DSEN ABSTRACT

A Systematic Review of Conditioning Regimens in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Summary

- Evidence from randomized trials is lacking or of limited size for many comparisons between conditioning regimens used for patients undergoing HSCT. Overall, inconsistency in measurement and reporting of outcomes, limited connectivity of evidence networks and between-study clinical heterogeneity limited the capacity for network meta-analyses, with the number of regimens compared varying by outcome.

- Findings from network meta-analysis suggest that CY+TBI was associated with significantly lower overall mortality at one year post-transplant compared to BU+CY, and at two and four years post-transplant compared to BU+CY and BU+FLUD.

- No statistically significant differences were found between conditioning regimens for relapse (four regimens compared), acute GVHD (nine regimens compared), or chronic GVHD (three regimens compared). Within the nine regimens compared, CY+TBI was ranked poorly regarding the occurrence of aGVHD.

What is the issue?

- Allogeneic hematopoietic stem cell transplantation (HSCT) has been used as a treatment for hematologic and lymphoid cancers since the 1960s, and continued improvements have refined HSCT to be the best curative option for many patients. To facilitate engraftment of donor cells, prior to transplantation, the patient's own immune cells must be weakened or destroyed through the use of a series of chemotherapeutic drugs and/or irradiation procedures called a conditioning regimen. While a variety of such regimens exist (including myeloablative, non-myeloablative and reduced intensity regimens), the best regimen is currently unknown.

What was the aim of the study?

- The objective of this review was to compare the benefits (e.g., reduction in mortality and relapse) and harms (e.g., increased risk of HSCT-related conditions) of competing regimens used to condition patients prior to undergoing HSCT.

How was the study conducted?

- Medline, PubMed, Embase, and the Cochrane Register of Controlled Trials were searched in 2013 for randomized controlled trials of patients undergoing HSCT. Searches were updated in 2017. Studies were included if patients underwent allogeneic HSCT in the treatment of hematologic neoplasias or benign disease and were randomly allocated to receive a conditioning regimen. Outcomes of interest included overall mortality, non-relapse mortality, relapse of underlying disease, risk of acute and chronic GVHD, and specific harms. We conducted Bayesian network meta-analyses to compare conditioning regimens for outcomes of interest, where feasible. For outcomes for which network meta-analysis was not possible, detailed narrative summaries were prepared.

What did the study find?

- Eighteen trials assessed 18 unique conditioning regimens in 2,361 total patients. Three trials were not included in network meta-analyses because either (1) they were conducted strictly on aplastic anemia patients (2 studies, n = 213) or (2) the conditioning regimens evaluated were not described in sufficient detail (i.e., "standard conditioning," with or without total lymphoid irradiation; 1 study, n = 235). A total of 1,913 patients in 15 trials (9 regimens: fludarabine (FLU) + total body irradiation (TBI), anti-thymocyte globulin (ATG) + TLI (total lymphoid irradiation), TBI, cyclophosphamide (CY) + TBI, busulfan (BU) + CY, ATG + FLUD + BU, etoposide (ETP) + TBI, melphalan (MELPH) + TBI, BU + FLUD) were available for inclusion in network meta-analyses. Overall, there was substantial variability in patient populations with respect to age, underlying hematologic disease, disease risk of relapse/mortality, and transplant donor status (i.e., related vs. unrelated, matched vs. unmatched). Trial publication dates ranged from 1988–2015.
- The networks for each outcome were sparse, with most comparisons between conditioning regimens informed only by indirect evidence, and many of the direct comparisons based on single studies with small numbers of patients. Clinical heterogeneity between study populations was noted. Separate network meta-analyses for overall mortality were conducted at the follow-up times of 100 days, and 1, 2, 4, and 5 years. For disease relapse, studies following patients for a median of 2–3 years were included in the network. Cyclophosphamide (CY) + total body irradiation (TBI) was considered the standard conditioning regimen for comparison purposes.

- CY+TBI and BU+CY were associated with similar rates of VOD at 28 days post-transplant (2 studies); however, at ≥100 days post-transplant, CY+TBI significantly reduced the risk of VOD compared to BU+CY (4 studies). CY+TBI was associated with reduced incidence of bronchiolitis obliterans compared to BU+CY (1 study).

- ***Overall Mortality.*** For 100-day mortality, no statistically significant differences were identified between the five regimens compared that included CY+TBI, CY + busulfan (BU), BU + fludarabine (FLUD), TBI + etoposide (ETP), and TBI + melphalan (MELPH). At 1 year, CY+TBI demonstrated significantly reduced overall mortality compared to BU+CY, and at 2 and 4 years, when compared to either BU+CY or BU+FLUD.
- ***Non-Relapse Mortality.*** Network meta-analyses could not be conducted for non-relapse mortality (NRM). Narrative summaries demonstrated significantly reduced NRM at 1, 2, and 5 years for BU+FLUD compared to BU+CY in one study (Rambaldi, 2014), but not in two other studies that compared the same regimens (Lee, 2013 and Liu, 2013). At 1 year of follow-up, there was a trend toward FLUD+TBI offering reduced NRM compared to CY+TBI in one study (Bornhauser, 2011). As well, early and late (7 year) cumulative incidence of NRM was significantly reduced for CY+TBI when compared to BU+CY; however, when adjusted for early vs. advanced disease and donor age > or < 30 years in a multivariable model, no significant difference was found between the regimens (Ringden, 1999).
- ***Disease Relapse.*** Four regimens provided data to the network meta-analysis for relapse at 2–3 years post-transplant (CY+TBI, BU+CY, BU+FLUD, and FLUD+TBI). There were no significant differences in the regimens with respect to the risk of relapse.
- ***Acute and Chronic Graft versus Host Disease (aGVHD, cGVHD).*** All nine regimens available were included in the network meta-analysis for aGVHD, while only three regimens (CY+TBI, BU+CY, and BU+FLUD) could be included in a network for cGVHD. In the risk of aGVHD, TBI alone was the top-ranked regimen; however, there was no significant difference in the risk of aGVHD when TBI was compared to any regimen other than ATG+BU+FLUD and MELPH+TBI. The standard conditioning regimen, CY+TBI, was ranked third lowest of all 9 regimens and was not significantly different from any other regimen. There were no significant differences in the 3 regimens included in the cGVHD network.
- ***Additional harms-related findings:*** A pairwise meta-analysis comparing CY+TBI to BU+CY for the risk of veno-occlusive disease (VOD) at 28 days post-transplant found no significant difference between the regimens. However, a network meta-analysis including CY+TBI, MELPH+TIB, BU+FLUD, and BU+CY, demonstrated that CY+TBI significantly reduced the risk of VOD compared to BU+CY at ≥100 days post-transplant. Other adverse events including specific organ toxicity and infections were described in a small number of studies, precluding meta-analysis. Based on one study, CY+TBI significantly reduced the risk of bronchiolitis obliterans when compared to BU+CY in long-term follow-up. CY+TBI was associated with a higher risk of a positive blood culture at 100 days compared to BU+CY in one study; however, in another study, there was no significant difference between the two regimens in the risk of bacteremia after 2 years. The single study comparing modified regimens of BU+CY and BU+FLUD identified a significantly higher risk of severe pneumonia in the modified BU+FLUD group after 1.4 years, which ultimately halted the study. Finally, the addition of FLUD to CY+ATG in conditioning regimens for aplastic anemia patients was associated with significantly reduced regimen related toxicity and pulmonary complications.

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