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Commentary

Total Body Irradiation–Based versus Chemotherapy-Based Myeloablative Conditioning for Allogeneic Hematopoietic Cell Transplant

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THE QUESTION

Which is better, myeloablative chemotherapy–based conditioning or total body irradiation (TBI)-based conditioning for younger (<60 years) and medically fit patients with hematologic malignancies in preparation for allogeneic hematopoietic cell transplant (HCT)? For this recurring question, why has a universally accepted answer been elusive despite more than 30 years of mainly multicenter, retrospective analyses and a handful of prospective trials? Let us review the relevant data, beginning with observational studies.

Multicenter Retrospective Analyses of Chemotherapy-Based versus TBI-based Regimens in Myeloid and Other Hematologic Malignancies

A 2018 observational, retrospective, single-center analysis from colleagues in Boston addressed the following question: Is fludarabine/busulfan (FLU/BU) or cyclophosphamide (CY)/TBI conditioning optimal for allogeneic HCT [1]? We do not believe they succeeded in definitively answering the question. The authors compared outcomes in 229 patients given CY/TBI conditioning with 158 patients given FLU/BU conditioning before allogeneic HCT. Because of its retrospective nature, this study was fraught with both uncontrolled and unknown variables, including a variety of hematologic malignancies for which HCT was carried out, some of which were preferentially directed to 1 regimen. For example, only 6 patients (3.8%) with acute lymphoblastic leukemia (ALL) received FLU/BU yet 58 (25%) received CY/TBI. In addition, patients received grafts from related and unrelated 8/8 and 7/8 HLA antigen-matched donors; marrow or peripheral blood as graft source; a variety of graft-versus-host disease (GVHD) prophylactic regimens; at least 2 TBI doses, 1200 and 1400 cGy, respectively, but unknown TBI dose rate, unknown lung shielding, and unknown patient numbers per TBI dose and schedules and no explanation why 1 TBI dose was chosen over the other; lack of information on why some patients received a TBI-based regimen and others FLU/BU; and why 35 additional patients, not included in the analysis, were conditioned with a BU/CY regimen. The authors adjusted for imbalances, and after doing so they concluded the results suggested that patients given CY/TBI experienced a higher nonrelapse mortality (NRM) and worse overall survival (OS) and progression-free survival compared with patients conditioned with FLU/BU.

Have other studies comparing TBI-based with chemotherapy-based conditioning regimens concurred with these conclusions? Results have been conflicting, both those derived from observational studies and prospective clinical trials (including some trials where different BU-based regimens were compared with each other). It is worthwhile to review these results and consider the evidence.

A large, retrospective, nonrandomized European Society for Blood and Marrow Transplantation (EBMT) registry analysis compared BU/CY with CY/TBI conditioning among 1659 patients transplanted for acute myeloid leukemia (AML) in first or second remission [2]. Donors were HLA-identical siblings. Both marrow (~30%) and peripheral blood (~70%) served as graft source. TBI doses ranged from 750 to 1440 cGy with unknown dose rates and schedules. Median follow-up was longer for CY/TBI-treated patients (33 versus 20 months). Most patients received methotrexate/cyclosporine (MTX/CSP) for GVHD prophylaxis, but other prophylaxis regimens were also used including antithymocyte globulin (ATG). After adjustment, the authors found less acute GVHD and less chronic GVHD, a higher rate of relapse (unadjusted 2-year estimates of 26% versus 21%), and comparable NRM (12% versus 15%) in the BU/CY arm as well as comparable 2-year leukemia-free

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survival (unadjusted 2-year estimates of 61% versus 64%) and OS (unadjusted 2-year estimates of 68% versus 69%) among patients in the 2 treatment arms [2].

