The impact of the combination of baseline risk group and cytogenetic response on the survival of patients with chronic myeloid leukemia treated with interferon-α

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Background and Objectives. This study was aimed at examining major cytogenetic response (MCR) as a valid predictor of the course of chronic myeloid leukemia (CML) and at assessing the survival of CML patients treated with interferon α (IFN) in dependence on the combination of MCR (yes or no) with the baseline risk group of the New CML score. MCR was defined as a reduction of Philadelphia chromosome-positive bone marrow cells to ≤ 35%. The New CML score discriminated three risk groups with significantly different survival probabilities.

Design and Methods. Data from individual patients with a confirmed diagnosis of Philadelphia chromosome-positive CML treated with IFN were collected from 10 prospective studies in Europe and Japan. Stratified for baseline risk group, patients with a major cytogenetic response by 21 months after the start of therapy (n=171) were compared with patients achieving a minor response or less (n=487). Survival probabilities after the landmark at 21 months were compared by using the two-sided log-rank test.

Results. MCR was a major predictor for low- and intermediate-risk patients (log-rank test, $p \leq 0.0001$), but not for high-risk patients. Ten-year survival probabilities for the low- and intermediate-risk patients who had a MCR were 75% (95 CI: 65-86%) and 56% (95 CI: 37-75%), respectively. The corresponding probabilities for patients who did not achieve a MCR were 21% (95 CI: 6-35%) and 16% (95 CI: 6-25%).

Interpretation and Conclusions. Cytogenetic response *per se* is not a valid surrogate marker, as it is dependent on the baseline prognostic profile. The combination of risk group and cytogenetic response does, however, provide useful clinical information. The survival data presented here can serve as a benchmark for the assessment of the long-term effectiveness of imatinib.

Key words: chronic myeloid leukemia, interferon α, prognosis

Haematologica 2005; 90:335-340

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Although there has been considerable progress in the treatment of chronic myeloid leukemia (CML) in recent years, this malignancy has remained a fatal disease for many patients. In the nineties, interferon-α (IFN)-based treatments had became the standard drug treatment, providing a median survival of about 70 months.[1] In 2001, the tyrosine kinase inhibitor imatinib was approved for the treatment of CML. Although there are not yet data on the long-term effectiveness of imatinib, the comparatively high rates of cytogenetic remissions are very promising.[2-5] Bone marrow transplantation (BMT) is regarded as the only curative option, but still carries a considerable 20-30% risk of early death.[6] In general, patients with CML who are transplanted within the first one or two years after diagnosis fare better than those who undergo transplantation later.[3,6] Thus, there is an urgent need to determine whether there are indicators that could allow early prediction of the long-term disease course. Since CML is the result of a translocation resulting in the Philadelphia chromosome (Ph), major cytogenetic response (MCR), i.e. the complete or partial disappearance of the Ph-chromosome-positive clone, is the obvious candidate as a valid surrogate measure for therapeutic response. We conducted this study - using the updated database established for the development and cross-sample validation of the New CML Score,[1] sometimes referred to as the *Euro Score* or the *Hasford Score* – with two objectives in mind: first, to determine whether MCR obtained by IFN-based therapy is a valid predictor of the future course of CML and second, to estimate the survival of CML patients who achieved MCR or not, stratified for risk group.

Design and Methods

Study patients and database

Individual patients' data were collected from 10 studies in Europe and Japan.

Table 1. Patients' characteristics at diagnosis.

	No. of patients	Mean (CI)* or proportion	Median	Min; Max
Age, completed years	773	48 (22; 75)	50	11; 83
Sex, proportion: male	773	0.58		
Hemoglobin, g/dL	760	11.9 (7.6; 16.2)	12.1	4.2; 17.5
White blood cell count,$\times 10^9$/L	756	140 (0; 354)	114	11; 626
Platelet count,$\times 10^9$/L	773	514 (0; 1185)	416	43; 3145
Blasts, %	773	1.7 (0; 5.6)	1	0; 10
Basophils, %	773	4.2 (0; 11.1)	3	0; 33
Eosinophils, %	773	2.4 (0; 7.1)	2	0; 20
Blasts in bone marrow, %	523	2.5 (0; 7.0)	2	0; 15
Additional chromosome abnormalities° (proportion)	481	0.07		
Spleen size, cm below costal margin	773	4.6 (0; 16.0)	2	0; 30
New CML Score,# proport.: low (l), intermediate (I) and high (H) risk)	773	L: 0.43; I: 0.45; H: 0.12		
Time from diagnosis to start of IFN treatment, days	773	48 (0; 148)	29	0; 182
Follow-up of all patients, days	773	1620 (0; 3376)	1556	60; 4235
Follow-up of patients still at risk and without bone marrow transplantation in first chronic phase, days	307	2123 (0; 3895)	2178	151; 4235

