Ⅲ. 研究成果の刊行に関する一覧表

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Ⅳ. 代表的論文

Excess treatment reduction including anthracyclines results in higher incidence of relapse in core binding factor acute myeloid leukemia in children

Patients with core binding factor acute myeloid leukemia (CBF-AML) with translocation (8;21)(q22;q22) [t(8;21)] and inversion of chromosome 16(p13q22.1), or its variant t(16;16)(p13;q22.1) [inv(16)], generally have favorable outcomes, as the probabilities of event-free survival (pEFS) and overall survival (pOS) were around 80% and 90%, respectively, in recent clinical trials of pediatric AML.(1-3) It is well recognized that intensive post-remission chemotherapy with high-dose cytarabine (HDCA) has contributed to the improved survival of CBF-AML.(4, 5) Although there is evidence that high doses of anthracyclines—another key component of AML chemotherapy—improves the outcomes in children and adults with AML,(6, 7) its effects in CBF-AML are not well established, unlike those of HDCA. Moreover, higher doses of anthracyclines are associated with increased risk of late cardiotoxicity, which could occur at a lower cumulative dose (e.g., >300 mg/m^2) in children than in adults.(8) Therefore, it needs to be evaluated whether intensive use of HDCA could compensate for a reduction in the other treatment components, especially the cumulative anthracycline dose, by maintaining high pEFS and pOS, and reducing the risk of late complications such as anthracycline-induced cardiotoxicity in particular.

Following the excellent outcomes of the study AML99 conducted by the Japanese Childhood AML Cooperative Study Group,(2) a nationwide multicenter study (termed the AML-05 study) was conducted by a new national study group established in 2003, the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), to optimize risk-stratified therapies for childhood AML. This trial is registered with UMIN

Clinical Trials Registry (UMIN-CTR, URL: http://www.umin.ac.jp/ctr/index.htm), number UMIN000000511. The main objective for the low-risk (LR) group, which included most of the patients with CBF-AML, was to evaluate the efficacy and safety of a chemotherapy regimen comprising a reduced cumulative dose of anthracyclines and etoposide. Between November 2006 and December 2010, 485 consecutive patients aged <18 years old with suspected AML treated at 118 centers and hospitals in Japan were registered in AML-05. Patients with acute promyelocytic leukemia, Down syndrome, secondary AML, myeloid/natural killer cell leukemia, and myeloid sarcoma were not eligible. AML was diagnosed using the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues (3rd edition).(9) Among the 443 eligible patients, 122 (27.5%) presented with t(8;21) and 32 (7.2%) with inv(16). Their data were compared with historical controls consisted of 89 CBF-AML children in the previous AML99 study. Written informed consent, provided according to the Declaration of Helsinki, was obtained from the guardians of the patients. All aspects of the study were approved by the institutional review boards at all participating institutions. The therapeutic regimens used in the AML-05 and AML99 studies are presented in Figure 1. Several changes were introduced in AML-05 compared with AML99. First, the initial induction course was unified to the ECM (consisted of etoposide, cytarabine, and mitoxantrone, with triple intrathecal chemotherapy). Second, the risk groups were redefined as follows: all of the CBF-AML patients with good initial responses after the initial induction course were included in the LR group, without considering the patient's age and leukocyte (WBC) count, while patients with Fms-like tyrosine kinase 3 internal tandem duplications (*FLT3*-ITD) were included in the high-risk (HR) group. We also reduced the total number of chemotherapy courses from six to five. Finally, the indication for

allogeneic hematopoietic stem cell transplantation (HSCT) was limited to the HR group. Therefore, most of the patients with CBF-AML [87.6% (135/154)] were included in the LR group and received five courses of intensive chemotherapy, of which four included HDCA, but the cumulative anthracycline dose was limited to 225 mg/m^2 daunorubicin-equivalents (the cumulative anthracycline dose was calculated relative to the amount of daunorubicin using a conversion rate of 5:1 for daunorubicin to mitoxantrone/idarubicin). A small subset of patients with HR CBF-AML [5.1% (8/154)], those with residual leukemia in any site after the initial induction course or those with *FLT3*-ITD, received HSCT at the first remission (1CR).

The characteristics of patients at diagnosis in the AML-05 and AML99 studies are reported in Table 1. Sex, age, and WBC count were comparable in both studies, but the distribution of French–American–British classification categories differed. This is because the patients were diagnosed according to the WHO classification (3rd edition) in AML-05, which included patients with low bone marrow blast percentages of 20% to 30% who are classified as having refractory anemia with excess blasts in transformation (RAEB-T). Additionally, while *FLT3*-ITD status was prospectively examined in all patients in AML-05, it was examined retrospectively in approximately 60% of patients in AML99, although the difference was not significant.

