Editorial Commentary

Radiation-free conditioning in acute lymphoblastic leukemia: is it time?

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Comment on: Zhang H, Fan Z, Huang F, *et al.* Busulfan Plus Cyclophosphamide Versus Total Body Irradiation Plus Cyclophosphamide for Adults Acute B Lymphoblastic Leukemia: An Open-Label, Multicenter, Phase III Trial. J Clin Oncol 2023;41:343-53.

Keywords: Acute lymphoblastic leukemia (ALL); total body irradiation (TBI); allogeneic transplantation; myeloablative conditioning (MAC)

Submitted Oct 04, 2023. Accepted for publication Dec 18, 2023. Published online Feb 02, 2024.
doi: 10.21037/cco-23-115
View this article at: https://dx.doi.org/10.21037/cco-23-115

B-cell acute lymphoblastic leukemia (ALL) accounts for 11% of all newly diagnosed acute leukemia cases in both children and adults. Treatment outcomes in B-cell ALL are affected by numerous factors, and survival rates are generally higher in children compared to adults. In the last few years, the therapeutic landscape of B-cell ALL has evolved substantially with the approval of bispecific T-cell engagers such as blinatumomab, antibody-drug conjugates such as inotuzumab ozogamicin and chimeric antigen receptor (CAR) T-cell therapy. Still, post-remission therapy for adults with ALL has traditionally involved allogeneic hematopoietic stem cell transplantation (allo-HSCT), particularly for high-risk features such as Philadelphia chromosome-positive disease, advanced age, high-risk cytogenetic abnormalities, and measurable residual disease (MRD) positivity post-induction (1-4). Total body irradiation (TBI)-based myeloablative conditioning (MAC) is preferred in eligible patients with ALL, and it is usually combined with cyclophosphamide (Cy). A large analysis published by the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) reported improving outcomes of patients with B-cell ALL over the years, particularly with the use of TBI-based, as compared to chemotherapy-based, conditioning regimens (5). It was hypothesized that TBI may have a better central nervous system (CNS) impact compared to chemotherapy alone which has limited CNS penetration. Nonetheless, TBI is associated with long-term adverse effects, including cataracts, cardiopulmonary toxicity, secondary malignant neoplasms, and other adverse effects (6). Therefore, there is a growing emphasis on exploring alternative regimens that offer the same efficacy, yet with lower toxicity.

In this open-label, multicenter, phase III randomized, non-inferiority trial published in the *Journal of Clinical Oncology*, Zhang *et al.* compared TBI-based and chemotherapy-based myeloablative regimens in adolescent and adults with B-cell ALL undergoing allo-HSCT, from fully matched sibling or unrelated donor, in first complete remission (CR1) (3). They included patients with only standard risk B-cell ALL between the ages of 14 and 65 years. In the TBI arm, patients received TBI 9 Gy, fractionated into 4.5 Gy on days 5 and 4, combined with Cy 60 mg/kg on days 3 and 2 (TBICy). In the chemotherapy arm, patients received busulfan (Bu) 0.8 mg/kg four times per day from days 7 to 4 and Cy 60 mg/kg on days 3 and 2 (BuCy). The primary endpoint of the study was 2-year overall survival (OS). The population consisted of 550 eligible patients, of whom 275 (50%) were randomized to the BuCy arm, and 275 (50%) were randomized to the TBICy arm. The 2-year OS rates were 76.6% and 79.4% in the BuCy and TBICy, respectively (P=0.457). The 2-year relapse incidence was 20.2% and 18.4% in the BuCy and TBICy arms, respectively (P=0.616). Extramedullary and CNS relapses were reported in both groups (BuCy 13 *vs.* TBICy 9 and BuCy 8 *vs.* TBICy 5, respectively). There

were no differences seen in the incidence of acute or chronic graft *vs.* host disease between the two groups. In the multivariable analysis, the conditioning regimen did not impact any of the outcomes, including OS (P=0.896), disease-free survival (DFS) (P=0.955), relapse (P=0.794), and non-relapse mortality (NRM) (P=0.840). The rates of early ≥ grade 3 toxicity were similar between groups and there were no differences seen in the late effects between the two regimens. In summary, this pivotal trial demonstrates equivalent outcomes when comparing chemotherapy-based *vs.* TBI-based MAC regimens in patients with standard-risk B-cell ALL.

Until now, the optimal myeloablative dosing of TBI for allo-HSCT in B-cell ALL remains debatable (7). As correctly stated by the investigators, the TBI dose used in this trial (9 Gy, fractionated into 4.5 Gy for 2 days) is lower than that used in most previous TBI-based studies, and may, therefore, be suboptimal (3). In fact, the antileukemic effect of TBI is dose-dependent and the highest tolerable dose should be used to achieve the desired effect (8). To date, there is no randomized trial that evaluates the optimal TBI dosage in B-cell ALL, and the current evidence is mainly based on the results from retrospective or registry studies. Initial efforts to decrease the dose of TBI in pediatric patients used TBI 9 Gy along with fludarabine and melphalan which resulted in decreased pulmonary toxicity without significantly affecting relapse (9). Additionally, retrospective cohorts of mixed acute leukemia patients showed worse outcomes in patients receiving TBI doses higher than 12 Gy as well as numerical survival advantage for low-dose TBI, although it did not reach statistical significance in the ALL subgroups (10,11). In an EBMT registry study, a lower dose of TBI (8 Gy) lead to similar outcomes compared to higher TBI dose (12 Gy) for patients with B-cell ALL receiving allo-HSCT in first remission. However, patients in the 12 Gy arm were much younger than those in the 8 Gy arm (40 *vs.* 56 years) and TBI was combined with fludarabine, instead of Cy (12). Nonetheless, these findings do provide some level of support to the selected dose in the TBI arm used by Zhang and colleagues.

