Variation in Supportive Care Practices in Hematopoietic Cell Transplantation

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Hematopoietic cell transplantation is an elective procedure that results in prolonged immune suppression and high treatment-related morbidity and mortality. Transplant centers and physicians use a variety of prophylaxis and monitoring strategies to prevent or minimize complications. Little is known about the variability in these practices. We conducted an international Internet-based survey of 526 physicians to describe the spectrum of supportive care practices employed. Consistency in pretransplant cardiac (96%) and pulmonary (95%) screening, informed consent documentation (93%), and use of antifungal prophylaxis (92%) was observed. Greater heterogeneity was seen in use of myelogenous growth factors, empiric antibiotic therapy, protective isolation procedures, posttransplant monitoring, and environmental and social restrictions. Although some practice differences were associated with physician characteristics and transplant type, most practice variation remained unexplained. These results suggest a need for well-designed observational and interventional studies to provide data about which supportive care practices improve outcomes. For practices proved to be beneficial, publication of guidelines and incorporation of monitoring into quality improvement initiatives may help standardize practices.


KEY WORDS: Practice variation, Supportive care, Autologous stem cell transplantation, Allogeneic stem cell transplantation

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a procedure in which high risks of morbidity and potential mortality are accepted by patients, families, and physicians in pursuit of curative or life-prolonging treatment. HCT is a complex medical treatment performed by multidisciplinary teams of physicians, nurses, pharmacists, psychosocial personnel, and other clinical staff within specialized treatment units. Patients are at high risk for organ toxicity, infections, and other life-threatening treatment complications for a prolonged period. As a result, a number of prevention and monitoring strategies and supportive care practices are common in HCT, although many of these practices have never been studied rigorously. The best-studied data about supportive care practices derives from randomized trials using prophylactic pharmacologic agents such as ursodeoxycholic acid, hematopoietic growth factors, and antifungal agents [1–7]. Considerably less information is available about the effectiveness of protective isolation procedures and posttransplant monitoring, although practices have been described previously [8,9].

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Barriers to conducting supportive care research include the small number of HCT patients per center, lack of interest or funding to pursue studies in supportive care, methodologic and logistical issues in conducting supportive care intervention studies, and great variability in other treatment practices that might obscure definitive conclusions even if such studies could be organized. Controlled trials may not be feasible for some approaches. In the absence of data, individual physicians and programs typically develop practice policies based upon local opinion, experience, and resources.

To better understand the breadth of variation in supportive care practices, we conducted an Internet-based international survey of transplant physicians. Although the main purpose of the current report is descriptive, we hypothesized that evaluation and supportive care practices may differ according to whether physicians performed primarily adult autologous, adult allogeneic myeloablative, adult allogeneic reduced-intensity conditioning (RIC) or pediatric procedures, because of differences in perceived risks for various complications.

METHODS

Physician Survey

Items were constructed to capture data about routine practices, including supportive care, usually used or recommended by the respondent. The self-administered survey contained 44-50 items and took 10-20 minutes to complete. The first section contained 8 questions about preparation before HCT, including the requirement for informed consent even if not on a clinical trial, pre-HCT physiologic testing, and attention to advance care planning and psychosocial issues. Clinical practices during HCT were assessed by 10 questions covering infectious prophylaxis, use of supportive care interventions, reverse isolation procedures, and management of fever without a clear source. Five questions collected data about practices after HCT, including routine testing and protective isolation restrictions. All questions asked physicians what they “routinely” did for the major population of patients they treated. The final section of 11 questions collected physician and transplant center characteristics. Data derived from questions about indications for HCT and prophylaxis and management of graft-versus-host disease (GVHD) have been previously reported [10]. A copy of the survey may be obtained from the corresponding author.

Data Collection

The Dana-Farber Cancer Institute’s institutional review board approved the study and waived the requirement for documentation of informed consent. Data collection procedures have been previously reported [10]. Briefly, a description of the survey and invitation to participate were emailed to a list maintained by the Center for International Blood and Marrow Transplant Research (CIBMTR). Each invitation included a unique link to allow survey completion or opting out. Three e-mail reminders were subsequently sent at weekly intervals. Surveying occurred between November 18, 2005, and December 15, 2005.

