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Brief Articles

Current Trends in Clinical Studies of Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) is a specialized intervention performed at select centers worldwide. The extent to which specific aspects of care in allogeneic HSCT have been studied and the types of studies performed for different aspects of care remains incompletely documented. Studies in allogeneic HSCT were systematically identified from selected high-profile transplant journals between July 2010 and June 2011 and previously reported in a study addressing the definition of clinical outcomes in HSCT. All articles were retrieved and assessed for study characteristics and categorized by specific aspects of care related to allogeneic HSCT. One hundred sixteen articles were retrieved and reviewed in detail by 2 investigators. The most studied aspect of care was conditioning regimens. Transfusion practices were the most understudied aspect of care. Interestingly, most studies included both adult and pediatric patients. Studies involving all hematological malignancies were encountered more often than disease-specific studies. Geographically, most patients described in the published reports were treated only in North America or only in Europe. Most studies were retrospective (78), and 25 reported on multicenter registry data. Of the 38 prospective studies, 8 were randomized controlled trials (RCTs) and predominantly focused on prevention and treatment of graft-versus-host disease (GVHD) and infections. Median follow-up was longer in retrospective registry studies (54 months) and shortest in RCTs (32 months). The proportion of positive outcomes in retrospective and prospective studies was remarkably high (>80% for all categories) and not significantly different across all aspects of care ($P > .05$). When comparing RCTs and registry data studies, this proportion was similar and high (95% and 100%, respectively, $P > .05$). Our study highlights the established and important role of retrospective registry studies for many aspects of care and suggests RCTs may be most relevant for studies on infectious complications and GVHD.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a highly specialized and complex intervention that can deliver a potential cure for a range of malignant and nonmalignant hematological disorders [1]. Many aspects of care in allogeneic HSCT have implications for patient morbidity and mortality and can impact resource utilization. Optimization of allogeneic HSCT involve decisions regarding the selection of donors, source of cells, choice of conditioning regimen, prevention and treatment of graft-versus-host disease (GVHD), transfusion medicine, and prevention and treatment of infections and other complications. Variation of transplant protocols to suit specific circumstances is essential for optimizing transplant outcomes [2-4].

Clinical research in allogeneic HSCT includes retrospective and observational studies using registry data submitted by many participating centers and prospective studies, including randomized controlled trials (RCTs). Although retrospective studies can analyze data from many more patients with long follow-up, data can be difficult to extract or find within the clinical records. Registries such as the Center for International Blood and Marrow Transplant Research (CIBMTR) have developed standardized forms that have improved the consistency of reporting and analysis of particular outcomes; however, they remain limited in their ability to analyze new

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ideas or concepts where data may be lacking. Conversely, prospective studies and randomized controlled studies in particular often have a more definitive scheme in terms of the data collected but can be resource intensive and require a period of enrollment and follow-up that limits the interpretation of the results. In the early days of HSCT, retrospective reports from single centers played a key role in establishing certain regimens and practices later addressed in larger registry studies and/or prospective trials. The conduct of RCTs in HSCT has emerged more recently, although the extent to which different study designs are amenable to different aspects of care in allogeneic HSCT remains incompletely understood and may help in the design and conduct of future studies aimed at optimizing care in allogeneic HSCT.

RCTs are considered by many as the gold standard in evidence-based medicine. Well-conducted RCTs can yield definitive answers regarding the potential benefits of particular interventions because of their ability to minimize confounding variables through randomization [5,6]. RCTs, however, are challenging to conduct in the transplant setting because of high cost, challenges with enrollment and follow-up, potential for reduced generalizability, and length of time from conception to publication, often exceeding 5 to 10 years [7]. According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, observational studies tend to offer a lower grade of evidence compared with RCTs [8], but in some areas of medicine, observational studies can provide important information that yield results concordant with the results of RCTs [9]. Moreover, Benson and Hartz [10] compared the results of RCTs and observational studies for 136 reports regarding 19 different treatments and concluded that the effects of observational studies were not consistently larger or qualitatively different from those obtained in RCTs. Others suggested that information from both RCTs and outcomes databases can be complementary and contribute to determining an appropriate treatment strategy [11].

