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Perspective

Current status and future directions of clinical research and practice in adult acute lymphoblastic leukemia patients in Korea

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PHILADELPHIA-NEGATIVE ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

The Adult Acute Lymphoblastic Leukemia Working Party of the Korean Society of Hematology (KAALLWP) conducted a phase II clinical study [1] from 2005 to 2010 on adult patients with Philadelphia-negative (Ph-neg) acute lymphoblastic leukemia (ALL), based on a four-drug induction chemotherapy regimen consisting of daunorubicin (DNR), vincristine, prednisone, and L-asparaginase. Based on previous studies showing promising results for dose-intensified DNR delivered during induction treatment for adult ALL [1, 2], the KAALLWP study evaluated whether the addition of higher doses of DNR early during the course of frontline therapy (during the induction cycle) could improve the prognosis (KALLA 0501). The results of our current study, which enrolled 191 patients, indicate a CR rate of 88.5% and a 3-year overall survival (OS) and relapse-free survival (RFS) rate of 46.1% and 43.1%, respectively. In addition, dose-escalated DNR as induction chemotherapy showed tolerable toxicities and a CR rate comparable to those of previous studies. However, in terms of long-term survival, this treatment regimen showed disappointing results, suggesting the need for stronger post-remission therapies in the future protocol.

Asparaginase is one of the drugs of the standard treatment for ALL and is used for remission induction and post-remission courses in the majority of pediatric-inspired adult treatment protocols [3, 4]. Recently, minimal residual disease (MRD) has been conclusively demonstrated as an independent prognostic factor in both childhood and adult ALL [5]. MRD is used in several clinical trials for risk assignment and to guide overall clinical management. However, at present, it is difficult to carry out MRD-based treatment strategies in adult ALL patients in Korea because of standardization of methods and difficulty in centralization of assessment.

The KAALLWP plans to perform a new multicenter study for adult ALL (KALLA 1406) that will adopt the pediatric concept of delayed intensification and integrate higher doses of non-myelotoxic agents, such as L-asparaginase and corticosteroid, especially in post-remission treatment courses. MRD-based risk stratification is currently difficult to perform across all centers in Korea due to the difficulty of standardization and sample delivery. Therefore, risk stratification is generally based on patient age, with the aim of excluding adolescents and young adults (<25 years) who could benefit from dose-intensified non-myelotoxic agents without allogeneic hematopoietic cell transplantation (alloHCT), and older (≥55 years) and/or frail patients, who could avoid treatment-related mortality with dose-reduced

regimens. The proposed study by the KAALLWP will be a pilot study to evaluate the clinical significance of MRD levels at designated time points on long-term outcome in order to provide a basis for MRD-based strategies.

PHILADELPHIA-POSITIVE ADULT ALL

The treatment paradigm for Philadelphia-positive (Ph-pos) ALL changed dramatically with the introduction of imatinib. However, new strategies are needed to improve the outcomes of Ph-pos ALL patients. First, further investigations are warranted into whether the administration of next-generation TKIs can improve patient outcome. The KAALLWP has performed two prospective trials for newly diagnosed Ph-pos ALL patients, one with imatinib (KALLA0502) and the other with nilotinib (KALLA0503). Combinations of nilotinib with cytotoxic agents during induction/consolidation followed by alloHCT achieved a 2-year RFS of 74% and a 2-year OS of 70%, which were superior to those with imatinib [6]. More specifically, patients who achieved MRD-negativity at 3 months after hematologic CR without alloHCT showed comparable outcomes to subjects with alloHCT, which suggests that alloHCT may not be necessary for patients who achieve deep molecular response with next-generation TKIs. The combination of dasatinib, another next-generation TKI, with corticosteroid achieved a hematologic CR rate of 100% among those who were not eligible for alloHCT [7]. These results suggest that the introduction of next-generation TKIs as a first-line agent may improve outcomes with feasible adverse effects in Ph-pos ALL patients. However, proving the superiority of next-generation TKIs for the treatment of adult ALL in large prospective controlled trials will be difficult due to the rarity of the disease. Currently, the use of next-generation TKIs such as nilotinib and dasatinib as first-line agents has not been approved by the KFDA or the Korean Health Insurance Program (KHIP); further evidence followed by a verification process is warranted to show possible improved outcome.

The next step will be to improve MRD monitoring. To this end, real-time quantitative (RQ)-PCR to identify BCR-ABL may aid in MRD monitoring. Unlike the situation in chronic myeloid leukemia, the standardization of *BCR-ABL* RQ-PCR and an optimal method to monitor MRD have not been established for ALL. Fortunately, *BCR-ABL* RQ-PCR will become reimbursable by the KHIP as of July 2014, making the early detection of molecular relapse and the prevention of overt hematologic relapse with early TKI administration feasible. Finally, new TKIs such as bosutinib should be considered, especially for patients who fail to re-achieve MRD negativity with second-line TKIs and progress to overt hematologic relapse. These new agents are currently under evaluation by various study groups, but local studies are needed to adopt these agents in Korea.

NEW TARGETED AGENTS FOR ALL

The clinical significance of CD20 expression has been evaluated in previous studies, and we are currently performing a prospective phase-2 study of combining rituximab with modified VPD+L-asparaginase or imatinib for newly diagnosed CD20-positive ALL (KALLA0504). The availability of effective agents for relapsed/refractory ALL is limited. Targeted agents, such as inotuzumab ozogamycin, and blinatumomab, are under investigation at various stages of clinical development, and new cytotoxic agents such as nelarabine for T-ALL are also being considered for clinical use. Nelarabine is currently available under a named patient supply program. In addition, chimeric antigen receptor-engineered T-cell (CAR T-cell) therapy is currently considered for patients with relapsed/refractory lymphoid malignancies. This patient-origin engineered cell therapy targeting common cell surface antigens of ALL such as CD19 or CD22 showed a hematologic response of more than 80% in phase I/II studies, and a number of large-scale studies are currently underway.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR ADULT ALL

Recent studies have emphasized the importance of alloHCT for adult ALL [8]. Many investigators agree that alloHCT is inevitable for patients with Ph-pos ALL and is highly recommended for those who are eligible for alloHCT in cases of Ph-neg ALL. However, the probability of finding a match in a sibling or unrelated donor is around 50–70%; therefore, alloHCT from third-party donors should be considered for those without a suitable donor. Other approaches such as a cord blood stem cell harvesting are currently available in Korea. In addition, alloHCT from haploidentical familial donors or partially mismatched donors can achieve comparable outcomes [9]. Further consideration of these alternative donor types should be made based on phase-2 study results, especially because ALL is a disease of young adults and has a potentially high cure rate.

CONCLUSION

In contrast to pediatric ALL, the prognosis of adult ALL is unsatisfactory. Many prospective studies on ALL have been performed worldwide, including three prospective multicenter studies and an ongoing study in Korea based on the 'modified VPDL' backbone protocol. Based on the results of our previous prospective studies, our study group developed new treatment protocols termed 'KALLA' (Korean ALL protocol for Adults)-'KALLA1406' for Ph-neg, 'KALLA1407' for Ph-pos ALL, and 'KALLA1408' for alloHCT with reduced-intensity conditioning, which act as guidelines for the treatment and reimbursement of adult ALL. This guideline describes backbone protocols for future

prospective multicenter studies, and we also prepared a fair rule for the decision of authorships. We hope that these guidelines will help hematologists in making treatment decisions in their clinical practice and encourage investigators to participate in multicenter studies to generate new evidence and standards for the treatment of adult ALL in Korea.

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