Mobilization and Transplantation Patterns of Autologous Hematopoietic Stem Cells in Multiple Myeloma and Non-Hodgkin Lymphoma

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Background: The mobilization of hematopoietic stem cells can be a limiting factor for transplantation, yet little is known about how the availability of novel mobilizing agents has affected the practices of oncologists and transplant specialists.

Methods: US-based oncologists (n = 48) and transplant specialists (n = 46) were separately surveyed with a partial overlap of assessed information.

Results: More transplant specialists than oncologists believed that the time between referral and first consultation is adequate (89.1% vs 54.2%; P < .001). The presence of comorbidities was the most common reason for patients not being referred for transplantation. Among oncologists, 31.3% avoided cyclophosphamide and 16.7% avoided lenalidomide to prevent mobilization impairment in patients with multiple myeloma (MM). Chemotherapy mobilization for MM was used by 23.9% of transplant specialists due to higher CD34+ yields and by 21.7% due to its anti-MM effect. In non-Hodgkin lymphoma (NHL), 26.1% of transplant specialists used chemotherapy mobilization due to higher CD34+ yields, and 26.1% collected hematopoietic stem cells on the rebound prior to chemotherapy. With regard to plerixafor use in MM, 36.9% of transplant specialists reported that they did not use it, and 28.3% said they reserved it for second mobilization. In NHL, 4.3% of transplant specialists reported not using plerixafor, and 39.1% reserved it for second mobilization.

Conclusions: Educational needs were identified to promote adequate referral for transplantation as well as successful and cost-effective methods for the mobilization of hematopoietic stem cells.

Introduction

Autologous hematopoietic stem cell transplantation (HSCT) is an increasingly important treatment option for several hematological malignancies, including multiple myeloma (MM) and non-Hodgkin lymphoma (NHL). The increasing use of autologous HSCT in individuals older than 65 years is partly due to the accumulation of data on the safety and efficacy of autologous HSCT for this age group. Furthermore, the emergence of novel mobilization agents has reduced the risk of mobilization failure, potentially extending the use of autologous HSCT to even more patients.

The mobilization of hematopoietic stem cells fails in approximately 20% of patients with MM and up to 40% of patients with NHL. Poor mobilization can lead to poor engraftment, increased morbidity, greater resource utilization, and increased costs. The cause of poor mobilization can be partially explained by clinical variables (ie, age, underlying disease, prior therapies, underlying marrow function) and cannot be predicted. To ensure optimal mobilization, factors such as mobilization strategy, timing of hematopoietic stem cell collection, and identification of risk factors for poor mobilization must be considered; such factors have been summarized in published guidelines. Early communication between the primary oncologist and the transplant specialist is key to the critical timing of patient referral to a transplantation center.
Inconsistencies in practice approaches to hematopoietic stem cell mobilization and collection exist among health care professionals.\textsuperscript{16,17} To further understand perceptions and practices from the points of view of both oncologists and transplant specialists, a national survey was conducted. An accredited medical education company (Med-IQ, Baltimore, Maryland) collaborated with academic-based faculty to identify perceptions and practices affecting hematopoietic stem cell mobilization and transplantation as well as to identify barriers to successful transplantation in MM and NHL.

Methods
Two separate electronic survey tools assessed oncologist and transplant specialist perceptions and current practices related to autologous hematopoietic stem cell mobilization and transplantation. Eligible health care professionals were US-based, English-speaking physicians or nurse practitioners specializing in oncology or hematology. A random sample of 16,707 health care professionals meeting the inclusion criteria was e-mailed or faxed an invitation to complete the online surveys. Eligible participants expressing interest were provided a link to the Web-based surveys and asked to self-identify as either an oncologist (defined as one who did not perform autologous HSCT for patients with MM, lymphoma, or both) or a transplant specialist (defined as one who did). A total of 132 health care professionals responding to the invitation and, after self-identification, were directed to the appropriate survey. All participants were required to complete a consent form prior to beginning the survey. Those who completed both the consent form and a survey received a $50 honorarium as compensation for their time.