The extent to which aspects of care in allogeneic HSCT have been studied and the types of studies performed remains incompletely documented [4,12]. Moreover, the degree of corroboration between retrospective and prospective studies has not been previously reported for allogeneic HSCT. In this study, we performed a scoping review of study characteristics in allogeneic HSCT from 116 articles identified in a time-limited systematic search of selected journals reporting on transplant studies [2]. Although a small number of journals were screened for inclusion of articles, our primary goal was to identify current trends regarding study characteristics published in journals with high readership that address specific aspects of care in allogeneic HSCT to guide future studies aimed at optimizing clinical outcomes of allogeneic HSCT.

METHODS

Articles and Data Extraction

All allogeneic HSCT articles published in *Biology of Blood and Marrow Transplantation*, *Blood*, *Journal of Clinical Oncology*, and *New England Journal of Medicine* between July 2010 and June 2011 that dealt with engraftment rates, GVHD, nonrelapse mortality, or relapse were identified in a recent study of endpoints [2]. This previously published search strategy yielded 116 articles (Appendix A). The selected journals were identified from a previously published literature search, and although the search does not provide an exhaustive list of studies in allogeneic HSCT, the search included journals with high readership and a high likelihood of clinical relevance to clinical practice in HSCT.

Relevant data were extracted from all articles by 2 independent investigators through the use of a standardized study extraction form. Each study was categorized into 1 of 8 aspects of care arbitrarily defined as follows: (1) donor choice (related, unrelated), (2) source of cells (bone marrow, peripheral blood or cord blood), (3) transplant conditioning regimens, (4) prevention/treatment of GVHD, (5) prevention/treatment of infections, (6) transfusion practices, (7) non-HLA genotype associations (recipient or donor), and (8) others (ie, relapse therapies, late complications, etc.). The following parameters were further extracted from each study: type of study, enrollment, patient characteristics, primary outcomes, median follow-up, funding source, recruitment period, and geographic region of intervention. Study types were defined according to whether they were retrospective (patients identified using a search or review of institutional records) or prospective (patients were enrolled and entered in the study using defined inclusion and exclusion criteria), and studies were defined as single center or multicentered based on the information provided in the published article. Randomized controlled studies were defined as prospective studies with a clear description of enrollment and randomization to 1 of 2 or more groups and where outcomes were compared between the groups. Registry studies were identified if patients were searched using a registry that systematically collects and stores defined information on patients within a defined jurisdiction. All study parameters were then tabulated and key observations were described.

Statistical Analysis

The chi-square test was applied to compare categorical variables. An alpha error of less than .05 was considered statistically significant.

RESULTS

One hundred sixteen published articles describing the treatment of 87,633 patients were included in our analysis. These studies were recently identified from a limited systematic search of key transplant journals to identify and define clinical outcome measures used in studies of allogeneic transplantation [2]. We categorized the studies into aspects of care related to allogeneic HSCT and observed the most common aspects of care studied were conditioning regimens (26 studies, 5112 patients), GVHD (14 studies, 11,908), and donor selection (14 studies, 11,121 patients). The least studied aspects of care were transfusion medicine practices (1 study, 229 patients), infectious disease prevention and/or treatment (9 studies, 1120 patients), and the source of cells (10 studies, 1888 patients) (Table 1). A number of additional studies were also published that addressed more peripheral issues related to allogeneic HSCT or were not focused on issues central to allogeneic transplantation. These additional studies addressed relapse therapies (8 studies), use of allogeneic transplantation compared with other treatment strategies (7 studies), late complications of allogeneic transplantation (3 studies), and identification of prognostic factors associated with transplant outcomes (6 studies).

Most published articles involved adult patients or a combination of adult and pediatric patients, with only 9 studies (8%, 2814 patients) enrolling exclusively pediatric patients. Most studies reported only public funding (52 studies, 45% of studies, 29,294 patients), whereas 21 studies (18%, 22,072 patients) reported a blend of private and public funding sources, and 11 studies (9.5%, 13,795 patients) reported only private funding. In 32 studies (28%, 22,372 patients), the source of funding was not stated. The studies reported were from North America (42 studies, 36%, 24,462 patients), Europe (31 studies, 27%, 4550 patients), and North America and Europe (14 studies, 12%, 33,022 patients), whereas only 29 studies (25%, 25,599 patients) described patients treated outside North America and Europe (Table 1).

Most studies were retrospective (78 studies, 67%, 81,511 patients), and 25 of these were from multicenter registry data (International Blood and Marrow Transplant Registry and the Autologous Blood and Marrow Transplant Registry of the Centre for International Blood and Marrow Transplant Research, National Marrow Donor Program, Japan Society for