A multicenter cohort study from the Center for International Blood and Marrow Transplant Research (CIBMTR) compared TBI-based regimens (CY/TBI or etoposide [VP16]/TBI) with those containing BU (either BU/CY or FLU/BU) in 1483 patients with AML, chronic myeloid leukemia (CML), and myelodysplastic syndrome (MDS) at various disease stages [3]. TBI doses ranged from 550 to 1440 cGy, given either in fractions or as a single dose with information on dose rates or lung shielding not provided. Donors of marrow or peripheral blood–derived hematopoietic cells (PBSCs) included HLA-matched related and unrelated individuals and HLA-mismatched individuals. Patients received a variety of GVHD prophylaxis regimens, and a number of patients were given ATG or Campath as part of the conditioning regimen (14% of TBI-treated versus 29% of BU-treated patients). They found that 2-year OS was better for patients given BU-based regimens (56% versus 48%), with comparable rates of relapse (34% versus 39%) and NRM (18% versus 19%) [3]. Of note, there were no statistically significant differences in outcomes between FLU/BU- and BU/CY-conditioned patients.

Another retrospective, multicenter CIBMTR report analyzed data from 1230 patients with AML in first remission who were conditioned with either CY/TBI (n = 586 at 117 centers) or BU/CY (n = 640) [4]. Multiple TBI regimens were used with total doses ranging from 550 to 1500 cGy, given either as a single dose or in fractions, but no further information was given. BU was given either orally (n = 408 at 86 centers) or intravenously (n = 236 at 80 centers). Again, as in the study by Bredesen et al. [3], donors were either related or unrelated and HLA-matched or partially HLA-matched, grafts were either marrow (~ 40%) or PBSCs (~ 60%), and a variety of GVHD prophylaxis regimens were used. The authors reported superior survival among patients who were conditioned with the intravenous (but not with oral) BU-based regimen compared with those conditioned with TBI-based regimens [4].

Are the conclusions drawn in these studies valid or flawed? One would prefer that comparative studies be done in the context of a randomized trial. As our Boston colleagues stated with respect to multicenter observational analyses [1], "These registry analyses incorporate patients from multiple centers, and are inherently susceptible to center effects and biases due to varying transplantation practices in different institutions[p.367-368]". When discussing their own single-center, retrospective analysis, the same authors then stated, "There have been no RCTs [randomized, controlled trials] performed comparing chemotherapy-only regimens with TBI-based regimens[p.367-368]". Although this statement is true for chemotherapy-only regimens that contain intravenous BU, a number of randomized trials have compared BU-containing with TBI-containing regimens, in addition to 4 trials comparing BU/FLU with BU/CY. The results from these trials need to be carefully considered before drawing conclusions from observational studies.

Prospective, Randomized Trials Comparing BU/CY with CY/TBI

In the 1990s results of 4 prospective, randomized trials were reported in the journal *Blood* comparing BU/CY conditioning with CY/TBI conditioning. The CY/TBI regimen used was first described by the Seattle team in 1975 [5], whereas the BU/CY regimen was reported by Santos et al. from Johns Hopkins in 1983 [6]. Two of the 4 randomized trials were from the multicenter French Marrow Transplant Group [7,8], the third was a multicenter Nordic group trial [9,10], and the fourth was a single-center study from the Fred Hutchinson Cancer Research Center (Fred Hutch) in Seattle [11,12]. All patients in these trials had HLA-identical sibling marrow donors, and all were given a short course of MTX and an extended course of CSP for GVHD prophylaxis [13], although a number of French patients received, in addition, treatment with an anti-IL-2 receptor antibody. All 120 patients in 1 of the French trials and all 142 patients in the Fred Hutch study had CML in first chronic phase, whereas the other French study treated 101 patients with AML in first morphologic remission, and the Scandinavian trial included 167 patients with a wide spectrum of hematologic malignancies. Unfortunately, center effects and varying transplant practices invoked by our Boston colleagues already were a problem in those early years. One example of this was TBI protocols in the French and Nordic Group trials with dosing, dose rates, dose schedules, and lung shielding varying from center to center. Close linkage between total TBI doses and toxicities had already been well documented in 2 earlier, prospective, controlled Fred Hutch trials, also published in *Blood*, 1 in patients with AML in first remission and the other in patients with CML in first chronic phase [14,15]. Also, targeting BU blood levels was as yet not widely used, and actual drug levels may have fluctuated considerably.

