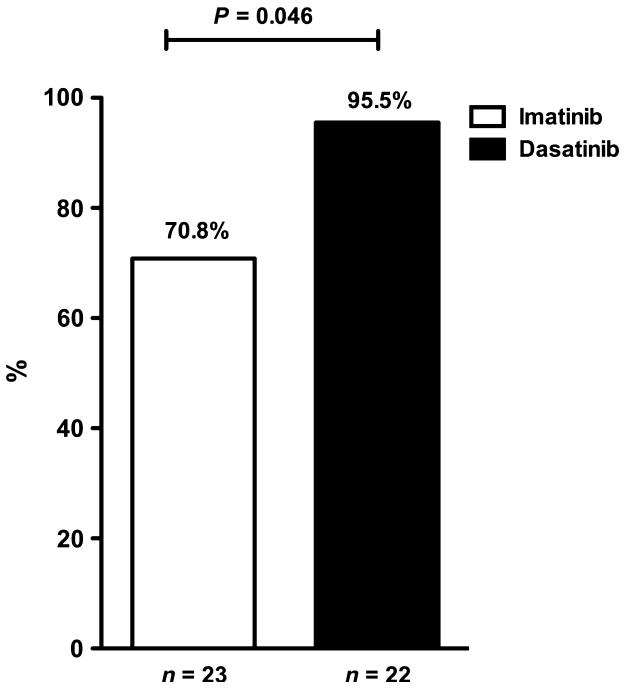

Figure 1 Early molecular response. Percentage of patients achieving ≤10% *BCR-ABL1* at 3 months in respective study arm.

