Selected Summaries

Optimal Therapy for Acute Lymphoblastic Leukemia in Second Remission

[Borgniann A, Schmid H, Hartmann R, et al. Autologous bone-marrow transplants compared with chemotherapy for children with acute lymphoblastic leukemia in a second remission: A matched pair analysis. Lancet 1995, 346: 873-876.1

This multicentric trial (Berlin, Frankfurt and Muster) compared the treatment results for children who received combination chemotherapy (CT) with those who underwent autologous bone-marrow transplant (BMT), after second remission of acute lymphoblastic leukemia (ALL).

Out of the enrolled 889 patients (up to 18 yr age) with first relapse of ALL, 682 received conventional chemoradiotherapy while 207 underwent either autologous (n = 66) or allogenic (n = 141) BMT after remission induction with combination CT (BFM or COALL). Fifty two of the patients in the CT group, matched with those who underwent autologous BMT, received alternative courses of polychemotherapy (ALL-REZ-BFM; n=85) with supplemental radiotherapy at the end of intensive phase and late conventional maintenance therapy for 2 years. In the autologous BMT group, 15 received autologous BM previously purged with monoclonal antibodies or mafosfamide while 37 received unpurged marrow.

In the CT group, after a median follow up of 55 months from achieving second remission, the cumulative proportion of all patients receiving CT with event free survival (EFS) at 9 years was 0.32. Out of 52 children, 1 expired, while 19 (37%) were in clinical remission. In 32 patients who relapsed, the 9 year estimates for EFS were 0.20 for early (<6 months of cessation of front line therapy) versus 0.55 for late relapse.

In the autologous BMT group, after a median follow up of 46 months from second remission, EFS at 9 years was 0.26. Sixteen (31%) achieved clinical remission, 34 (65%) relapsed and 2 (4%) expired. The 9 year estimate for EFS were 0.17 and 0.41 for early and late relapses, respectively. The EFS rates for patients in CT of BMT were similar (p=0.035). Similarly, there was no statistically significant difference in the EFS in children with early (p=0.876) or late relapse (p=0.164) in the two treatment groups.

The authors thus concluded that there was no advantage of autologous bone marrow transplant over chemotherapy as post induction treatment for children with ALL in a second remission with regard to event free survival.

Comments

It is unclear how best to treat children with ALL who are in a second remission. The available options include allogenic BMT, continuation CT or autologous BMT. Conventional CT achieves complete remission rates of 90-100%(l) and EFS of 15-25%(2). Allogenic BMT results in EFS rates of 40-50% but, less than 25% of the patients have an HLA identical sibling(3). Children without a matched donor are the candidates for autologous BMT, which achieves EFS rates of 20-30%(4).

The quoted matched pair design study demonstrated no significant advantage of autologous BMT over CT for relapsed ALL. The lack of superiority of high dose marrow ablative chemotherapy followed by rescue with hemopoietic stem cell transplant (employed in BMT) over conventional continuation chemotherapy alone may be explained on the basis of either existence of tumor cells unresponsive to CT or due to reintroduction of malignancy by transplanted stem cells contaminated with tumerogenic cells(5). These tumor cells may grow even more rapidly in children, already immunocompromized due to conditioning high dose chemotherapy. Assuming equivalent control of leukemia with both methods, the choice of therapy becomes even more difficult. Although the duration of therapy is shorter with BMT as compared to CT, associated late sequelae because of high dose conditioning chemoradiotherapy dictate against it's preferential use(4). Recent research has focused on immunological approaches to disease eradication after autologous transplantation. Attempts have been made to recruit immune mechanisms after autologous BMT by administrating immuno-stimulatory cytokines (IL-2), but the results, so far, have been disappointing(5).

In the absence of a convincing evidence of superiority of autologous BMT over conventional CT, CT appears to be the best option for patients with late relapse and allogenic BMT for those with early relapse or high risk variants of ALL. However, the concept of autologous BMT for relapsed ALL should not be abandoned, but methods should be sought to complement autologous BMT by immuno-therapy, molecular biotherapy, chemotherapy or combination of these.

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