The French AML study [8] concluded that 2-year outcomes after CY/TBI conditioning were significantly better than after BU/CY conditioning (survival, 75% versus 51%; disease-free survival, 72% versus 47%; relapse, 14% versus 34%; NRM, 8% versus 27%, respectively). In contrast, the French CML study [7] showed comparable survival with the 2 regimens (62.9% for CY/TBI versus 60.6% for BU/CY; disease-free survival, 55% versus 59.1%). These authors concluded that BU/CY conditioning was an acceptable alternative to CY/TBI in patients with CML in first chronic phase.

The Nordic group trial included patients with a variety of hematologic malignancies with a broad range of disease stages [9,10]. The investigators saw more grades III to IV acute GVHD among BU/CY-conditioned patients, whereas relapse rates were comparable. Three-year survival was 76% among CY/TBI-treated patients compared with 62% among BU/CY-treated patients ($P < .03$). The report concluded that CY/TBI was the conditioning of choice, especially in patients with more advanced disease.

Researchers at Fred Hutch in Seattle published early results of a controlled, prospective, randomized trial in patients with CML in first chronic phase in 1994 [11], with an update in 1999 [12]. The patients' ages ranged from 6 to 55 years (mean, 38). They were enrolled on study between October 1988 and November 1992. All received marrow grafts from HLA-identical sibling donors, and all were given a short course of MTX and at least 180 days of CSP [13]. For conditioning, all patients received CY, 60 mg/kg/day i.v. for 2 days. They were randomized to receive either 1200 cGy TBI delivered in six 200-cGy fractions over 6 days at 6 to 7 cGy/min from 2 opposing cobalt-60 sources without lung shielding after CY or BU at 4 mg/kg/day p.o. for 4 days, preceding CY. Fever days, acute GVHD, and hospital days were significantly more common in the CY/TBI group compared with the BU/CY group. Figure 1 summarizes the trial outcomes with updates as of July 1999 (left) and February 2019 (right). CY/TBI-conditioned patients experienced slightly more relapse, slightly more NRM, and slightly worse OS and event-free survival than BU/CY-conditioned patients; however, none of the comparisons was statistically significantly different. Twenty-year survival for BU/CY-treated patients was 63% compared with 58% for CY/TBI-treated

