Benefit of intermediate-dose cytarabine-containing induction in molecular subgroups of acute myeloid leukemia

The outcome of acute myeloid leukemia (AML) is affected by disease characteristics as well as treatment regimens. In the CALGB8825 trial, patients with core binding factor (CBF)-positive leukemia benefited from consolidation with a high dose of cytarabine. More recently, high-dose daunorubicin (60-90 mg/m²) has become widely used. High-dose daunorubicin confers a favorable prognosis for patients with NPM1 mutations.

Intermediate-dose cytarabine did not increase the conventional-dose group and 43 in the intermediate-dose mutations (dose cytarabine groups, respectively; = 0.504). Intermediate-dose cytarabine did, however, produce better RFS and EFS rates and showed a marked tendency to improve the OS of patients with CEBPA dm in both univariate and multivariable analyses, as shown in Online Supplementary Table S2. Five-year RFS, EFS, and OS rates were 85%, 81%, and 88% in the intermediate-dose compared with 56%, 56%, and 68% in the conventional-dose group, respectively (Figure 1). In total, 13 of 75 (17%) patients with CEBPA dm AML underwent allogeneic transplantation in CR1, including five of 32 (16%) in the conventional-dose group and eight of 43 (19%) in the intermediate-dose group. To analyze results in the absence of any possible contributory effect of transplantation, patients were censored at the time of transplantation in CR1. Patients with CEBPA dm AML exposed to intermediate-dose cytarabine achieved an increase in 5-year RFS, censored at the date of transplantation, from 56% to 83% (hazard ratio [HR], 0.313; 95% confidence interval [95% CI]: 0.119-0.824; Wald = 0.019) (Online Supplementary Figure S3). Intermediate-dose cytarabine showed a tendency to improve RFS and OS in patients with favorable cytogenetics in CR1, including five of 32 (16%) patients with RUNX1-RUNX1T1 dm AML compared with 11 of 43 (26%) in the conventional-dose cytarabine group (Figure 1). The data indicated that the favorable RFS of patients with CEBPA dm AML depended on treatment assignment. After adjusting for the presence of FLT3-ITD and transplantation in CR1, the interaction between treatment assignment and CEBPA dm status still existed for RFS (P = 0.042), but not EFS (P = 0.184) or OS (P = 0.119). The hazard ratios for relapse or death of CEBPA dm AML compared with other types of AML were 0.298 (95% CI: 0.130-0.682; Wald = 0.004) in the intermediate-dose cytarabine group and 0.829 (95% CI: 0.473-1.453; Wald = 0.513) in the conventional-dose cytarabine group (Figure 1). The data indicated that favorable RFS of patients with CEBPA dm AML depended on treatment assignment. After adjusting for the presence of FLT3-ITD and transplantation in CR1, the interaction between treatment assignment and CEBPA dm status still existed for RFS (P = 0.042), but not for EFS (P = 0.215) or OS (P = 0.148). The OS and RFS rates of AML patients with CEBPA dm are approximately 54%-63% and 44%-48%, respectively.

However, relapsed patients with CEBPA dm have a favorable outcome after reinduction followed by allogeneic transplantation. Schlenk et al. proposed both strategies, allogeneic or autologous transplantation in CR1 versus intensive chemotherapy in CR1, and reinduction followed by allogeneic transplantation in the case of relapse. We demonstrated that CEBPA dm AML patients receiving intermediate-dose cytarabine had a remarkable increase in RFS as well as in RFS rates censored at the date of allogeneic transplantation. This indicated that more patients would not relapse and did not need transplantation after intermediate-dose cytarabine induction therapy.

Overall, there were 131 patients with RUNX1-RUNX1T1 in our cohort, including 60 in the conventional-dose group and 71 in the intermediate-dose group. Intermediate-dose cytarabine did not increase the complete remission rate in patients with RUNX1-RUNX1T1 compared to that in patients treated with conventional-dose cytarabine (97% and 93%; P = 0.528). However, intermediate-dose cytarabine produced better RFS and EFS and showed a marked tendency to improve OS in patients with RUNX1-RUNX1T1 in both univariate and multivariable analyses, as shown in Online Supplementary Table S2. The 5-year RFS, EFS, and OS rates in patients with RUNX1-RUNX1T1 AML were 72%, 70%, and 74% in the intermediate-dose cytarabine group compared to 56%, 52%, and 58% in the conventional-dose group, respectively (Figure 2). There was no interaction between
Figure 1. Patients with acute myeloid leukemia with CEBPA double mutations had more favorable outcomes only when treated with intermediate-dose cytarabine induction. (A) Relapse-free survival, (B) event-free survival, and (C) overall survival are shown for patients with CEBPA double mutations and other types of acute myeloid leukemia by receipt of intermediate-dose or conventional-dose cytarabine induction. AML: acute myeloid leukemia; HR: hazard ratio; 95% CI: 95% confidence interval.
Figure 2. Outcomes of patients with RUNX1-RUNX1T1 acute myeloid leukemia by treatment assignment. (A) Relapse-free survival, (B) event-free survival, and (C) overall survival. HR: hazard ratio; 95% CI: 95% confidence interval.
the treatment assignment and \textit{RUNXI-RUNXI}T1 status (RFS: \( P=0.300 \); EFS: \( P=0.383 \); OS: \( P=0.391 \)). All patients with \textit{CBFB-MYH11} AML achieved complete remission after both intermediate-dose and conventional-dose cytarabine. We were unable to determine the impact of intermediate-dose cytarabine in patients with \textit{CBFB-MYH11} AML since there were only 33 patients with \textit{CBFB-MYH11} in our cohort.