There were 2229 e-mails sent to potentially eligible subjects. Of these, 407 were not eligible to respond because of confirmation of undeliverable e-mail, duplicate addresses, or confirmation that the recipient was ineligible (eg, not a transplantation physician, retired); 540 responses were received, of which 526 were evaluable. Surveys (n = 14) were excluded if respondents answered fewer than half of the medical decision making or supportive care questions. Only 84 recipients actively declined to participate in the study; 1036 did not respond in any way to the 3 e-mails and we are unable to further classify this group into passive nonrespondents versus inactive e-mail addresses. Thus, the evaluable response rate was 526 of 627 (84%) confirmed invitations or 526 of 1823 (29%) of all invitations.

Biostatistical Analysis

Descriptive statistics are reported for sociodemographics and practice characteristics according to whether physicians self-identified primarily as adult autologous (n = 152), adult allogeneic myeloablative (n = 178), adult allogeneic reduced intensity conditioning (n = 54), or pediatric practitioners (n = 142). Individual respondents were considered ineligible for particular questions if either they did not answer the question, indicated they did not see those types of patients, or otherwise indicated the question did not pertain to them.

Logistic and linear modeling approaches were used to examine associations between physician characteristics and various supportive care practices. The physician characteristics we evaluated included: predominant type of procedure performed (adult autologous, adult allogeneic myeloablative, adult allogeneic RIC, and pediatric), year training completed (dichotomized at the median: before 1991, 1991, or later), sex, affiliation (academic, community, or both), center size (dichotomized at the median number of annual transplants: 70), percentage of time devoted to patient care (<60%, 60%, or more), and clinical research (<20% vs. 20% or more), and country (United States, other) as potential predictors. The multivariate analyses were limited to the 500 physicians for whom we had complete demographic and practice data.

For the social and environmental recommended protective practices, respondents were asked “Please tell us how long you recommend limitations on the
following (for those responding for allogeneic recipients, assume the patient does not have acute or chronic GVHD [aGVHD, cGVHD]). A summary variable called the “total isolation score” was created by summing the responses to the 7 questions. Each item score ranged from 1 (no restrictions) to 5 (>1 year) with a possible range of 7-35, with lower score indicating less restrictive policies. Forward stepwise selection methods were used, and variables with $P < .05$ were retained in the final model.

RESULTS

Physician Characteristics

Physician and center descriptions are presented in Table 1 according to the self-identified physician group. Most characteristics were similar across the 4 groups. Of the 142 pediatricians, 124 (87%) practiced myeloablative procedures, 13 (9%) RIC procedures, and 5 (4%) autologous procedures.

Preparation before Transplantation

There was strong agreement on evaluation and counseling practices prior to HCT (Table 2). The majority endorsed measuring cardiac function (96%), pulmonary function tests (95%), having all patients give written informed consent even if not on a clinical trial (93%), and having a psychosocial provider meet with the patient before scheduling HCT (83%). Discussion of advance care planning issues was reported commonly in all groups. Overall, 38% reported giving postpubertal females leuprolide to suppress menses. Of physicians primarily practicing allogeneic transplantation, 130 of 355 (37%) have a psychosocial provider meet with donors, whereas 45 of 343 (13%)
collect backup autologous stem cells before unrelated donor HCT.

Factors associated with discussion of advance care planning issues, giving postpubertal females leuprolide, and having a psychosocial provider meet with donors were explored. In multivariate analysis (n = 476), discussion of advance care planning was associated with participation in clinical research (odds ratio [OR] 1.6, \( P = .02 \)) and practicing in the United States (OR 1.6, \( P = .03 \)). Prescribing leuprolide to postpubertal women was associated with being a pediatrician (OR 1.9, \( P = .005 \)) and a female physician (OR 1.6, \( P = .03 \)). Of physicians practicing primarily allogeneic transplantation, pediatricians (OR 3.9, \( P < .0001 \)) and physicians spending >60% clinical time (OR 1.7, \( P = .04 \)) were more likely to have donors meet with psychosocial providers.