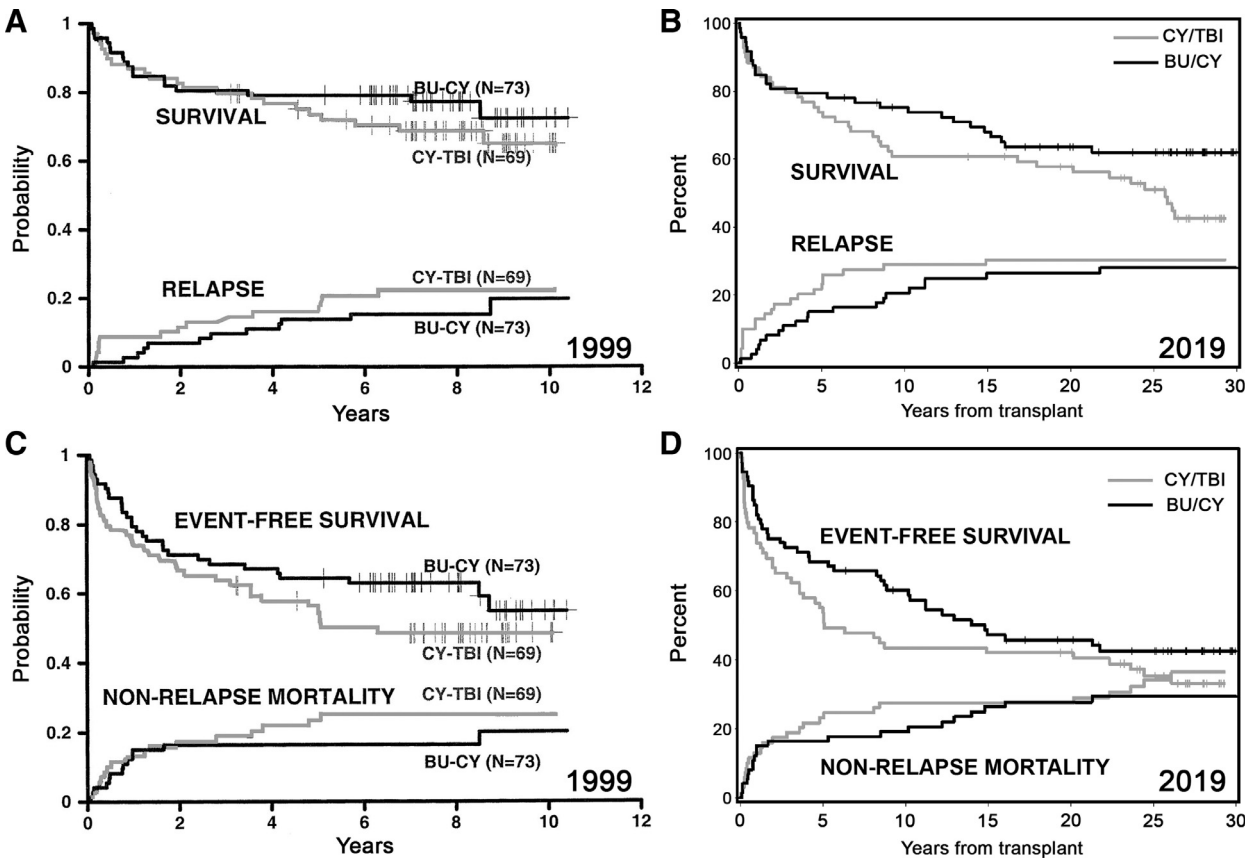

Figure 1. Kaplan-Meier estimates. (A and B) Survival and cumulative incidence of relapse for patients with CML randomized to either BU-CY or CY-TBI conditioning before HLA-identical marrow transplant. Endpoints were as described in the original report [11]. Results were updated to July 1999 (left) and February 2019 (right). (C and D) Event-free survival (relapse and death were defined as events) and death from causes other than relapse for CML patients conditioned with BU-CY or CY-TBI regimens. Endpoints were calculated as in the original report [11]. (A and C reproduced with permission [12].)

patients, and corresponding event-free survivals were 45% and 41%, respectively. Some of the late deaths were age-related, which was not surprising given that a number of patients were 50 years and older at study entry in the late 1980s and early 1990s. The team concluded that BU/CY was better tolerated than CY/TBI and was associated with survival, relapse, and NRM probabilities that compared favorably with the CY/TBI regimen. Since the findings of this tightly controlled trial were published, BU/CY conditioning has been standard practice at Fred Hutch, not only for patients with CML in first chronic phase but also for those with AML in remission and with MDS. Additional support for this decision, which was made in 1994, was provided by later reports describing lesser rates of subsequent malignancies in BU/CY-conditioned patients compared with their CY/TBI-conditioned counterparts [16,17].

Prospective, Randomized Trials Comparing BU/FLU with BU/CY

A prospective trial conducted by a Korean cooperative group randomized 126 patients with various hematologic malignancies at various disease stages to receive either FLU/BU or BU/CY conditioning before HCT from either HLA-matched sibling or unrelated donors (4.7% and 11.3%, respectively, of the donors were HLA mismatched) [18]. Other variables, apart from center effects, included bone marrow, peripheral blood, or unrelated cord blood as graft source and either CSP alone or MTX/CSP for GVHD prophylaxis. The study showed similar NRM in the 2 arms; however, the BU/CY arm had significantly better OS, relapse-free survival, and event-free survival at 2 years (67.4% versus 41.4%, 74.4% versus 54.9%, and 60.7% versus 36.0%, respectively). The authors concluded that BU/FLU conditioning was not a suitable replacement for BU/CY conditioning in young adults who were eligible for myeloablative allogeneic HCT.