In this subgroup analysis of our trial, our data suggested that AML patients with \textit{RUNXI-RUNXI}T1 benefited from intermediate-dose cytarabine induction. Previous reports also indicated that a higher dose of cytarabine improved the outcome in patients with \textit{RUNXI-RUNXI}T1 AML.\textsuperscript{14,15} Hence, all these data suggest that an induction regimen with an intensified dose of cytarabine benefits patients with \textit{RUNXI-RUNXI}T1 AML.

There were a total of 89 patients with \textit{NPM1} mutations, regardless of \textit{FLT3-ITD} mutation status, in our cohort.

\textbf{Figure 3.} Outcomes of \textit{NPM1} and \textit{FLT3-ITD} mutant acute myeloid leukemia by treatment assignment. (A) Relapse-free survival, (B) event-free survival, and (C) overall survival of patients with \textit{NPM1} mutations. (D) Relapse-free survival, (E) event-free survival, and (F) overall survival of patients with \textit{FLT3-ITD} mutation. HR: hazard ratio; 95%CI: 95% confidence interval.
including 51 in the conventional-dose group and 38 in the intermediate-dose group. There were 66 patients with FLT3-ITD mutations, regardless of NPM1 mutations, including 35 in the conventional-dose group and 31 in the intermediate-dose group. Intermediate-dose cytarabine did not increase the complete remission rate or improve RFS, EFS, or OS compared to conventional-dose cytarabine in patients with NPM1 or FLT3-ITD mutations, as shown in Online Supplementary Table S2. In patients with NPM1 mutations, the 5-year RFS, EFS, and OS rates were 68%, 63%, and 70% in the intermediate-dose cytarabine group compared to 61%, 53%, and 65% (Figure 3A-C), respectively, in the conventional-dose group. In patients with FLT3-ITD mutations, the 5-year RFS, EFS, and OS rates were 68%, 48%, and 58% in the intermediate-dose cytarabine group compared to 50%, 34%, and 45% (Figure 3D-F), respectively, in the conventional-dose group. We then investigated the impact of intermediate-dose cytarabine in NPM1/FLT3-ITD, NPM1/FLT3-ITD, and NPM1–FLT3-ITD subgroups. Intermediate-dose cytarabine did not increase complete remission rate or improve RFS, EFS, or OS compared to conventional-dose cytarabine in all these subgroups, as shown in Online Supplementary Table S3.

Death rates within 30 days were similar in the intermediate- and conventional-dose cytarabine induction cohorts. There were no significant differences in RFS, OS, cumulative incidence of relapse or cumulative incidence of death in complete remission between the consolidation regimens even with longer follow-up (data not shown). With inclusion of the second randomization in multivariable analyses, the conclusions regarding outcomes depending on induction treatment were not modified by the second randomization, as shown in Online Supplementary Table S4, except that the OS in the intermediate cytogenetic-risk group was not significantly different, but with a trend, and no difference in EPS in the poor cytogenetic-risk group.

In this subgroup analysis with updated follow-up, we demonstrated that AML patients with CEBPAdm and RUNX1-RUNX1T1 might benefit from intermediate-dose cytarabine induction. AML patients with CEBPAdm had a more favorable RFS than others only when treated with intermediate-dose cytarabine induction. Intermediate-dose cytarabine did not, however, improve outcomes in AML patients with NPM1 or FLT3-ITD mutations. Luskin et al. suggested that anthracycline dose intensification conferred a favorable prognosis for AML patients with NPM1 mutations. These data indicate that AML patients with different mutations might benefit from intensified doses of different drugs. Recently, novel drugs, such as gemtuzumab ozogamicin, FLT3 inhibitors and so on, are being used in clinical practice. Prospective trials would be needed to confirm the benefit of induction with intermediate-dose cytarabine, especially when novel drugs are used.

References