**Infectious Disease Practices**

Table 3 shows reported infectious disease practices. Most respondents (92%) reported routine use of antifungal prophylaxis. Prescribing myelogenous growth factors was more common among US physicians (OR 3.4, \( P < .0001 \)), smaller centers (OR 1.9, \( P = .001 \)), and adult autologous transplant physicians (OR 2.9, \( P < .0001 \)). Routine antibiotic prophylaxis was more common in the United States (OR 1.7, \( P = .01 \)) and less common among pediatricians (OR 0.3, \( P < .0001 \)). Considerable heterogeneity in practice was seen in empiric treatment of neutropenic fever, viral monitoring and prophylaxis, and inpatient protective isolation procedures.

**Supportive Care and Monitoring during and after Transplantation**

Table 4 shows frequency of prophylactic ursodeoxycholic acid use, routine posttransplant restaging of patients with acute myelogenous leukemia (AML), and use of routine pulmonary function testing after transplantation. Depending on the group, ursodeoxycholic acid prophylaxis use was prescribed by 22% to 40% of respondents. Routine use of ursodeoxycholic acid was predicted by performing adult allogeneic myeloablative procedures (OR 1.8, \( P = .005 \)), practicing in the United States (OR 1.7, \( P = .01 \)), and <60% clinical time (OR 1.7, \( P = .006 \)). Pediatricians were more likely than adult transplant physicians to obtain routine pulmonary function tests after transplantation.

**Protective Isolation**

After transplantation, policies on environmental and social restrictions were highly variable, as shown in Table 5. The overall median “total isolation score” was 17 with a range of 7-33. In multivariate modeling, pediatricians (median total isolation score = 19) were the most restrictive, followed by adult allogeneic myeloablative (median = 17), adult allogeneic RIC (median = 16), then adult autologous providers (median = 15) (\( P < .0001 \)). Younger physicians were more restrictive than older physicians (\( P = .002 \)).

**DISCUSSION**

We report the results of a cross-sectional survey of 526 adult and pediatric HCT physicians participating in the CIBMTR. We found a high degree of...
agreement about certain practices such as pre-HCT organ function measurement and posttransplant routine antifungal prophylaxis. Use of other practices, however, was much more heterogeneous.

One of the purposes of the pre-HCT evaluation is to ensure that patients have adequate organ function to meet clinical and protocol requirements for HCT. Although it is customary to require a certain minimum cardiac left ventricular function and pulmonary function testing results to proceeding with transplantation, it is not clear how physicians otherwise use these results to adjust treatment plans or counsel patients differently about risks [11,12]. More than 90% of physicians have all patients sign informed consent documents for HCT, reflecting a firm belief in the need for written documentation of a patient’s agreement to the procedure. Between 71% and 87% of respondents reported discussions of advance care planning issues with their patients, a much higher percentage than suggested by single institution studies [13,14].

Another purpose of the pre-HCT evaluation is to prepare patients mentally to undergo transplantation. Eighty-three percent of physicians had their patients met with a psychologist or social worker prior to HCT. Although psychosocial evaluation is unlikely to alter the treatment plan [15,16], the support of a psychologist and/or social worker prior to and during HCT may alter the level of distress experienced by