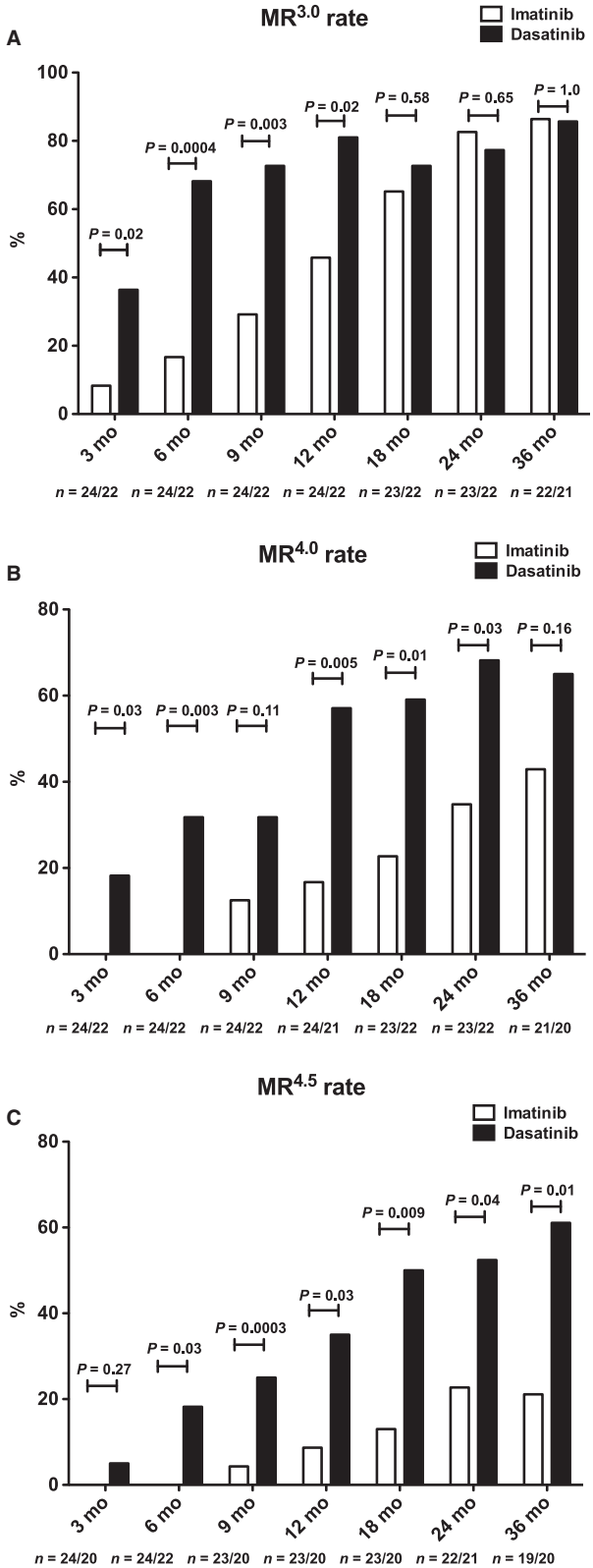

Figure 2 Molecular response. Percentage of patients reaching (A) $MR^{3.0}$, (B) $MR^{4.0}$ and (C) $MR^{4.5}$ on TKI therapy in respective study arm at indicated time points. The number of evaluable patient samples per treatment arm and time point is given in Table 3.

$MR^{3.0}$ rates were superior for the dasatinib group as compared to the imatinib group all through the first year of therapy (3, 6, 9 and 12 months) (Fig. 2A). The largest difference, 4-fold higher, was seen at 6 months (68% for dasatinib and 17% for imatinib). However, at later time points, from 18 months and onwards, the $MR^{3.0}$ rate was not significantly different between the two cohorts, as the imatinib-treated patients caught up and both groups plateaued around 80%. With regard to deep molecular responses, $MR^{4.0}$ and $MR^{4.5}$, a different pattern was seen. The fraction of patients reaching $MR^{4.0}$ was higher for dasatinib at all measured time points throughout the study, (although not reaching statistical significance at 9 and 36 months) (Fig. 2B). Similarly, an even deeper molecular response, $MR^{4.5}$, was reached by significantly more dasatinib-treated patients at all time points after 3 months (Fig. 2C). Of note, the poorest responder to imatinib in the study was the patient who progressed to blast phase. He was also the first to attain $MR^{4.5}$ in the imatinib arm because of a successful stem cell transplant. Regardless of this, the median level of *BCR-ABL1* remained approximately 10-fold lower in the dasatinib arm than in the imatinib arm at each time point according to ITT analysis (Table 3).

Progression and deaths

Three patients progressed on study, see also Fig. 3. One patient developed blast phase after 2 months of imatinib treatment (HR Sokal and an extra chromosome 19 at diagnosis; still alive and in $MR^{4.5}$ after allogeneic stem cell transplantation). One patient on imatinib showed increased Ph+ metaphases after 9 months from 1/25 to 4/25 and was successfully switched to dasatinib. One patient on dasatinib lost cytogenetic and molecular response after 9 months on treatment. Subsequent mutation analysis of the BCR-ABL1 kinase domain showed the appearance of V299L, a mutation which conveys resistance to dasatinib. The patient is presently alive treated with nilotinib, last *BCR-ABL1* transcript level 0.13% at month 36. One patient treated with imatinib died from lung cancer diagnosed 9 months after diagnosis of

Table 3 Median $BCR\text{-}ABL1^{IS}$ between study arms

Month	Median $BCR\text{-}ABL1^{IS}$ (%) (n = number of evaluable samples)		P
	Dasatinib	Imatinib	
1	16.6 (n = 21)	23.0 (n = 24)	0.38
3	0.22 (n = 22)	2.69 (n = 24)	0.011
6	0.06 (n = 22)	0.40 (n = 24)	0.011
9	0.020 (n = 22)	0.21 (n = 24)	0.005
12	0.007 (n = 21)	0.16 (n = 24)	0.009
18	<0.0032 (n = 22)	0.05 (n = 23)	0.048
24	<0.0032 (n = 22)	0.04 (n = 23)	0.035
36	<0.0032 (n = 21)	0.01 (n = 22)	0.09