Radiation-free conditioning regimens have also emerged as an alternative to TBI aiming at mitigating the long-term adverse effects of TBI. Initial efforts using Bu-based MAC regimen in pediatric ALL in second complete remission (CR2) did not demonstrate superiority over TBI-based regimens (13). Contrarily, trials showed improved outcomes using BuCy MAC in acute myeloid leukemia, as evidenced by improved NRM, and consistently favorable outcomes after 20 years of follow-up, along with lower rates of secondary neoplasm (14,15). Subsequent renewed efforts in ALL from developing countries showed that chemotherapy-only MAC regimens had comparable outcomes to TBI-based MAC in pediatric and adult patients (16,17). Yet, these findings appear to be limited to B-cell ALL as a registry-based study in T-cell ALL (T-ALL) patients showed superiority of TBI-based regimens (18). The choice of the experimental arm in the study by Zhang *et al.* was based on the improved pharmacokinetics of intravenous (IV) Bu compared to oral Bu (3). In a registry-based Japanese study, IV Bu combined with Cy was superior to oral BuCy and comparable to TBICy ≥8 Gy (fractionated) (19). Interestingly, a randomized phase III trial comparing TBI-based *vs.* either Bu- or Treosulfan-based regimen in pediatric ALL patients with a fully matched related or unrelated donor in CR1 and CR2 was terminated prematurely due to worse OS in the chemotherapy-only arm. Importantly, the study included more patients with T-ALL and high-risk disease including, high rates of pre-transplant MRD positivity and early relapse ALL. These findings raise the hypothesis that these patients might derive greater benefit from TBI (20). There is currently an ongoing phase 2 randomized study in the United Kingdom evaluating low-dose TBI-based (8 Gy) to a chemotherapy-based conditioning regimen in ALL (NCT03821610). Another trial evaluating radiation-free to TBI-based (12 Gy) MAC regimens, in pediatric patients with ALL, was terminated due to poor accrual (NCT00002961).

Notably, baseline CNS involvement information was not provided in this article where TBI would specifically lead to improved outcomes (3). The study reported a similar incidence of relapse in both groups. Although a low number of CNS relapse were reported, longer follow-up is needed to draw definitive conclusion regarding the equivalence of chemotherapy- and TBI-based MAC in that regard. Contrarily, in a large EBMT study, TBI-based regimen was associated with lower incidence of relapse (21). In the subgroup of patients with CNS disease, this translated into an improved leukemia-free survival (LFS) and OS. Thiotepa, an alkylating agent known for its ability to cross the blood-brain barrier and proven efficacy in primary and secondary CNS lymphoma, gained increasing interest in ALL (22). It may be used as an alternative to TBI in MAC ALL as suggested by the retrospective registry analysis of the EBMT (22).

Zhang *et al.* reported a similar outcome pertaining to pre-transplant MRD positivity and choice of conditioning

regimen. However, the number of patients with MRD positive disease at the time of transplant was small in both groups and therefore may not be able to show a difference in TBI *vs.* non-TBI strategies to overcome this adverse prognostic marker. Pre-transplant MRD status has clearly emerged as an important prognostic factor, with retrospective studies showing that MRD-positive patients might derive greater benefit from TBI-based MAC regimens in a mixed cohort of ALL patients (23). At the same time, the role of transplant in early MRD negative patients with ALL is also being further investigated. In the Philadelphia chromosome positive cohort, when stratified by similar MRD status, MAC and reduced intensity regimens performed equally (24). Furthermore, the additive benefit of allo-HSCT in patients with Philadelphia chromosome positive B-cell ALL who achieve deep molecular remission at 3 months after chemotherapy plus tyrosine kinase inhibitor, is questionable (4). The current study had only standard-risk B-cell ALL patients with the majority having achieved MRD negativity at the time of transplant. Further data regarding the role of TBI in high-risk disease as well as more MRD positive cases is required to facilitate data interpretation. Additionally, haploidentical transplants remain an understudied setting in this modality, especially given its incremental use, with a large registry-based study showing persistent superiority of TBI-based regimens in this setting (2).

As aforementioned, there is a pressing need for alternative regimens, given the known long-term morbidity and mortality from TBI (7). Efforts to minimize the toxicity associated with TBI have included administering it as either total marrow irradiation (TMI) or total marrow and lymphoid irradiation (TMLI). TMI/TMLI are considered to be organ sparing, with the main focus of irradiation being the bone marrow, lymph nodes, and spleen. In certain circumstances, the brain and testes can be targeted with TMI/TMLI. Critical organs, particularly the lungs, are thought to be spared with TMI/TMLI, without compromising efficacy. Several studies are ongoing to evaluate the efficacy and safety of TMI/TMLI in both adults and children (25,26). Despite its documented efficacy in lymphoid leukemias over decades, efforts to reduce the dose of TBI and transition to chemotherapy-based regimens yielded mixed results (27). This study by Zhang *et al.* showed the noninferiority of MAC BuCy compared to TBICy 9 Gy in patients with standard-risk B-cell ALL (3). However, generalizing these results to higher doses of TBI remains a pertinent clinical question, especially in the context of high-risk disease either based on cytogenetics or MRD positivity. Yet, it sets the ground for future prospective trials aimed at evaluating novel radiation-free conditioning regimens and perhaps incorporating maintenance strategy as a means to mitigate relapse, particularly, CNS relapse.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Chinese Clinical Oncology*. The article has undergone external peer review.

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-115/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-115/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Espinoza-Gutarra M, Mohty R, Jamy O. Radiation-free conditioning in acute lymphoblastic leukemia: is it time? Chin Clin Oncol 2024;13(2):29. doi: 10.21037/cco-23-115