Re: Consolidation Therapy With Autologous Bone Marrow Transplantation in Adults With Acute Myeloid Leukemia: A Meta-analysis

The comprehensive meta-analysis reported by Nathan et al. (1) used comparable methods and produced results similar to those in our recent meta-analysis (2), which dealt with the same group of patients and clinical trials. Despite these similarities, the authors of the two studies reached different conclusions. Nathan et al. concluded that the data did not support the routine use of autologous bone marrow transplantation (ABMT) in adult acute myeloid leukemia patients in first complete remission. Indeed, Nathan et al. concluded that their data supported the use of non-myeloablative chemotherapy for patients who do not have a matched sibling donor because there was no statistically significant difference in overall survival between the treatment groups. By contrast, we believe the data do support the routine use of ABMT in adult acute myeloid leukemia patients in first complete remission. With the current increasing use of peripheral blood stem cells in ABMT, the development of new and safer transplant techniques, and the availability of supportive therapy, toxicity and treatment-related mortality is now substantially lower [i.e., 0%–6% (3)] compared with the high rate of 14% reported in 1998 by Cassileth et al. (4). As a result, we expect that disease-free survival and overall survival will be longer for patients who receive ABMT than for those who do not.

To test this assumption, we calculated the expected death rates for the ABMT arms of each of the six studies included in both meta-analyses (1,2). Our calculations were designed to assess three different simulations concerning treatment-related mortality: The first analysis assumed similar death rates in both groups (ABMT versus chemotherapy or no further treatment); the second and third simulations assumed death rates of 3% and 5%, respectively, for patients who received ABMT with peripheral blood stem cells (3). The number of expected deaths in this arm was calculated according to the following formula: (number of patients receiving ABMT) \( \times \) (assumed percentage of treatment-related mortality) + (actual number of patients who died in complete remission) \( \times \) (actual death rate of relapsed patients) + (actual number of patients

| Table 1. Ratio of death probabilities for autologous bone marrow transplantation versus chemotherapy or no further treatment according to different assumptions about treatment-related mortality rates* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Study           | Identical to other arm | 3%              | 5%              |                  |
|                 | RR (95% CI)       | RR (95% CI)     | RR (95% CI)     |                  |
| BGM 84          | 0.56 (0.27 to 1.14) | 0.56 (0.27 to 1.14) | 0.56 (0.27 to 1.14) |                  |
| BGMT 87         | 0.97 (0.6 to 1.56)   | 1.03 (0.65 to 1.63) | 1.03 (0.65 to 1.63) |                  |
| GOELAM          | 1.05 (0.71 to 1.53)   | 1.05 (0.71 to 1.53) | 1.08 (0.74 to 1.57) |                  |
| ECOG/SWOG/CALGB | 1.03 (0.78 to 1.34)   | 1.01 (0.77 to 1.32) | 1.05 (0.80 to 1.37) |                  |
| EORTC/GIMEMA    | 0.84 (0.62 to 1.12)   | 0.78 (0.57 to 1.05) | 0.79 (0.59 to 1.07) |                  |
| MRC AML 10      | 0.71 (0.55 to 0.93)   | 0.69 (0.52 to 0.90) | 0.71 (0.55 to 0.93) |                  |
| All studies     | 0.86 (0.75 to 0.99)   | 0.85 (0.77 to 0.94) | 0.86 (0.76 to 1.00) |                  |
| Phetetogeneity  | .273              | .187            | .176             |                  |