<table>
<thead>
<tr>
<th>Practice</th>
<th>Adult autologous*</th>
<th>Adult allogeneic - myeloablative†</th>
<th>Adult allogeneic – reduced intensity conditioning‡</th>
<th>Pediatricians§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine myelogenous growth factors, n (%)</td>
<td>Yes</td>
<td>118 (79)</td>
<td>80 (45)</td>
<td>28 (52)</td>
</tr>
<tr>
<td>Routine antibacterial prophylaxis, n (%)</td>
<td>Yes</td>
<td>118 (79)</td>
<td>136 (76)</td>
<td>41 (76)</td>
</tr>
<tr>
<td>Empiric treatment of neutropenic fever, n (%)</td>
<td>Single agent broad spectrum cephalosporin, beta-lactam or carbapenem</td>
<td>84 (56)</td>
<td>105 (59)</td>
<td>30 (56)</td>
</tr>
<tr>
<td></td>
<td>Combination therapy with 1 of the above and an aminoglycoside</td>
<td>46 (30)</td>
<td>59 (33)</td>
<td>16 (30)</td>
</tr>
<tr>
<td></td>
<td>Alternative antibiotic regimen</td>
<td>21 (14)</td>
<td>14 (8)</td>
<td>8 (15)</td>
</tr>
<tr>
<td></td>
<td>Yes, regardless of herpes simplex virus status</td>
<td>137 (91)</td>
<td>160 (90)</td>
<td>49 (91)</td>
</tr>
<tr>
<td>Routine acyclovir or similar antiviral prophylaxis, n (%)</td>
<td>Yes, if herpes simplex virus positive</td>
<td>79 (52)</td>
<td>110 (62)</td>
<td>36 (67)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>65 (43)</td>
<td>60 (34)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Management of cytomegalovirus, n (%)¶</td>
<td>Monitoring by PCR testing, preemptive therapy</td>
<td>77 (53)</td>
<td>99 (56)</td>
<td>33 (61)</td>
</tr>
<tr>
<td></td>
<td>Monitoring by antigenemia testing, preemptive therapy</td>
<td>51 (35)</td>
<td>98 (55)</td>
<td>24 (44)</td>
</tr>
<tr>
<td></td>
<td>Antiviral prophylaxis with ganciclovir or foscarine</td>
<td>17 (12)</td>
<td>22 (12)</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>No routine management strategy</td>
<td>6 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Isolation during hospitalization, n (%)¶¶</td>
<td>Hepa-filtration</td>
<td>110 (73)</td>
<td>153 (86)</td>
<td>40 (74)</td>
</tr>
<tr>
<td></td>
<td>Masks</td>
<td>50 (33)</td>
<td>93 (52)</td>
<td>26 (48)</td>
</tr>
<tr>
<td></td>
<td>Laminar-airflow rooms</td>
<td>39 (26)</td>
<td>62 (35)</td>
<td>15 (28)</td>
</tr>
<tr>
<td></td>
<td>Gloves</td>
<td>39 (26)</td>
<td>66 (37)</td>
<td>21 (39)</td>
</tr>
<tr>
<td></td>
<td>Gowns</td>
<td>32 (21)</td>
<td>60 (34)</td>
<td>13 (24)</td>
</tr>
<tr>
<td></td>
<td>Gut decontamination</td>
<td>22 (15)</td>
<td>50 (28)</td>
<td>11 (20)</td>
</tr>
<tr>
<td></td>
<td>Shoe covers</td>
<td>24 (16)</td>
<td>32 (18)</td>
<td>7 (13)</td>
</tr>
</tbody>
</table>

*Missing 1-3 responses.
†Missing 0-1 responses.
‡No missing responses.
§Missing 0-2 responses.
¶Categories not mutually exclusive. Percentages may add to >100%.

Table 4. Supportive Care and Monitoring Practices during and after Transplantation

<table>
<thead>
<tr>
<th>Practice</th>
<th>Adult autologous*</th>
<th>Adult Allogeneic - Myeloablative†</th>
<th>Adult Allogeneic - Reduced- Intensity Conditioning‡</th>
<th>Pediatricians§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic use of ursodeoxycholic acid, n (%)</td>
<td>Yes</td>
<td>33 (22)</td>
<td>71 (40)</td>
<td>21 (39)</td>
</tr>
<tr>
<td>Routinely restage patients with acute myelogenous leukemia at specific time point(s), n (%)</td>
<td>No, only according to clinical status</td>
<td>100 (66)</td>
<td>137 (77)</td>
<td>41 (77)</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>40 (26)</td>
<td>40 (23)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Routinely perform pulmonary function tests at specific time point(s) after transplantation in asymptomatic patients, n (%)</td>
<td>No, only if symptoms</td>
<td>39 (26)</td>
<td>82 (46)</td>
<td>18 (34)</td>
</tr>
<tr>
<td></td>
<td>Only if other chronic GVHD signs</td>
<td>90 (60)</td>
<td>74 (42)</td>
<td>27 (51)</td>
</tr>
</tbody>
</table>

GVHD indicates graft-versus-host disease.
*Missing 1-2 responses.
†Missing 1 responses.
‡No missing responses.
patients and their families. Some studies have observed an association between pre-HCT psychosocial distress and higher mortality after HCT [17,18]. The Institute of Medicine recently concluded that inadequate attention to psychosocial problems associated with cancer care can lead to compromise in the effectiveness of health care and the overall health of the cancer patients [19]. One barrier to more frequent referral may be the availability of support staff; a previous study suggested that between 20% and 50% of centers do not have dedicated psychosocial support staff [20].

