would be useful to confirm its superior ability to recognize a true rise in BCR-ABL.

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The authors declare no competing financial interests.

To the editor:

Improved outcome after stem-cell transplantation in FLT3/ITD-positive AML

In the July 1, 2006, issue of Blood, Meshinchi et al1 comment on the role of stem-cell transplantation (SCT) in FLT3/ITD-positive acute myeloid leukemia (AML). In their interpretation of data previously presented by Gale et al,2 they conclude that the occurrence of a FLT3/ITD may not be regarded as a negative prognostic factor in patients undergoing allogeneic SCT. The dispute between both authors concerns the fact that although an “intention-to-treat” analysis does not suggest a clinically relevant improvement in survival in patients for whom a donor could be identified, the “as-treated” comparison shows a lower probability of relapse and better overall survival in FLT3/ITD-positive patients undergoing allogeneic transplantation compared with chemotherapy.

We would like to add to this discussion by presenting the results of the AML 96 study of the DSIL (German study initiative leukemia), in which 999 patients 60 years or younger were prospectively included between 1996 and 2003 and stratified according to cytogenetic risk category.3 Of 555 intermediate-risk patients evaluable for FLT3 mutation status, 175 (31.5%) were FLT3/ITD-positive. The treatment protocol included 2 cycles of induction chemotherapy including high-dose Ara-C for all patients as previously described. Since the rate of remission was not different in patients with and without a FLT3/ITD (68% vs 63%),4 we decided to determine the impact of different consolidation therapies on overall survival (OS) and probability of relapse in patients with respect to FLT3/ITD mutation status. Allogeneic SCT using an HLA-matched sibling donor was performed in 103 patients after standard conditioning therapy. If no donor was available, the next treatment priority was to obtain G-CSF–mobilized autologous blood stem cells after induction and/or first postremission chemotherapy and to perform an autologous SCT (n = 141). If patients could not mobilize autologous cells, conventional consolidation chemotherapy consisted of 2 cycles of high-dose Ara-C (n = 132).

Figure 1 shows that after a median follow-up of 53 months for surviving patients, overall survival is not significantly different between FLT3/ITD-positive and -negative patients having undergone either autologous or allogeneic SCT. In contrast, FLT3/ITD-positive patients receiving chemotherapy as consolidation therapy had an inferior probability of survival (21% vs 46%; hazard ratio [HR] = 2.2; 95% confidence interval [CI], 1.4-3.5; P = .001). The probability of relapse in the group of patients receiving chemotherapy was significantly higher in FLT3/ITD-positive compared with FLT3/ITD-negative patients (94% vs 59%; HR = 4.0; 95% CI, 2.5-6.6; P < .001). Of interest, as reported by Gale et al,2 the probability of relapse tended to be higher in FLT3/ITD-positive than FLT3/ITD-negative cases (35% vs 19%; HR = 2.7; 95% CI, 1.1-6.5; P = .03) after allografting but not after autologous transplantation.

Although we absolutely agree with Gale et al in that a donor—versus—no donor or a good mobilizer—versus—poor mobilizer comparison should be the cornerstone of valid prognostic analyses, we believe it is fair to say that patients with a FLT3/ITD-positive AML achieving remission should be scheduled for an autologous or allogeneic SCT within a controlled clinical study. Our data as well as reports from other

References


Figure 1. Probability of overall survival and relapse according to postremission therapy. After a median follow-up of 53 months for surviving patients, the probability of overall survival and relapse (from remission) are shown for patients having received either chemotherapy (n = 132), autologous transplant (n = 141), or allogeneic transplant (n = 103) as postremission therapy. Tx indicates transplantation.
study groups suggest that until alternative strategies including new targeted therapies will be introduced, allogeneic or autologous SCTs in first remission seem to be warranted to compensate for the negative prognostic impact of FLT3/ITD.5

Martin Bornhäuser, Thomas Illmer, Markus Schaeik, Silke Soucek, Gerhard Ehninger, and Christian Thiede, for the AML SHG 96 study group

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

A complete membership list for the AML SHG 96 study group is provided in Document S1, available at the Blood website; click on the “Supplemental Document” link at the top of the online article.

Response:

Still a need for more robust evidence that FLT3/ITD status should influence the decision to proceed to transplantation in AML patients

We welcome the contribution from Bornhäuser and colleagues on the impact of a FLT3/ITD in acute myeloid leukemia (AML) patients treated with different types of consolidation therapy in the AML 96 study of the DSIL. There is general agreement that the presence of a FLT3/ITD is a poor prognostic factor associated with a higher relapse rate, but the controversial issue is whether the demonstration of this poor prognosis is an indication for a transplantation.

In our published series of 970 non–acute promyelocytic leukaemia AML patients entered into the UK MRC AML 10 or 12 trials who achieved complete remission,1 we found that, for patients receiving standard chemotherapy consolidation, those who were FLT3/ITD positive had a significantly higher relapse rate than those who were FLT3/ITD negative (76% versus 53%, respectively; odds ratio [OR] = 2.41; 95% confidence interval [CI] = 1.85-3.13). In those who received an autograft, the relapse rate was lower, but the difference between those who had a FLT3/ITD and those who did not was of a similar magnitude to the chemotherapy recipients (56% versus 35%, respectively; OR = 2.39; CI = 1.24-4.63). In the allograft recipients, the relapse rate was lower still, and there was little difference between those who were FLT3/ITD positive and FLT3/ITD negative (31% versus 25%, respectively; OR = 1.31; CI = 0.56-3.06). This might suggest that allografting was a good idea but, crucially, the analysis of heterogeneity showed no significant difference in the impact of a FLT3/ITD between the 3 types of consolidation. The results in the patients receiving an allograft may be due to the small cohort size of 170 patients, of whom only 35 were FLT3/ITD positive, and we therefore advised a cautious interpretation of our data.

Bornhäuser et al report on 376 patients with intermediate-risk cytogenetics who achieved remission, of whom 132 subsequently had chemotherapy consolidation, 141 an autograft, and 103 an allograft. They found a significant impact of a FLT3/ITD in the chemotherapy consolidation group, in accord with our data. They also found an impact of a FLT3/ITD on the relapse rate in the allograft recipients but not the autografted patients, but as no tests of heterogeneity are provided it is not possible to comment on the significance of these differences. Furthermore, the findings in the autograft and allograft groups were the opposite of what we observed, again raising concerns about small numbers.

It is also worth noting that the presence of a FLT3/ITD predicts for early relapse (P = .03 for trend in our cohort). If patients in whom a transplantation is intended relapse before the procedure can be carried out and are then omitted from the transplantation series, this will decrease the difference between the FLT3/ITD-positive and -negative groups. If these early relapses are considered in the chemotherapy-only group, then the impact of the FLT3/ITD in chemotherapy recipients will be exaggerated.

A large meta-analysis might help resolve this important clinical issue, but will still not be a substitute for a well-powered randomized trial. We do not support the view of Bornhäuser et al that all patients with a FLT3/ITD “should be scheduled for an autologous or allogeneic SCT [stem-cell transplantation] within a controlled clinical study” unless by this they mean a randomized trial.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

Reference


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