*ABMT = autologous bone marrow transplantation; RR = relative risk for death in autologous bone marrow transplantation arm divided by that in the chemotherapy or no further treatment arm; CI = confidence interval; BGM 84 = Bordeaux Grenoble Marseille 84; BGMT 87 = Bordeaux Grenoble Marseille Toulouse 87; GOELAM = Groupe Ouest Est Leucemies Aigues Myeloblastiques; ECOG/SWOG/CALGB = Eastern Cooperative Oncology Group/Southwestern Oncology Group/Cancer and Leukemia Group B; EORTC/GIMEMA = European Organization for Research and Treatment of Cancer/Gruppo Italiano Malattie Ematologiche Maligne dell’ Adulto; MRC AML 10 = Medical Research Council Acute Myeloid Leukemia Trial 10.
who died during relapse). We then calculated the relative risk (RR) and 95% confidence intervals (CIs) of death among patients in the ABMT arm compared with that among patients in the other treatment arm by dividing the new assumed death rate in the first arm by the actual death rate in the other treatment arm for each study. We used the Mantel-Haenszel test to perform a meta-analysis of the six studies for all three assumptions (5).

Table 1 presents the relative risk of death for the individual studies and for the overall meta-analysis according to the assumed treatment-related mortality rates. For all three assumptions, patients in the ABMT arm had a statistically significantly lower relative risk of death than patients in the other treatment arms. The lowest relative risk of death for all studies, 0.85 (95% confidence interval = 0.77 to 0.94), was found using an assumed treatment-related mortality rate of 3%.

To conclude, we believe that the continuous decline in treatment-related mortality following autologous peripheral stem cell transplantation will ultimately lead to an increase in disease-free survival rates and a statistically significant improvement in overall survival.

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RESPONSE

In their letter to the Journal, as well as in their meta-analysis (1), Levi et al. contend that a decline in the treatment-related mortality associated with the use of peripheral blood stem cells instead of bone marrow for autologous transplantation supports the routine use of autologous stem cell transplantation (ASCT) in adults with acute myeloid leukemia in first remission. Although we agree that this strategy warrants further study in a prospective, randomized clinical trial, we have several concerns about the assumptions that the authors have made in order to reach their conclusions.

First, the simulations presented by Levi et al. assume that improvements in supportive care and the development of safer transplant techniques have decreased treatment-related mortality among patients who receive an ASCT. The simulations do not account for improvements in survival as a result of better supportive care in patients who receive chemotherapy alone. Such a decrease in treatment-related mortality over time, for example, was observed among children who were treated with chemotherapy alone on the Tenth Medical Research Council Acute Myeloid Leukaemia Trial (MRC AML 10) (2). The authors’ supposition that treatment-related mortality has decreased only among transplant recipients biases their analysis in favor of ASCT. In our meta-analysis, we noted that the pooled treatment-related mortality among patients who were randomly assigned to receive chemotherapy (or no further treatment) was 4.4% (3). The authors’ assumption of a 3% treatment-related mortality in the ASCT arm of their second simulation suggests that ASCT results in a lower risk of treatment-related mortality than chemotherapy alone—a contention that is not supported by the available literature.

Second, the authors’ assertion that the treatment-related mortality among patients receiving ASCT is currently 0%–6% is based on data from patients who actually received ASCT (4). However, such an analysis by treatment received is biased in favor of ASCT. Patients who actually undergo transplantation will have better outcomes when compared with all patients randomly assigned to receive transplantation because some of the latter patients will relapse or die before receiving the procedure or will be too ill to proceed to transplantation. Therefore, an intent-to-treat analysis is more appropriate for comparing transplantation with chemotherapy than an analysis by treatment received. Both the original meta-analysis published by Levi et al. (1) and our meta-analysis (3) based calculations of survival on intent-to-treat analyses. In the absence of data from a randomized clinical trial, it is impossible to know whether a decrease in mortality among patients who receive peripheral blood stem cells is attributable to a true reduction in treatment-related mortality or, at least in part, to the use of an analysis of only patients who received the treatment.

Third, the formula used by Levi et al. to calculate the expected deaths in the ASCT arm is unconventional. We urge the authors to clarify their calculations and provide a reference for their approach.

Although we agree that the role of ASCT among patients in first remission of acute myeloid leukemia warrants further study, we caution against drawing conclusions by combining the results of previous randomized studies of autologous bone marrow transplantation with estimates of survival of ASCT derived from current single-arm studies.

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