The oncologist survey consisted of 17 multiple-choice questions; 4 questions required estimates of average number of patients and 1 question was open ended. The transplant specialist survey was composed of 21 multiple-choice questions and 1 open-ended question. Ten questions were common between the 2 surveys.

The study protocol, including surveys, was submitted to an independent institutional review board (Chesapeake Review, Columbia, Maryland) and deemed exempt from oversight. For each survey, responses were anonymously pooled and data were downloaded from the online survey program and saved in an unidentified format.

We described continuous numerical variables on the basis of median and interquartile range (IQR) and, where appropriate, categorical variables in terms of percentage with a 95% confidence interval (CI). Comparisons between proportions were performed using a chi-square test. All statistical analyses were performed utilizing SPSS (IBM, Armonk, New York). In all inference analyses, 2-sided P values less than .05 were considered statistically significant.

Survey Completion
Forty-eight oncologists completed the survey (44 physicians and 4 nurse practitioners). The majority (n = 38) practiced in a nonacademic setting. The median number of new MM cases seen by oncologists each month was 2 (IQR, 1.37–4), and the median number of new NHL cases was 3.5 (IQR, 2–6). Oncologists managed a median of 20 patients with MM (IQR, 10–40) and 40 patients with NHL (IQR, 22.25–67) in their practices at the time they completed the survey.

Overall, 46 transplant specialists completed the survey (44 physicians and 2 nurse practitioners). Eleven (23.9%) practiced in an academic setting and were fully dedicated to HSCT. Twenty-eight practiced in an academic setting dedicated to HSCT and also managed hematological malignancies. Seven transplant specialists were in nonacademic practices. The volume of HSCT procedures performed each year (including autologous and allogeneic) was self-reported to be less than 25 by 8.7% of transplant specialists, 25 to 49 by 4.3%, 50 to 99 by 41.3%, 100 to 200 by 17.4%, and more than 200 by 6.1%.

Transplantation Referral
We examined the possibility of delays in the referral process from the oncologist to the transplant specialist. Overall, oncologists perceived the process to be lengthier than transplant specialists (Fig 1), with 80.5% of transplant specialists stating that it took less than 2 weeks from referral to first encounter with a candidate for transplantation, whereas 39.6% of oncologists stated that patients referred to transplantation were typically seen within 2 weeks of referral (P < .001). The majority of oncologists (54.2%) believed the time between referral and first appointment was adequate (95% CI: 40.3–67.4), whereas 41.7% believed it was long but thought that the wait time had no detrimental effect on patient care (95% CI: 28.8–55.7). A total of 4.2% of oncologists believed that the time from referral to transplantation was too long and affected patient care (95% CI: 1.1–14.0). A higher proportion of transplant specialists (89.1% vs 54.2% of oncologists) believed that the time between referral and first appointment was adequate (95% CI: 76.9–95.2 vs 95% CI: 40.3–67.4, respectively; P < .001).

Referral Patterns
Multiple Myeloma
When asked what percentage of their patients with MM younger than 65 years of age consulted with a transplant specialist in the first 6 months following diagnosis, 6.25% of oncologists indicated fewer
than 5% (95% CI: 2.1–16.8), 25% indicated 6% to 20% (95% CI: 14.9–38.8), 39.6% indicated 21% to 50% (95% CI: 27.0–53.7), 16.7% indicated 51% to 80% (95% CI: 8.7–29.6), and 12.5% indicated more than 80% (95% CI: 5.8–24.7). In regard to the reasons patients with MM younger than 65 years of age would not be referred for consultation with a transplant specialist, 50% of oncologists cited comorbidities (95% CI: 36.9–63.6), 31.2% cited patient preference (95% CI: 19.9–45.3%), 6.3% cited lack of insurance coverage (95% CI: 1.2–14.0), 4.2% cited lack of response to salvage therapy (95% CI: 1.2–14.0), and 27.1% cited none of the survey-suggested reasons (95% CI: 16.6–41.0). Similarity existed between the opinions of oncologists and transplant specialists on when patients with diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma should be referred to autologous HSCT (Fig 3). More transplant specialists than oncologists believed that patients with diffuse large B-cell lymphoma and high-risk disease should be evaluated for transplantation during initial therapy ($P$ = not significant), and a larger proportion of transplant specialists believed that all patients with mantle cell lymphoma should be considered for autologous HSCT while still undergoing first-line therapy ($P$ = .02).