**Standard 95% confidence intervals; °apart from the Philadelphia chromosome 9: chromosome 22 translocation and the abnormalities that led to exclusion; #also know as the 'Euro Score' or the 'Hasford Score'.*

Patients with a confirmed diagnosis of Ph-positive CML and treated with IFN, either alone or in combination, were included. Further details on inclusion and exclusion criteria have been extensively described elsewhere.[1] Ph-positive patients with additional chromosome abnormalities other than the two Philadelphia chromosomes, trisomy 8, or isochromosome 17 were not excluded. The survival probabilities of the patients with other abnormalities were comparable to the survival probabilities of the patients with no additional chromosome abnormalities. With regard to cytogenetic response, at least 20 metaphases had to be evaluated for a patient to be included in this study. Since either not all cytogenetic data on the patients and/or no metaphase numbers were available, some trials used for the development of the New CML Score could not be included in this study. Cytogenetic response was classified as by Talpaz:[7] complete response, no Ph-positive metaphases; partial response, 1-35%; minor response, 36-95% Ph-positive metaphases. For this study, patients with MCR (complete or partial response) were compared with patients achieving a minor response or less.

Statistical considerations

If a physician wants to decide how to proceed further, depending on the result of a certain therapy, he/she needs to know how long to wait for this result. For patients with disease progression, it is obvious that an immediate change in treatment is advisable. However, for patients with no MCR but stable disease, a maximum waiting time for MCR should be imposed. In these circumstances, a landmark analysis[8] should be regarded as the method of choice. With respect to the observation of a first event (e.g. MCR), only patients who were under observation for a specified time period (the defined landmark) become part of the patient sample finally analyzed. The second event (e.g. death) is then analyzed depending on the occurrence of the first event (MCR, yes or no) for which the landmark was set. Survival after the landmark was compared using the log-rank test. All *p*-values presented are two-sided. To check for the impact of the prognostic profile at baseline, we used the New CML Score,[1] a validated prognostic model incorporating information on age, spleen size, blasts, eosinophils, basophils and platelets. The statistically significant correlations between the risk groups according to this score and survival[1,9] as well as between cytogenetic response and survival[10,11] have been reported several times. Our intention was to confirm previous reports and to combine information thus validated in a practical and simple manner.

Results

Patients

Seven hundred and seventy-three patients had complete data with regard to the New CML Score and at least one cytogenetic evaluation on the basis of 20 or more metaphases during their follow-up. These patients' characteristics are displayed in Table 1. The survival time of the 133 patients with bone marrow transplantation in first chronic phase (17% of 773) was censored at the time of the transplantation. Of the remaining 640 patients, 307 were still alive (40% of 773) and 333 (43%) had already died. Causes of death were assessed to be CML-related in 246 cases, not CML-related (e.g. cardiac failure, pulmonary embolism, second neoplasia, and suicide) in 52 cases and unknown in 35 cases. The median observation time was 51 months, with a range from 2 to 139 months. The New CML Score discriminated three statistically significant

Table 2. Major cytogenetic response up to various times after treatment initiation.

	All patients	*Low-risk* patients*	*Intermediate-risk patients*	*High-risk patients*
Patients with CCR° in 9 months	19 (3%)	7 (2%)	12 (4%)	0 (0%)
Patients with PCR# in 9 months	63 (9%)	36 (12%)	22 (7%)	5 (6%)
Patients without MCR@ in 9 months	658 (89%)	269 (86%)	304 (90%)	85 (94%)
Patients with CCR in 12 months	32 (4%)	15 (5%)	17 (5%)	0 (0%)
Patients with PCR in 12 months	82 (11%)	45 (15%)	31 (9%)	6 (7%)
Patients without MCR in 12 months	616 (84%)	248 (81%)	285 (86%)	83 (93%)
Patients with CCR in 15 months	44 (6%)	23 (8%)	20 (6%)	1 (1%)
Patients with PCR in 15 months	100 (14%)	51 (17%)	43 (13%)	6 (7%)
Patients without MCR in 15 months	562 (80%)	222 (75%)	263 (81%)	77 (92%)
Patients with CCR in 18 months	48 (7%)	25 (9%)	22 (7%)	1 (1%)
Patients with PCR in 18 months	108 (16%)	55 (20%)	46 (14%)	7 (9%)
Patients without MCR in 18 months	525 (77%)	201 (72%)	252 (79%)	72 (90%)
Patients with CCR in 21 months	61 (9%)	35 (13%)	25 (8%)	1 (1%)
Patients with PCR in 21 months	110 (17%)	53 (20%)	50 (16%)	7 (9%)
Patients without MCR in 21 months	487 (74%)	181 (67%)	239 (76%)	67 (89%)