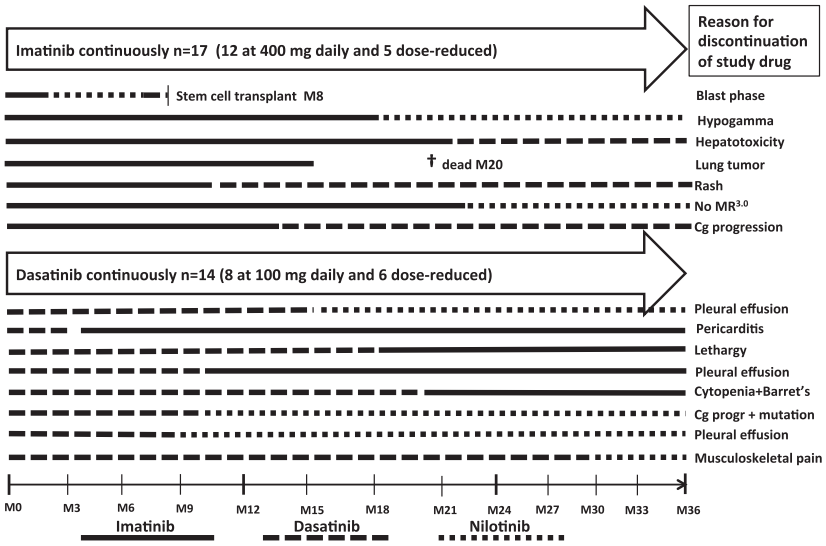

Figure 3 Patient treatment course up to 36 months on study. Treatment at assigned or reduced dose is indicated in the major arrows. Patients who discontinued study drug are shown as individual lines, and type of TKI therapy during the whole period is indicated. Reason for discontinuation of study drug is given to the right of the individual patient lines. Stem cell transplant and death as indicated.

CML, and this was assessed as unrelated to CML and its treatment.

Safety

Severe adverse events (mainly hospital admissions) occurred in 13 dasatinib- and 10 imatinib-treated patients. These and other adverse events are listed in Table 4. In terms of non-haematological toxicity, six patients (27%) on dasatinib developed pleural or pericardial effusions, frequently with accompanying signs of inflammation. Imatinib treatment was associated with more rash, hypophosphataemia (three patients had grade 3) and gastrointestinal side effects. One patient on imatinib had long-term elevated liver enzymes and underwent a liver biopsy, which showed histological signs of a suspected drug reaction with histopathological resemblance to the 'vanishing bile duct syndrome'. Liver enzymes normalised after switch to dasatinib. Dasatinib, as expected, induced more haematological toxicity than imatinib, mostly short-term and grade 2. Dasatinib also suppressed two or more cell lineages more frequently. Long-term cytopenias were similar in both treatment groups, probably indicating individual biological characteristics of the disease rather than TKI toxicity.

Study drug discontinuation and dosing

Eight patients discontinued dasatinib and the reasons were serosal effusions (five patients), progression (one patient) and constitutional symptoms/lethargy (two patients) which continued after change to another TKI. Discontinuation because of serosal effusion was considered as drug-related; the other three not. Seven patients discontinued imatinib, and the reasons were blast phase (one patient), cytogenetic progression (one patient), suboptimal response (less than $MR^{3.0}$ in two patients), rash (one patient), severe hypogammaglobulinaemia with airway infections (one patient), liver affliction (one patient) and one patient with lung cancer. Hypogammaglobulinaemia, rash and liver affliction were considered imatinib-related, the others not. In Fig. 3, the individual fates of patients are depicted up to 36 months.

The mean daily drug intake was calculated for the period, the patient was on study drug including interruptions, but not after discontinuation. During the first 2 yr of treatment, dasatinib patients on average received 92.7% of assigned dose, that is, 92.7 mg daily, whereas imatinib patients received 96.8% of assigned dose, that is, 387 mg daily. During treatment year 3, the mean dose of dasatinib decreased to 84.6 mg daily, but the dose of imatinib was maintained at 388 mg daily. Dose reductions occurred in 6 dasatinib-treated patients, and at 3 yr, their mean dose was 50 mg daily. Compared with the eight patients who remained on full-dose dasatinib throughout the study, these 6 dose-reduced patients did very well in terms of molecular response (median $MR^{4.5}$ in both groups, $P = 0.53$). Three patients who discontinued imatinib switched to dasatinib and also these patients performed well on low dose of dasatinib (mean 63 mg OD). Also, when we combined all nine patients on reduced dose of dasatinib to compare with the eight patients on full-dose, we found no difference (both groups attained median $MR^{4.5}$ and $P = 0.53$).