### Prior Therapy and Mobilization

Because they were aware that some MM drugs influence the efficacy of mobilization, 4.2% of oncologists avoided the use of bortezomib in patients who might be eligible for transplantation (95% CI: 1.1–14.0), 31.3% avoided cyclophosphamide (95% CI: 19.9–45.3), 16.7% avoided lenalidomide (95% CI: 8.7–29.6), 8.3% avoided liposomal doxorubicin (95% CI: 3.3–19.5), 0.8% avoided gemcitabine (95% CI: 0.2–2.5), and 0.6% avoided melphalan (95% CI: 0.2–2.0). Among the oncologists, 18.7% considered the role of autologous HSCT in MM to be in front-line therapy alone (95% CI: 10.2–31.9), 66.7% felt that autologous HSCT should be employed in both front-line and relapsed settings (95% CI: 52.5–78.3), and 14.6% believed it should be used in relapsed MM alone (95% CI: 7.3–27.2). Yet, little difference was seen between opinions of when patients with MM should be referred for transplantation consult (Fig 2).

### Non-Hodgkin Lymphoma

When asked to identify reasons why patients younger than 65 years of age with relapsed diffuse large B-cell lymphoma would not have a transplantation consult, 41.7% of oncologists cited comorbidities (95% CI: 28.8–55.7), 16% cited patient preference (95% CI: 8.7–29.6), 4.2% cited lack of insurance coverage (95% CI: 1.2–14.0), 4.2% cited lack of response to salvage therapy (95% CI: 1.2–14.0), and 27.1% cited none of the survey-suggested reasons (95% CI: 16.6–41.0). Similarity existed between the opinions of oncologists and transplant specialists on when patients with diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma should be referred to autologous HSCT (Fig 3). More transplant specialists than oncologists believed that patients with diffuse large B-cell lymphoma and high-risk disease should be evaluated for transplantation during initial therapy ($P$ = not significant), and a larger proportion of transplant specialists believed that all patients with mantle cell lymphoma should be considered for autologous HSCT while still undergoing first-line therapy ($P$ = .02).

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and 2.1% avoided thalidomide (95% CI: 0.4–10.9). A total of 54.2% of oncologists did not avoid any specific MM drug for this reason (95% CI: 40.3–67.4). When asked how the known impairment of lenalidomide on mobilization should be managed, similarity was seen between opinions: 4.2% of oncologists and 2.2% of transplant specialists believed that lenalidomide should not be used in induction therapy for MM, and 35.4% of oncologists and 28.3% of transplant specialists believed that lenalidomide could be used for induction, but patients would require chemomobilization to obtain an adequate number of CD34+ cells. The majority of responders (56.2% of oncologists and 63.0% of transplant specialists) believed that lenalidomide could be used, but hematopoietic stem cell mobilization and collection should occur after no more than 4 cycles of therapy. A small minority — 4.2% of oncologists and 6.5% of transplant specialists — answered that lenalidomide could be used for induction, but hematopoietic stem cell mobilization would be possible with the use of plerixafor alone. When oncologists were asked how the known effect of lenalidomide on mobilization affected their choice to use lenalidomide in patients with MM eligible for transplantation, 4.2% indicated that they did not use lenalidomide (95% CI: 1.1–14.0), 77.1% indicated that they used this agent but referred patients to transplantation before 4 completed cycles of therapy (95% CI: 63.5–86.7), and 18.8% used this agent without a specific cycle limit and were confident that the transplantation team could collect hematopoietic stem cells regardless of prior lenalidomide use (95% CI:
Similarly, because treatment for NHL can also influence the success of hematopoietic stem cell mobilization, 18.8% of oncologists avoided using bendamustine in patients eligible for transplantation (95% CI: 10.2–31.9), 4.2% avoided bortezomib (95% CI: 1.1–14.0), 60.4% avoided fludarabine (95% CI: 46.3–73.0), 16.7% avoided the hyperfractionated regimen of cyclophosphamide/vincristine/doxorubicin/dexamethasone (95% CI: 8.7–29.6), and 50.0% avoided radio immunotherapy (95% CI: 36.9–63.6). A total of 18.7% of oncologists did not avoid the use of any specific treatment in NHL for this reason (95% CI: 10.2–31.9).