**Risk group according to the New CML Score;[1] °CCR: complete cytogenetic response; #PCR: partial cytogenetic response; @MCR: major cytogenetic response. Percentages summing up to 99 or 101% are due to rounding effects.*

risk groups (log-rank test, $p<0.0001$). The median survival times in the low-risk group (330 patients, 94 died), intermediate-risk group (350 patients, 171 died), and high-risk group (93 patients, 68 died) corresponded to 96, 72, and 43 months. In the low-risk group, the 10-year survival probability was 0.42, in the intermediate- and high-risk group, the respective probabilities were 0.25 and 0.05.

Choice of the landmark

As 82% (n = 183) of the patients who achieved an MCR (n = 222, 29% of 773) did so within 21 months, we used 21 months as the landmark. An earlier landmark would have neglected too much information without avoiding a decisive amount of risk of death by sticking to IFN while waiting for response. Table 2 displays the number of patients observed for various time periods after treatment initiation with IFN. The percentage of patients with MCR was continuously increasing by at least 3% every three months. The percentages of MCR were highest among patients with low-risk according to the New CML Score and lowest in the high-risk group ($p=0.0003$). The remaining 18% first observations of an MCR *after* 21 months (n=39; 22 low-risk, 15 intermediate-risk, and 2 high-risk patients) were distributed over a couple of years and the risk of dying while waiting for response became too high for the non-responders. Of the 171 patients who were observed for at least 21 months and who had an MCR, 61 (36% of 171) achieved a complete (CCR) and 110 a partial cytogenetic response (PCR) (Table 2). The survival probabilities between patients with PCR and patients with CCR up to 21 months were similar (log-rank test, $p=0.2552$). Up to the first 21 months, neither the time to achieve PCR nor the time to achieve CCR had any statistically significant correlation with survival.

Within the first 21 months, 57 patients were transplanted in first chronic phase, 35 died and 23 were censored for reasons other than transplantation. At the end of month 21, the survival probability was 0.95. The 171 major cytogenetic responders had a 10-year survival probability of 0.64 and 38 patients died. The 10-year survival probability of the 487 non-responders was 0.16. Their median survival time was 66 months and 260 patients died. The log-rank test between both groups was highly significant ($p<0.0001$).

Combination between major cytogenetic response and baseline risk group

Figure 1 shows the correlation between MCR and survival in the low-risk group. Between the start of IFN therapy and the end of month 21, 9 patients died and 52 patients were censored. Survival probability at the end of month 21 was 0.97. In the remaining 269 low-risk patients, the achievement of MCR was a major predictor of the future course of disease. The median survival time had not yet been reached for the cytogenetic responders, whereas for the non-responders the median survival time was 78 months ($p<0.0001$)

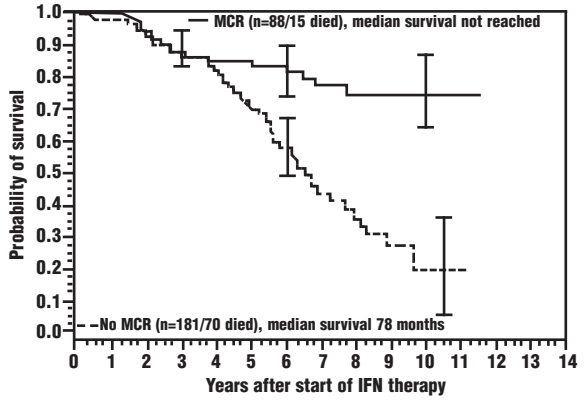

Figure 1. Patients with low risk at diagnosis according to the New CML Score (n=330, 43% of 773). For the 269 patients still under observation after 21 months, two Kaplan-Meier curves were plotted from this landmark. The affiliation of a patient to either curve depended on whether a major cytogenetic remission (MCR) was recorded within the first 21 months of IFN therapy, or not. The notation (*n=88/15 died*) indicates that 15 out of 88 patients died (similarly for the second group). Confidence intervals for probability of survival are given at 3, 6, and 10 years for each group. The log-rank test between *MCR* and *No MCR* for survival probabilities after 21 months was significant ($p \leq 0.0001$).