A prospective trial from Peking University randomized patients to receive BU/CY or FLU/BU, each regimen also containing hydroxyurea, cytarabine, and semustine [19]. The trial was intended to randomize 178 patients but was terminated early (after 105 patients) because of an increased risk of severe pneumonia in the FLU/BU group (19.2% versus 5.7%; with further follow-up, severe pneumonia was observed in 26.9% and 9.4% of patients, respectively). Patients included those with AML (37%), ALL (28%), CML (25%), or MDS (10%). Despite the apparent increase in severe pneumonia seen with FLU/BU, both OS and leukemia-free survival were similar in the 2 groups but with numerically less relapse in the FLU/BU group.

Contrasting with the conclusions of the Korean and Chinese trials are results of 2 other prospective trials comparing BU/CY with FLU/BU. One trial was conducted by 25 Italian centers of the Gruppo Italiano Trapianto di Midollo Osseo and 1 Israeli center [20]. The authors randomized 252 patients with AML, predominantly in first remission, between 2 conditioning regimens. Donors included HLA-matched related and unrelated individuals, and some donors were HLA mismatched. All recipients were given MTX/CSP for GVHD prevention; however, unrelated recipients received, in addition, ATG. Marrow or peripheral blood was allowed as graft source. The authors found less NRM, slightly more relapse, better leukemia-free

survival, and comparable OS (2-year OS, 64.2% versus 62.4%) among FLU/BU-treated patients and recommended that FLU/BU should be the standard of care.

The other trial that contrasts with the conclusions of the trials that favor BU/CY was another Chinese study [21]. In this study 108 patients with AML in first complete remission were randomized to receive BU/CY or FLU/BU. Efficacy outcomes were similar between groups (5-year estimates of relapse, 16.5% versus 16.2%; disease-free survival, 67.4% versus 75.3%; OS, 72.3% versus 81.9%). Grades 3 to 4 regimen-related toxicity was less in the FLU/BU group (0% versus 16.7%), and 5-year NRM was 18.8% with BU/CY versus 9.9% with FLU/BU.

A meta-analysis of 15 reports (including the 4 randomized studies above, with 11 observational studies) comparing BU/FLU with BU/CY conditioning before allogeneic HCT [22] concluded that both regimens had similar efficacy profiles, whereas toxicity was lower with the BU/FLU regimen. The authors concluded that BU/FLU was not inferior to BU/CY as a myeloablative preparative regimen and may be associated with lower early NRM. However, they further argued that well-controlled randomized trials that assess the BU/FLU regimen among specific subgroups are warranted.

Summary of Studies Comparing BU/CY with CY/TBI or BU/FLU with BU/CY

The randomized trials summarized above comparing BU/CY with CY/TBI were somewhat conflicting, with 2 studies overall favoring BU/CY and 2 favoring CY/TBI. One of the trials [9] that favored CY/TBI was conducted among a variety of hematologic malignancies, roughly 25% of which were lymphoid. Moreover, the advantage purported for CY/TBI was in comparison with oral drug in the BU/CY regimen as opposed to intravenous drug. We consider the conclusions from the randomized trials comparing BU/CY with CY/TBI cited above to be largely in favor of using BU/CY rather than CY/TBI for myeloid malignancies, and the observational studies summarized above are consistent with this conclusion. Taken together, we consider these data to be in support of BU-based regimens for most patients with myeloid malignancies with relatively low tumor burden. Whether this conclusion holds true for patients with high tumor burden, say, AML in relapse or CML in myeloid blast crisis, is not clear. The same uncertainty holds true for patients with minimal residual disease at the time of HCT. Well-controlled comparisons to address this question have not been done, and some centers have intuitively continued using CY/TBI in such patients. However, among the 4 randomized clinical trials that have addressed the question of what is preferable, FLU/BU or BU/CY, 2 have favored FLU/BU and 2 have favored BU/CY. The 2 trials that favored BU/CY contained a variety of hematologic malignancies (AML, ALL, CML, MDS), whereas the 2 that favored FLU/BU were conducted solely in AML (either in first complete remission exclusively or predominantly). These results support the conclusion of the meta-analysis cited above, where the authors suggested that additional well-controlled randomized trials were needed in specific subgroups of patients.