**Mobilization Practices**

We explored how decisions regarding hematopoietic stem cell mobilization were made at different centers. Two decision-making processes were equally common: (1) the transplantation center had a uniform method of mobilization accepted and followed by all practitioners, and (2) a mobilization strategy was chosen based on stratification for perceived risk of mobilization failure (34.8% of responders for both; 95% CI: 22.7–49.2). Other frequently reported processes were that each individual physician at his or her site chose the mobilization method for his or her patients or that his or her center followed an algorithm to stratify patients to different strategies of mobilization based on peripheral blood CD34+ enumeration (15.2% of responders for both; 95% CI: 7.5–28.3).

A notable discrepancy existed between oncologists and transplant specialists in terms of their perceived risk of inadequate mobilization in both MM and NHL (Fig 4). Although 83.4% of oncologists believed that the risk of mobilization failure in NHL was less than 10%, 50.9% of the transplant specialists thought the same ($P = .02$). Similarly, the risk of mobilization failure in MM was considered to be less than 5% by 58.3% of oncologists, whereas 41.3% of the transplant specialist assessed this risk in the same way ($P = .09$).

The preferred method of hematopoietic stem cell mobilization among transplant specialists varied according to underlying disease. Overall, 47.8% of transplant specialists mentioned that their preferred method of hematopoietic stem cell mobilization for patients with MM was growth factor and planned or “just-in-time” plerixafor, followed by high-dose cyclophosphamide and growth factor (26.1%) or growth factor alone (17.4%). For patients with NHL, 47.8% of transplant specialists utilized growth factor following the last cycle of disease-appropriate chemotherapy as a mobilization strategy, 34.8% utilized growth factor with or without planned or “just-in-time” plerixafor. Growth factor following high-dose cyclophosphamide was the preferred method of hematopoietic stem cell mobilization in patients with NHL for 10.9% of transplant specialists.

In regard to the use of chemotherapy mobilization in MM, 54.3% of transplant specialists indicated that they did not use it because it is more
toxic than other modalities and not necessary (95% CI: 40.2–67.8). By contrast, 23.9% indicated that they utilized chemomobilization primarily because of the higher CD34+ yields, and 21.7% indicated that they used chemomobilization because they believed the additional dose of chemotherapy would help the patient with better disease control. When asked when they utilized plerixafor for hematopoietic stem cell mobilization, 36.9% of transplant specialists indicated that they never used it because the drug is expensive or unnecessary (95% CI: 24.5–51.4), 28.3% indicated that they used it following mobilization failure (95% CI: 17.3–42.6), 39.1% indicated that they used it in patients with MM at risk of mobilization failure (95% CI: 26.4–53.5), and 17.4% indicated that they used it “just in time” for patients with a low number of CD34+ cells in peripheral blood following the use of a growth factor (95% CI: 9.1–30.7).

For the use of chemomobilization in NHL, 39.1% of transplant specialists indicated that they did not use this modality (95% CI: 26.4–53.6), 26.1% used chemomobilization due to higher CD34+ yield (95% CI: 15.6–40.3), and 26.1% indicated that they used chemomobilization because the patient was already receiving chemotherapy for the management of NHL (95% CI: 26.4–53.6). A total of 8.7% indicated a preference for chemomobilization (95% CI: 3.4–20.3), citing the belief that the extra chemotherapy could help consolidate remission and prevent post-transplantation relapse. In regard to hematopoietic stem cell mobilization in NHL, 4.3% of the transplant specialists reported that they did not use plerixafor because it was expensive and unnecessary (95% CI: 1.2–14.5), 17.4% used plerixafor in all mobilizations (95% CI: 9.1–30.7), 26.1% used this agent in patients at risk of mobilization failure (95% CI: 15.6–40.3), 36.9% used a “just-in-time” approach with administration for patients with low CD34+ cells in peripheral blood (95% CI: 24.5–51.4), and 39.1% used plerixafor following first mobilization failures (95% CI: 26.4–53.6).