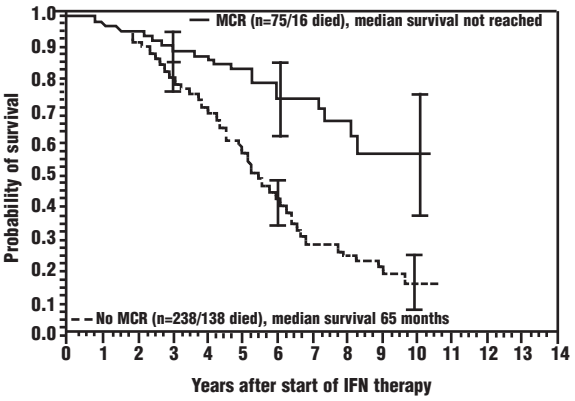

Figure 2. Patients with intermediate risk at diagnosis according to the New CML Score (n=350, 45% of 773). For the 314 patients still under observation after 21 months, two Kaplan-Meier curves were plotted from this landmark. The affiliation of a patient to either curve depended on whether a major cytogenetic remission (MCR) was recorded within the first 21 months of IFN therapy, or not. The notation (*n=75/16 died*) indicates that 16 out of 75 patients died (similarly for the second group). Confidence intervals for probability of survival are given at 3, 6, and 10 years for each group. The log-rank test between *MCR* and *No MCR* for survival probabilities after 21 months was significant ($p \leq 0.0001$).

(Figure 1). Regarding the intermediate-risk group, 17 patients died and 19 were censored before the end of month 21 (Figure 2). The survival probability at the landmark was 0.95. As before, for the remaining 314, a survival advantage for patients with MCR was observed: median survival time was not reached vs. 65 months for non-responders ($p<0.0001$) (Figure 2). Interestingly, for high-risk patients (n=75), MCR did not show any effect. However, the number of patients with MCR was small (Figure 3). Survival probability at the end of 21 months was 0.90 and 9 out of 18 with a shorter observation time had already died. The corresponding 10-year survival probabilities for low- and intermediate-risk patients with MCR were 75% (95 CI: 65-86%) and 56% (95 CI:37-75%), and those for patients without MCR were 21% (95 CI: 6-36%) and 16% (95 CI: 6-25%); none of the high-risk patients lived that long (Table 3).

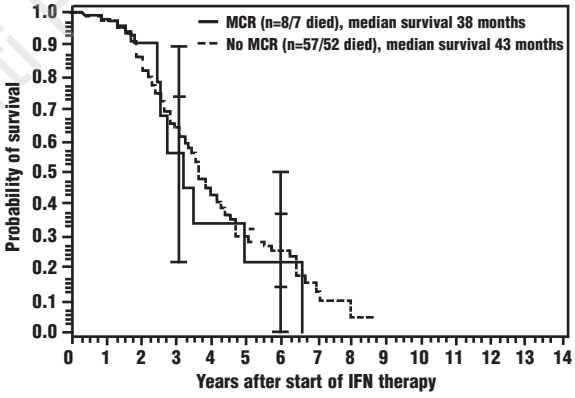

Figure 3. Patients with high risk at diagnosis according to the New CML Score (n=93, 12% of 773). For the 75 patients still under observation after 21 months, two Kaplan-Meier curves were plotted from this landmark. The affiliation of a patient to either curve depended on whether a major cytogenetic remission (MCR) was recorded within the first 21 months of IFN therapy, or not. The notation (*n=8/7 died)* indicates that 7 out of 8 patients died (similarly for the second group). Confidence intervals for probability of survival are given at 3 and 6 years for each group. The log-rank test between *MCR* and *No MCR* for survival probabilities after 21 months was not significant.

