Is drug treatment superior to allografting as first-line therapy in chronic myeloid leukaemia?

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A study comparing the survival times of patients who received allogeneic transplantation for early-stage CML with those of patients who received drug treatment showed that, with very few exceptions, drug treatment is the therapy of choice for this group of patients.

Since allografts for chronic-phase chronic myeloid leukaemia (CML) became an accepted therapy in the 1980s, the choice between drugs and allograft as first-line therapy has been actively debated.[1–3] The study by Hehlmann et al. (see opposite) is the first to compare these options in a randomised fashion, and reported drug therapy to be superior to allografting. The difference was impressive, particularly given that the drug therapy being compared with allograft was interferon alfa and hydroxyurea. The tyrosine kinase inhibitor imatinib has now replaced these drugs, leading to marked improvements in response rates and survival.[4] If this study was repeated today, the results would almost certainly demonstrate the superiority of drug treatment over allograft even more emphatically than do the present results.

The study by Hehlmann et al. shows similar patterns of survival to earlier comparisons.[2] Survival with drug therapy is clearly superior for the first five or more years, after which point, the two curves converge owing to the steady death rate from progression in the drug treatment arm. After convergence, survival with drug therapy falls more rapidly than that with allograft. This rapid drop in survival is unlikely to occur with imatinib treatment, as the annual risk of death beyond five years with imatinib therapy is <1% – similar to the rate for long-term allograft survivors.[5] Given this fact, the early survival benefit of drug treatment with imatinib will probably not be diminished by a more rapid decline in survival beyond five years.

One issue that is currently under debate is whether younger patients should still be considered for upfront allografts. The justification for carrying out such treatment is made on the basis that transplant-related mortality is lower in those less than 20 years old and because of concern about the possible life-long imatinib requirement for these young patients. In a review of outcomes for children (median age 14 years) with CML receiving matched sibling allografts that was conducted by the European Group for Blood and Marrow Transplantation, survival at three years was 73% in patients receiving allografts within six months of diagnosis. In the International Randomized Interferon versus STI-571 (IRIS) study, recipients of imatinib had a survival of 95% at three years and 89% at six years.[4] With annual rates of progression to acute phase of <1%, it is likely that survival on imatinib will remain

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Synopsis

Rüdiger Hehlmann, Ute Berger, Markus Pfirrmann et al. (2007) **Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia.** *Blood 109:4686–4692*

Background. For patients with chronic myeloid leukaemia (CML), allogeneic transplantation is considered the first-line treatment option; however, persistent transplantation mortality and the development of new drug therapies have challenged this concept. Until recently, there have been no randomised studies comparing the treatment outcomes of transplantation with those of drug therapy in patients with CML.

Objective. To compare the survival times of patients who received allogeneic transplantation for early-stage CML with those of patients who received drug treatment.

Design and intervention. Patients with Philadelphia chromosome and/or BCR-ABL-positive CML in chronic phase were enrolled in this study between January 1995 and December 2001. Randomisation was carried out according to the availability of a matched related donor. The patients eligible for allogeneic transplantation comprised two groups: those with, and those without a donor. The baseline characteristics of these two groups were similar. By contrast, there were significant differences in age, white blood cell count, symptoms due to organomegaly, and differential, haemoglobin, and prognostic score between patients who were eligible for transplantation and those who were not. Survival documentation was available for all but one patient.

Outcome measure. The primary endpoint of the trial was survival time.

Results. The study included 621 patients with chronic phase CML who were registered and stratified according to eligibility for primary allogeneic transplantation. Overall, 354 patients (62% male; median age 40 years) were randomised to receive either an allograft from a related donor (38%; n=135) or best available drug treatment (62%; n=219). Overall, 91% of the patients randomised to the allograft group received transplantation within a median of 10 months (range 2–106 months) from the time of diagnosis. The median observation time for living patients was 8.9 years (range 4.2–11.2 years). Patients who received drug treatment had a higher rate of survival than patients who received allografts, both until year eight and over the entire observation period up to year 11 (P=0.041 and P=0.049, respectively). Among patients with low-risk features at the time of diagnosis, those allocated to drug therapy had a higher rate of survival at both eight and 11 years' follow-up than did patients who received transplants (P=0.027 and P=0.032, respectively). The difference in survival between the two treatment arms was not significant for non-low-risk patients. At the time of evaluation, 55% of patients in the allograft group and 60% of patients in the drug-treatment group were alive. Analyses of their health status did not identify any differences between the two groups. Patients who survived at least five years were also analysed for cytogenetic and molecular responses. Patients who received transplantation had significantly higher rates of complete cytogenetic remissions than did patients who did not receive transplantation at any phase (91% and 48%, respectively; P=0.002). Major molecular responses were also more frequent in patients who underwent transplantation than in those who did not (81% and 45%, respectively; P=0.001).

Conclusion. Allogeneic transplantation should be recommended as a second-line rather than first-line treatment option in patients with chronic phase CML.

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superior to survival with an allograft. The case for upfront allografts in young patients with CML is now difficult to sustain.

Patients defined as high risk by a high Sokal score might also have been considered suitable candidates for an upfront allograft. In the study by Hehlmann et al. there was no significant difference in the rate of survival between high-risk patients with a related donor and those without. In the IRIS study, survival for imatinib-treated patients at high risk as measured by Sokal score was 81% at 4.5 years, clearly superior to the survival of 52% at five years for high-risk patients with a matched donor in the study by Hehlmann et al.[6]

Is the debate now over? There have been innovations in allografting that may reduce early mortality, including the use of reduced-intensity conditioning. These innovations might increase survival of allografted patients. An increase in the progression rate in long-term imatinib recipients or emerging serious long-term toxicity with imatinib might also change the situation; however, for the foreseeable future, allografts should be considered a second-line option in chronic-phase CML.

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