FUTURE OF HIGH-DOSE TBI-BASED REGIMENS

So, are myeloablative TBI-based regimens history and have they been replaced by BU-based regimens? Not so fast. Let us look at HCT for ALL and other lymphoid malignancies.

ALL and Other Lymphoid Disorders

Multicenter trials and retrospective analyses

The situation is even more unsettled when the focus is on ALL. A small, randomized, multicenter study in pediatric patients with ALL compared BU/CY/VP16 with 1200 cGy TBI (6 fractions in 3 days)/CY/VP16 [23]. Donors were either related or unrelated. Marrow was the predominant graft source, and GVHD prevention consisted mainly of MTX/CSP. The authors concluded that the BU-based regimen was inferior to the TBI-based regimen in pediatric patients with ALL (3-year event-free survival, 29% versus 58%; $P = .03$).

A randomized International Pediatric ALL Forum 2012 study in more than 400 patients had randomization suspended, and ultimately closed, after an interim analysis showed a survival benefit among patients conditioned with TBI/VP16 over those conditioned with either FLU/thiotepa/treosulfan or FLU/thiotepa/i.v. BU (88% versus 71% 2-year OS). Although transplant-related mortality was comparable among the groups, there was a large increase in relapse rates among chemotherapy-treated patients compared with TBI-treated patients. This carefully controlled randomized trial is the most definitive statement for a continued role of TBI for patients with ALL undergoing allogeneic HLA-matched HCT (https://clinicaltrials.gov/ct2/show/study/NCT01949129).

A retrospective EBMT analysis of 601 patients with T cell ALL compared outcomes after BU/CY with those after TBI-based regimens [24]. As in other registry analyses, TBI doses and schedules varied and detailed information was not given. Unrelated and related donors were lumped, as were marrow and PBSCs as graft sources, and multiple GVHD prophylaxis regimens, including ATG, were used. The analysis concluded that TBI-based conditioning gave superior results compared with BU/CY (5-year leukemia-free survival rate of 50% versus 18%).

Another retrospective EBMT analysis included patients with ALL in remission and with active disease, of whom 180 received thiotepa conditioning and 540 received CY/TBI conditioning (TBI doses and dose schedules not provided) [25]. B cell ALL and T cell ALL patients were included, of whom some were Philadelphia chromosome positive (Ph+) in first complete remission, although in most patients this information was unknown. Marrow or PBSC grafts were from HLA-matched related or unrelated donors. Information on GVHD prophylaxis was not provided, although apparently some patients received ATG or Campath in the conditioning. Patients conditioned with CY/TBI had less relapse, comparable NRM, and marginally better event-free survival at 2 years in multivariate analysis (39% versus 33%; $P = .06$).

A recent retrospective study [26] compared outcomes of ALL patients (approximately 75% in first remission and 25% in second remission; 83% B cell lineage) given CY/TBI or VP16/TBI conditioning (TBI doses ranging from 1200 to 1600 cGy—no information on dose schedules or rates or lung shielding) with BU/FLU, BU/clofarabine, BU/melphalan, or BU/CY. The TBI-based cases (n = 819) and 67 BU-based cases were from the CIBMTR database, which included results from 504 transplant centers. The remaining 232 BU-based cases were from the MD Anderson Cancer Center and Moffitt Cancer Center. This kind of selection, of course, introduced a considerable bias from the start. Also, it was not clear how patients were chosen to receive CY/TBI versus VP16/TBI or, say, BU/FLU versus the remaining 3 BU-based regimens. Marrow or PBSCs were transplanted. Approximately half of the donors were HLA-identical siblings and half were HLA-matched unrelated donors. TBI-based cases had a median follow-up of 63 months versus