Induction responses in children with CBF-AML were not significantly different between AML-05 and AML99. Among the 147 CBF-AML patients who achieved 1CR in AML-05, 135 patients were assigned to the LR group, while the other 8 patients were assigned to the HR group and underwent HSCT at 1CR. Four patients with CBF-AML discontinued the study because of incorrect risk assignment in three and the guardian's decision in one. Among 87 CBF-AML patients who achieved 1CR in the AML99 study, 77

were assigned to the LR group, 7 to the intermediate-risk group, and 3 to the HR group.

The three year pEFS, pOS, and cumulative incidence of relapse (CIR) for all CBF-AML, t(8;21), inv(16), and CBF-AML without unfavorable factors [t(8;21) and WBC>50 000/μL, RAEB-T, and *FLT3*-ITD] in AML-05 and AML99 are reported in Table 1. The median follow-up was 3.08 years (range, 0.04 to 5.28 years) and 4.78 years (range, 0.17 to 6.08 years) in AML-05 and AML99, respectively. Among all CBF-AML patients, the CIR was significantly higher in AML-05 [29.9% (95% CI, 23.1% to 38.1%) vs. 17.1% (95% CI, 10.7% to 26.8%); $P = 0.041$], although relapsed patients are likely to be salvaged by variable second-line chemotherapy followed by HSCT (37/38 relapsed LR patients received HSCT after the first relapse). The three-year pEFS, pOS, and CIR for RAEB-T patients were 84.0% (95%CI, 62.8% to 93.6%), 85.3% (60.6% to 95.1%), and 16.0% (6.3% to 37.1%), respectively, which were comparable to the other CBF-AML patients in AML-05. Predictive factors for pEFS, treatment (AML-05 vs. AML99), age at initial diagnosis (≥10 years vs. <10 years), sex (female vs. male), WBC count at initial diagnosis (≥50 000/μL vs. <50 000/μL), and cytogenetics [inv(16) vs.t(8;21)], were evaluated by univariate and multivariate analyses (patients receiving HSCT at 1CR were excluded). In Cox regression analysis, the adjusted hazard ratio for pEFS was significantly worse for patients treated in AML-05 than in patients treated in AML99 [hazard ratio, 2.088 (95% CI, 1.125 to 3.875); $P = 0.020$] and was significantly better in patients age ≥10 years at diagnosis compared with those aged <10 years at diagnosis [hazard ratio, 0.494 (95% CI, 0.271 to 0.899); $P = 0.021$].

Thus, our attempt to reduce the cumulative dose of anthracyclines to <300 mg/m^2 for CBF-AML patients in AML-05, while maintaining the treatment intensity by using intensive HDAC in 4/5 treatment courses, resulted in decrease of pEFS by

approximately 10% because of the higher cumulative incidence of relapse. Interestingly, this effect was prominent in patients aged <10 years at diagnosis, as the pEFS in children aged <10 years vs. ≥10 years was 57.4% vs. 82.6% in AML-05, while it was 82.0% vs. 82.0% in AML99. Of course, it is not only the cumulative dose of anthracycline, but also the number of treatment courses and the cumulative dose of etoposide that were changed in AML-05 relative to those in AML99 (Fig. 1). However, high pEFS and pOS for CBF-AML were achieved with four to five treatment courses and a similar dose of etoposide in other studies. (1, 3, 10) In addition, decrease in pEFS was not observed for non CBF-AML cases in AML-05 with similar changes in number of treatment courses and cumulative etoposide dose while cumulative anthracycline dose was not changed from AML99 (to be reported in detail in a separate manuscript). Considering these facts, it is likely that the reduced cumulative anthracycline dose was responsible for the higher CIR in the current study than in AML99. Despite of higher CIR among CBF-AML patients in AML-05, pOS was identical to that in AML99. However, the overall transplantation rate was higher in AML-05 than in AML99 [33% (51/154) vs. 19% (17/89)] because most of the patients who experienced relapse underwent HSCT as second-line treatment, which is unlikely to be accepted by patients with CBF-AML. Therefore, we re-introduced the AML99-based post-remission chemotherapeutic regimen for CBF-AML patients included in our subsequent study, AML-12. Nevertheless, the finding that nearly 70% of the CBF-AML patients were cured with very low doses of anthracyclines suggests that other underlying biological factors, such as *KIT* mutations,(11) should be identified for future stratification of CBF-AML in children.

In conclusion, the results of this study indicate that caution is needed

when reducing the cumulative anthracycline dose to <300 mg/m^2 as part of conventional combination chemotherapy for treating CBF-AML in children. Several novel agents, including gemtuzumab ozogamicin, had clinical benefits for CBF-AML patients as part of induction chemotherapy.(12, 13) The introduction of such agents into combination chemotherapy might be required before considering further reduction of the anthracycline dose.

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DISCLOSURE OF CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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