Several infectious disease practices also varied substantially. Routine myelogenous growth factor use by adult autologous transplant physicians was higher than adult allogeneic or pediatric physicians, but still not consistent with published guidelines, which recommend its use in autologous but not allogeneic transplantation using adult or child donors [1]. Routine use of antibacterial prophylaxis was common among adult transplant physicians but less common in pediatrics. In contrast, routine antifungal prophylaxis was common in all groups, as supported by data from a randomized trial [3]. Other infection prevention procedures during hospitalization varied substantially. Hepa-filtration was widespread, whereas shoe covers and gut decontamination were the least common.

Supportive care and monitoring during and after transplantation also varied. Fewer than half of allogeneic practitioners routinely prescribe ursodeoxycholic acid, although several studies have shown improved outcomes in both adults and children [4-7]. Routine restaging of patients with AML and pulmonary function testing after HCT was common, but not universal. In particular, 42% to 51% of adult allogeneic transplant physicians would order pulmonary function tests only if the patient had symptoms. In patients diagnosed with cGVHD, routine pulmonary function testing is recommended to detect unsuspected airflow obstruction, which may not become symptomatic until extensive irreversible damage has occurred [21].

Protective social and environmental isolation restrictions following transplantation appear common, and are predicted by both physician characteristics and transplant type. Scant data provide guidance for recommendations [22-26], although it has been argued that common sense should prevail in these situations [27]. During hospitalization, protective isolation may exacerbate emotional isolation [28-31]. Anecdotally, many patients strictly abide by dietary, hygienic, and social contact restrictions, which may contribute to social isolation. Unless avoidance of friends, public places, and work/school for prolonged periods improves outcomes, liberalization of policies might facilitate resumption of important roles and reintegration into society.

A number of caveats to our conclusions should be noted. First, the common practices may reflect external factors rather than physician prerogative. For example, the homogeneity in pretransplant testing may relate to insurance or to institutional or protocol requirements, rather than to physicians’ beliefs about their necessity for individual patient care. If so, then their ubiquity highlights the opportunities to enforce proven supportive care practices through accrediting approaches or quality measures. We also caution that results should be interpreted with the awareness that these are self-reported physician practices from a subset of practitioners. Physicians may endorse what they believe the standard of care should be (eg, discussing advance care directives) rather than their actual practices. Respondents may represent a select group of motivated and interested physicians more inclined than nonrespondents to be aware of and adhere to best practices. Finally, the survey instrument may lack precision in capturing the range of practices or the ways in which physicians modify their practices and recommendations based on individual patients’ risks.

In summary, our study suggests that there is substantial variation in supportive care practices in HCT. These data have several practical implications. In some cases, published literature is available to bring practices into better compliance with proved approaches or consensus recommendations. Some simple practices such as routine use of ursodeoxycholic acid have been shown to improve outcome, but are still used by only a minority of practitioners. Serial pulmonary function tests are recommended to monitor patients with cGVHD, but almost half of adult allogeneic transplant physicians would obtain them only if
a patient was symptomatic. These observations indicate that successful randomized studies alone or published guidelines are not sufficient to change practice. Practice implementation studies, so-called “translational or T2” research, may be needed to identify more effective strategies for incorporating clinical guidelines into practice [32]. Second, in many cases where resources are not available to conduct randomized trials, the intrinsic heterogeneity of supportive care practices offers an opportunity to compare outcomes in observational studies to determine best practices [20,33,34]. For example, our study suggests that if detailed infection and outcome data were available, one could compare practitioners who routinely include an aminoglycoside in their empiric neutropenic fever regimens with those who do not. Third, knowledge of practice variation can identify areas where randomized trials may be possible. For instance, our results indicate that approaches to menses suppression vary, and could be studied prospectively. Finally, documentation of practice variation and dissemination of these results allows physicians to compare their practices with what others are doing in a way that may provoke introspection. We believe that assessing practice variation represents a promising tool to initiate the process of improving transplant outcomes by identifying practice variation patterns where further study and/or education is warranted.

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REFERENCES