Discussion

Large clinical trials with 2GTKIs have shown that dasatinib and nilotinib induce more rapid and deeper responses in

Table 4 Adverse effects and discontinuation of study drug by 24 months classified by CTCAE 3.0

	Dasatinib (n = 22)		Imatinib (n = 24)	
Severity	Grade 2	Grade 3-4	Grade 2	Grade 3-4
All non-haematological events	11 (50%)	7 (32%)	12 (50%)	12 (50%)
Progressive disease	NA	1 (5%)	NA	2 (4%)
Pleural effusion	3 (14%)	2 (9%)	0 (0%)	0 (0%)
Pericardial effusion	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Unclear febrile conditions	3 (14%)	1 (5%)	0 (0%)	0 (0%)
Cholecystitis	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Perianal abscess	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Hypogammaglobulinaemia	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Second cancer	0 (0%)	1 (5%)	0 (0%)	3 (13%)
Nausea/vomiting/dyspepsia	2 (9%)	0 (0%)	4 (17%)	1 (4%)
Cardiac infarction	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Rash	2 (9%)	0 (0%)	4 (17%)	0 (0%)
Any haematological toxicity	10 (45%)	6 (27%)	4 (17%)	5 (22%)
Anaemia	10 (45%)	0 (0%)	3 (13%)	0 (0%)
Neutropenia	6 (27%)	3 (14%)	3 (13%)	5 (22%)
Thrombocytopenia	4 (18%)	3 (14%)	2 (9%)	1 (4%)
≥2-cell lineages affected	NA	9 (41%)	NA	5 (22%)
>6 months duration	NA	5 (23%)	NA	5 (22%)
Laboratory abnormalities				
Liver enzymes		0 (0%)		1 (4%)
Hypophosphataemia		0 (0%)		3 (13%)
Discontinuation of study drug	7 (32%)		7 (29%)	

The number (percentage) of patients with adverse events is shown. The list of grade 2 non-haematological events is not comprehensive but consists of events judged as clinically relevant, for example, for duration or need of symptomatic treatment. Haematological toxicity was assessed in all patients, except the patient with early blast crisis. The highest degree of toxicity is annotated.
NA, Not applicable.

newly diagnosed CP-CML patients as compared to imatinib (4, 5). Despite this, no improvement of the excellent overall survival of imatinib-treated patients has been observed with 2GTKIs, even though a small but significant benefit with regard to progression to advanced phase is notable, at least with nilotinib (2, 7). In many respects, data from the current smaller study are in line with previous studies and even appears to compare favourably with these. Furthermore, dasatinib showed a clear benefit over imatinib with respect to depth of molecular response. As an example, at 12 months, $MR^{3.0}$ rate was 80% with dasatinib compared to 45% with imatinib, and $MR^{4.0}$ rates were 60% and 17%, respectively. For both treatment arms, these numbers compare favourably with data from DASISION, the dasatinib registration study that was almost identically designed, but also with data from Radich *et al.* (3, 5, 15). In DASISION, the $MR^{3.0}$ rate by 12 months was 46% for dasatinib and 28% for imatinib. In our study, a higher proportion of dasatinib patients achieved an even deeper molecular response, $MR^{4.5}$, compared with imatinib patients, at 24 months (52% vs. 23%) and 36 months (61% vs. 21%). Again, comparing with DASISION, the $MR^{4.5}$ rates by 24 months were 17% and 8% and after 36 months 22% vs. 12% (2, 7, 16).

There is no clear explanation to this difference between our and previous studies of similar design. We applied a strict ITT analysis with complete follow-up, which is a strength of this study. ITT analysis also includes patients who progressed or discontinued study drug and subsequently received highly efficacious rescue treatment by alternative TKIs or allogeneic transplantation. In other studies, discontinuation for whatever reason may be denoted as treatment failure and excluded from further analysis. Also, classification of missing or inconclusive response assessments as 'no response', may lead to falsely low estimates of response rates compared to our study. The ITT approach provides a clinician the best reflection of expected treatment course and outcome in real life. We have also previously noted in our imatinib+/-pegylated interferon-α2b study NordCML002, that responses in Nordic patients treated both with imatinib alone or the combination were superior to those in studies with similar design (IRIS, French SPIRIT, CML-IV) (see also supplementary table in ELN treatment recommendations 2013) (1, 17–20). In addition, in the recent update from the Swedish population-based CML registry, very good responses to TKI therapy were reported (21). Particular characteristics of Nordic patients related to drug compliance and/or genetic variation are possible explanations for these results. The treatment groups in the current study were representative of Nordic CML patients with an ordinary distribution of Sokal, Hasford and EUTOS risk scores. Notably,