Discussion

This study shows that achieving MCR has considerable impact on the prognosis of chronic-phase CML patients treated with IFN. As the achievement of MCR within 21 months was twice able to differentiate two groups with statistically different survival probabilities within one baseline risk group, within the low- and the intermediate-risk groups, we concluded that MCR provided independent additional prognostic information of clinical relevance. This impact, however, depended on the baseline prognosis. Baseline low-risk patients benefited most from achieving an MCR. The prognosis of high-risk patients was unaffected by cytogenetic response. Analysis of the impact of complete hemato-

Table 3. Survival according to the combination of risk groups of the New CML Score and major cytogenetic response (MCR).

	No. of patients alive at month 21	*10-year survival probability (CI)* (Min; Max)*
Low-risk patients with MCR up to month 21	88	0.75 (0.65; 0.86)
Low-risk patients with no MCR up to month 21	181	0.21 (0.06; 0.36)
Intermediate-risk patients with MCR up to month 21	75	0.56 (0.37; 0.75)
Intermediate-risk patients with no MCR up to month 21	239	0.16 (0.06; 0.25)
High-risk patients with MCR up to month 21	8	0 (-;-)
High-risk patients with no MCR up to month 21	67	0 (-;-)

**Standard 95% confidence intervals.*

logic response, for which larger numbers (n=105) were available, showed the same picture.[12]

Thus, major cytogenetic response *per se* is not a valid surrogate marker, but is dependent on the baseline prognostic profile. Our results confirm an earlier analysis of complete cytogenetic responders among whom substantial long-term survival was restricted mainly to low-risk and possibly intermediate-risk risk patients.[11] This is important information for the clinical management of patients with CML. Whereas it may make sense to delay BMT while waiting for MCR in low- and intermediate-risk patients, our study does not support this strategy for high-risk patients.

It took 21 months after the start of IFN-based treatment to obtain 82% of all major cytogenetic responses ever observed in the total sample. A similar time window has been reported by a registry study of complete cytogenetic responders.[11] However, we presume that if patients were cytogenetically examined more frequently, this interval may be reduced to 15-18 months. Delaying BMT for such a period will only slightly worsen the prognosis for survival,[6] if at all, and may be balanced by the considerably higher survival probabilities with conservative treatment in the first year.

In the long term, decision-making for low-risk patients with MCR becomes even more difficult. After 8 years, this group was far from reaching its median survival time and the 10-year survival rate was about 75%. Currently, it is difficult to specify when the survival curves of low-risk CML patients with MCR cross the curves of comparable patients who have undergone BMT. Considering the data presented by Gratwohl *et al.*,[6] this may well take 10 years or more.

Conclusions

We consider the data presented here to be highly relevant even in the era of imatinib, as they show empirical evidence that non-high-risk patients with MCR under IFN-α achieve 10-year survival rates of 56% to 75%. At present, it is not yet known whether comparable 10-year survival rates will be achieved for low- and intermediate-risk patients treated with imatinib. Likewise, it is not yet known whether MCR achieved with imatinib generates a similar increase of survival time as seen with IFN, as the mechanisms of action of the two drugs are quite different. It seems that the Ph+ clone is reduced even more by imatinib than by IFN[13,14] and first reports suggested that cytogenetic response is a predictor for survival under imatinib, too.[15] On the other hand, whereas IFN, probably due to its immune modulating property, has a protracted effect leading to long-lasting unmaintained remissions, remissions with imatinib appear not to be durable once imatinib has been stopped even if a MCR had been achieved (*unpublished observations*). Emerging evidence that imatinib rarely leads to complete molecular remission and that many patients are still at risk of relapse and other clonal disorders is concerning.[16,17] Due to the promising efficacy and safety profile of imatinib and the convenience of oral administration, it has become difficult to perform sound standard phase III randomized clinical endpoint trials, since too many patients refuse to continue with IFN and cross over to imatinib, as the IRIS-trial showed.[4] The survival data of the well-characterized sample of CML patients presented here can also be used as a benchmark to assess, in years to come, the long-term effectiveness of imatinib compared to IFN.

JH and MP developed the concept, designed the study, analyzed the data and drafted the manuscript. The other co-authors were involved in the interpretation of the data and in revising the manuscript. All authors have approved the final version of the manuscript. The authors declare that they have no potential conflicts of interest.

Supported by unrestricted grants from Schering-Plough Ltd.
Manuscript received July 27, 2004. Accepted January 20, 2005.

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