43 months for BU-based patients. More BU-based Ph+ patients received post-transplant tyrosine kinase inhibitors than TBI-based Ph+ cases. The authors reported a 3-year NRM of 19% for BU-treated patients versus 25% for TBI-treated patients. Corresponding percentages for relapse, disease-free survival, and OS were 37% versus 28%, 45% versus 48%, and 57% versus 53%, respectively. Having compared the experience of 4 BU-based regimens, which was largely generated at 2 transplant centers, with that of 2 TBI regimens used at 504 other centers, the authors concluded that BU-based regimens were better tolerated than TBI-based regimens.

Fred Hutch

Fred Hutch investigators have generally preferred using TBI-based over BU-based conditioning regimens for allogeneic HCT in patients with ALL and other lymphoid disorders, although this practice was not based on randomized, prospective, clinical trials. The rationale for this preference goes back to extensive preclinical animal studies that uniformly showed little effect of BU on B cell and T cell function, whereas comparably intense TBI nearly completely suppressed the immune function. We reasoned that drug and irradiation effects on normal immune cells were representative of their respective effects on malignant B and T cells.

In 1958 Elson et al. [27] already noticed that "the lymphoid organs after BU administration (in rats) showed no changes throughout the experiment," whereas "from 8 to 14 days [when] depletion of normoblasts, granulocytes, and granulopoietic cells (in marrow) was maximal." Studies in dogs given highest tolerated doses of i.v. BU showed profound depletion of marrow and peripheral blood neutrophil and platelet counts. However, primary antibody responses to sheep RBCs, bacteriophage ΦX174, and allogeneic buffy coat cells were little or not at all affected [28]. Also, dog leukocyte antigen (DLA)-mismatched marrow grafts were all rejected [28], and sustained engraftment of dog leukocyte antigen (DLA)-identical littermate grafts was only seen in 50% of recipients after BU [29]. Of note, complete engraftment was achieved when BU was combined with ATG. Similarly, Santos and Tutschka [30] treated both Lewis and Sprague-Dawley rats with single LD_{50} doses of BU and saw no effect on antibody production against sheep RBCs and on allogeneic skin graft rejection. Buckner et al. [31] failed to achieve allogeneic marrow engraftment in monkeys given the highest tolerated doses of i.v. BU. More recently, Kang et al. [32] confirmed that hematologic effects of BU in rhesus monkeys were most profound in the myeloid compartment, resulting in profound declines of neutrophils and platelets, whereas lymphocytes were less affected. In contrast to the only marginal effect of BU on B and T cell compartments, equitoxic doses of TBI completely suppressed antibody production to sheep RBCs and bacteriophage ΦX174 [33] and enabled sustained marrow engraftment.

Taken together, we consider these results (both preclinical and clinical) to provide a compelling rationale for continuing the use of TBI-based conditioning for HCT in patients with lymphoid-based disorders. The lone outlier to this conclusion comes from the study where the overwhelming majority of BU-based patients were from 2 centers and compared with registry patients who received TBI. It is virtually impossible to separate institutional effects from treatment effects in such a study, and we therefore view these results with great caution.

Summary: Future of High-Dose TBI-Based Regimens

Results of a few retrospective multicenter studies and a single small, randomized trial in pediatric patients are consistent with the compelling preclinical findings and suggest that BU-based conditioning is inferior to TBI-based conditioning in patients with ALL. The single retrospective analysis that suggested BU-based conditioning was approximately equivalent to TBI for patients with ALL was heavily influenced by selection bias. The interim analysis results from the ALL SCTped 2012 FORUM randomized trial (NCT01949129) showed superior survival for patients treated with TBI-based regimen. Until future randomized, prospective trials indicate otherwise, the current data support the use of TBI-based regimens for ALL. BU-based conditioning for ALL remains experimental and cannot be considered an equivalent substitute for TBI.