our patients with a mean age of 56 yr were clearly older than patients in most published CML studies (in DASISION patients were median 47 yr of age, i.e., 9 yr younger) and thus also in this respect is more in accordance with the everyday clinical setting.

Dasatinib was in the present study highly efficacious despite treatment interruptions, dosing reductions and a high rate (27%) of serosal effusions. From earlier studies with dasatinib, the occurrence of pleural effusions has been associated with a better treatment response, and our data are in line with this (10). In the current study, only 36 % of patients randomised to dasatinib remained on full dose of the drug after 36 months, while another 27% were on a reduced dosing schedule mainly due to toxicity. However, also patients that were dose-reduced exhibited deep molecular responses. In fact, when comparing the patients remaining on full-dose dasatinib and those on reduced dose of the drug, their molecular responses at 36 months were equally good (median MR4.5 in both groups, $P = 0.53$). This supports other retrospective reports where it has been suggested that dasatinib at reduced or intermittent dosing improves tolerability of the drug without loss of efficacy (22–24). These observations pose the question whether dasatinib at 100 mg QD is the optimal dose for long-term use. A lower dose from diagnosis of CP-CML or alternatively an induction phase with standard dose followed by a lower maintenance dose which might optimise the side effect profile without compromising efficacy and also improve affordability of the drug. Prospective studies to address this issue would be of interest.

In recent years, discontinuation of TKI therapy in CML patients with very good therapeutic responses has become a topic of high interest in academia and pharmaceutical industry (25, 26). One example is the ongoing pan-European discontinuation study EURO-SKI, in which patients with stable deep molecular responses ($MR^{4.0}$ for at least 1 yr) can be included. The treatment responses achieved primarily with dasatinib in our study are promising in this respect. Our results indicate that a substantial proportion of patients reach minimal residual disease levels that may allow for a future attempt to discontinue TKI therapy. Of note, 67 % of the dasatinib-treated and 23% of imatinib-treated patients were in $MR^{4.0}$ at 3 yr and would be eligible for participation in EURO-SKI. If discontinuation is the goal of treatment, our data support the use of dasatinib rather than imatinib as first line therapy in newly diagnosed CML. Aiming for maximal response is also supported by a recent report which showed that achievement of $MR^{4.5}$ on TKI therapy at 4 yr was associated with a better survival at 8 yr as compared to lower degrees of molecular response (27).

In summary, the treatment outcome in the current study was very good in both treatment groups, both by cytogenetic and by molecular evaluation, and the results compare favourably with data from similarly designed larger trials. The data give a realistic picture of the patient treatment results as analysis is strictly on an intention-to-treat basis and no patients were lost to follow-up. With respect to cytogenetic response and achievement of $MR^{3.0}$, there was a short-term benefit of dasatinib, but imatinib patients caught up with time. With respect to achievement of $MR^{4.0}$ and $MR^{4.5}$, there was a clear advantage with dasatinib. In our opinion, the optimal dose for long-term use of this potent drug still is an open question, but dasatinib appears to have an advantage if the treatment goal is to induce a deep response. This may possibly influence long-term survival, but more importantly may allow for a larger proportion of patients to attempt discontinuation of TKI therapy and be operationally cured. Future studies are needed to clarify whether achieving a deep molecular response with potential treatment-free survival should be a standard clinical treatment goal in line with, for example, achievement of CCgR and $MR^{3.0}$. Issues such as quality of life, economy and toxicity will be important in this context.

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Conflicts of interest

SM, JR, BS and KP have received honoraria and research funding from Novartis and Bristol-Myers Squibb. HE, TGD and HHjH have received honoraria and travel grants from Novartis and Bristol-Myers Squibb.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Study design and duration NordCML006.

