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Therapies to Acute Myelogenous Leukemia in JAPAN ADULT LEUKEMIA STUDY GROUP (JALSG)

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Background:

In 1987, JALSG was organized by fourteen institutions to establish the standard chemotherapy for leukemia in Japan and to contribute to improvement of leukemia chemotherapy. As of the end of 2003, 199 institutions are participating in JALSG. More than 200 AML patients are enrolling in JALSG AML trials every year. Six clinical trials for AML and three for APL have been conducted by JALSG. The results of five clinical trials for AML that have been completed were reviewed.

Patients and Methods:

In the AML87 study which started in 1987, 265 patients were randomly assigned to induction therapy with or without vincristine (VCR) and 4 courses or 12 courses of maintenance therapy. The results of induction and consolidation treatment with enocitabine (BHAC), a derivative of cytarabine developed in Japan, were compared with the results achieved with AraC in 326 assessable patients in the AML89 trial. The usefulness of etoposide (VP16) for induction therapy was examined in the AML92 trial. Since this study, APL patients have been treated by separate protocols using all-trans retinoic acid (ATRA). Six hundred and fifty-five non-APL patients and 196 APL patients entered this study. In the AML87, 89 and 92 trials, the doses of daunorubicin (DNR) for induction therapy were modulated based on the degree of myelosuppression in a response-oriented individualized (ROI) way, which has traditionally been common in Japan. ROI induction therapy and set therapy were compared in the AML95 trial. Four hundred and thirty eligible patients were assigned to either the ROI group or the set therapy group. The AML-97 trial had three aims; 1) Intensified

consolidation therapy without maintenance therapy was compared with conventional post remission therapy of the previous JALSG trials. 2) Remitted patients were stratified by risk factors identified by the previous JALSG trials. 3) Disease-free survival (DFS) rates of patients who were an intermediate or poor risk and had an HLA-matched sibling donor were compared with the DFS rates achieved in non-donor patients assigned to the chemotherapy group. Over four and half year period, 809 patients were enrolled in this trial.

Results:

In the AML87 trial, the addition of VCR unexpectedly reduced the CR rate significantly (84% to 70%, $P=0.007$) and also the group receiving VCR had a significantly worse event-free survival (EFS) ($P=0.0122$) due to the lower CR rate. Twelve courses of maintenance therapy yielded a better DFS than 4 courses. The AML 89 study showed that the use of BHAC in CR induction therapy and consolidation therapy resulted in poor CR (72% and 81% $P=0.035$) and EFS (23% and 35%, $P=0.0253$) compared with the use of AraC. The addition of VP16 to AML92 induction therapy was not beneficial for CR (77% and 75%, $P=0.925$) or DFS (25% and 35% $P=0.352$). The AML95 study showed that the results of set therapy were comparable to those of ROI therapy with regard to CR rate (81.9% and 79.4%) and DFS (50.2% and 49.6%). Induction therapy in the AML97 protocol, which consisted of a set treatment with idarubicin (IDR) and AraC, yielded a CR rate of 78.4%. The four year DFS rate after intensified consolidation therapy without maintenance treatment was comparable to that of JALSG conventional post remission treatment (36.5% and 34.2%). The JALSG

scoring system using risk factors that had been identified by the previous AML trials clearly stratified the patients into three risk groups. A comparison of DFS rate in allogeneic hematopoietic stem cell transplantation group with that in the chemotherapy group showed that superiority of the former was marginally significant and there was no significant difference in over-all survival between those two groups.

Discussion:

AML patients treated by JALSG protocols achieved a good CR rate of about 80%. However, four trials for AML intending to improve the CR rates were unsuccessful. In the AML97 trial, intensified consolidation therapies yielded a comparable DFS rate to those of the previous JALSG protocols consisting of three courses of consolidation and six courses of intensification/maintenance therapy. If the results of the AML87 and AML97 trials were taken into consideration, intensified post remission therapy might be essential for the improvement of DFS. In our next trial, AML201, DFS rate following high dose AraC which had been available in Japan since April 2000, will be compared with the DFS rate following AML97 consolidation therapy. Allogeneic hematopoietic transplantation may be the most intense post remission treatment, however, the high mortality rates might offset the relapse-free effect.