CONCLUSION

Although randomized clinical trials are the accepted gold standard to obtain the most definitive assessment of treatment effect in clinical research, quality results from a randomized trial are only obtainable if the trial is well designed. Moreover, if there are subgroups of patients who have differential treatment effects, the overall treatment effect cannot and should not be generalized to the entire population. Also, well-controlled, prospective, randomized trials may end up showing differences in primary endpoints that are small and fail to reach statistical significance, but secondary endpoints may point in the same direction or statistically favor 1 arm, leading to the preference of the arm that is not statistically significantly better for the primary outcome. An example of such a trial is the Fred Hutch study in patients with CML, reviewed above, that compared BU/CY with CY/TBI. Even after nearly 30 years of follow-up, NRM, relapse, event-free survival, and OS were only slightly but not statistically significantly in favor of BU/CY. However, during the conduct of that trial it became apparent that BU/CY had a more favorable toxicity profile than CY/TBI. It was this finding that made BU/CY the regimen of preference for patients with myeloid malignancies. Another such example is the Blood and Marrow Transplant Clinical Trials Network trial comparing bone marrow versus PBSCs as the source of stem cells from unrelated donors [34]. The 2-year estimates of OS in this study were 46% and 51%, respectively ($P = .29$). The estimates of chronic GVHD were 41% and 53%, respectively ($P = .01$). A long-term follow-up study from the same randomized trial showed superior quality of life in the bone marrow arm (higher mean Mental Health Inventory Psychological Well-Being score, 78.9 versus 72.2; $P = .01$) and lower mean Lee Chronic Graft-versus-Host Disease Symptom scores (13.1 versus 19.3, $p = .004$) [35]. The totality of these results led to the recommendation that bone marrow is the preferred stem cell choice among recipients of unrelated allografts. If such subtle differences are seen in well-controlled trials, it may not come as a surprise that conflicting findings can be observed in larger, retrospective registry analyses.

Not all questions of interest in HCT can be addressed in a randomized clinical trial, however, and in the absence of a randomized trial, observational studies can provide useful information. However, analysis of such studies needs to be carefully performed, and given the lack of randomization and the presence of factors that cannot be controlled, results from such studies cannot be considered definitive and, at best, can only be hypothesis-generating. For the questions addressed in this commentary ("which is the preferred conditioning regimen in certain HCT settings?"), there have been both randomized and observational studies conducted, each with some conflicting conclusions. However, the results from randomized trials comparing BU-based conditioning with TBI-based conditioning largely favor the use of BU among patients with myeloid malignancies.

Results from many observational studies are consistent with this preference, and we therefore believe until a future well-designed randomized trial dictates otherwise, the data support the use of BU-containing conditioning for use with allogeneic HCT for myeloid malignancies, for example, in patients with AML in remission. In patients with AML in relapse or CML in myeloid blast crisis, a number of centers have continued using TBI-based conditioning. The case for lymphoid malignancies is not as clear, because the experience with randomized trials in this setting is limited. However, based on this limited experience, including the recent large randomized trial in pediatric ALL, the observational studies that have been conducted, and the compelling preclinical data, TBI-based conditioning appears to be the recommended choice. Even less clear is the choice of which BU-containing regimen to use in the setting of myeloid malignancies, because results from randomized trials have favored FLU (with BU) over CY and others have favored CY over FLU. Two trials conducted in AML showed less toxicity and non-inferior efficacy with FLU, and based on this one might recommend BU/FLU for myeloid malignancies, or at least for AML. However, to definitely settle this issue, we believe that a well-designed randomized clinical trial comparing FLU/BU and BU/CY is warranted.

DECLARATION OF COMPETING INTEREST

The authors have no conflicts of interest to report.

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