Discussion
Surveys provide a fast and relatively inexpensive approach to gather information. However, a caveat of selection bias can be present such that the small proportion of responding health care professionals has dissimilar characteristics and opinions from all other practicing oncologists and transplant specialists. It is difficult to assess the representativeness of this sample because no detailed characterizations of these groups are available, particularly with regard to transplant specialists as discussed in a recent assessment of the transplant specialist workforce. Nevertheless, it appears that the survey captured the opinions of oncologists with intense activity in MM and NHL, as reflected in the high number of patients reported; in addition, the transplant specialist group represented different practice types and volumes of patients treated.

We identified that a high proportion of patients with MM younger than 65 years of age was not referred for transplantation consultation early in the course of disease, despite the fact that most oncologists supported a role for early HSCT in MM. This is in synchrony with data showing the increasing but low utilization of autologous HSCT among younger patients with MM.

In terms of NHL, an overlap was seen in the opinion of oncologists and transplant specialists on the appropriate time for referral, although more transplant specialists believed that patients with mantle cell lymphoma should be referred for autologous HSCT while undergoing primary therapy. Even though oncologists and transplant specialists agreed on when patients should be referred for transplantation, a large number of oncologists perceived the referral process to be lengthy. This perception was not shared by a large majority of transplant specialists, who indicated that time from oncologist referral until first encounter with a transplant specialist may be a barrier and transplant centers may want to re-examine their processes to ensure that access is prompt and effective.

Among oncologists, comorbidities were cited as the most frequent reason patients younger than 65 years of age with a clinical indication for autologous HSCT would not be referred. Even though some of these patients may have obvious contraindications (eg, end-stage heart failure, liver failure, dementia), we found it concerning that autologous HSCT may be ruled out as a therapeutic option without the recommended assessment of a transplant specialist. Transplant eligibility based on age, comorbidities, and underlying disease are best evaluated by a transplant specialist. Even though the age of 65 years is frequently cited as a limit for autologous HSCT, the safety and efficacy of this treatment in older individuals has been demonstrated. Similarly, common comorbidities may be compatible with autologous HSCT, including chronic kidney disease, stable coronary artery disease, controlled cardiac arrhythmias, hypertension, diabetes, and prior treated malignancies. Therefore, oncologists should be encouraged to refer patients for evaluation by a transplant specialist in accordance with accepted guidelines.

Nearly one-third of oncologists avoided cyclophosphamide-containing regimens in patients with MM because they believed the drug would impair mobilization despite evidence suggesting otherwise. This proportion was even higher than the proportion of oncologists who avoided lenalidomide, a drug shown to impair mobilization. More than one-half of health care professionals from both specialties acknowledged that lenalidomide can be used
in induction as long as patients proceed with early hematopoietic stem cell mobilization. However, 1 in 3 oncologists and 1 in 4 transplant specialists believed that patients who received lenalidomide induction should be mobilized with chemotherapy despite data that demonstrate these patients can be effectively mobilized with growth factor or growth factor plus plerixafor, particularly when referred early for mobilization.\textsuperscript{25,26} In regard to NHL, oncologists seemed concerned about the use of fludarabine and radioimmunotherapy in patients who are candidates for transplantation.

Several important observations were made in regard to mobilization practices. Oncologists perceived mobilization failure to be a less frequent problem than transplant specialists. This lack of awareness may be a contributing factor for late referral for autologous hematopoietic stem cell collection. In approximately one-third of the cases, we found that transplantation programs have a standard mobilization strategy; in another one-third of cases, mobilization strategy is chosen based on perceived risk of inadequate mobilization. A minority of transplant specialists adapted mobilization strategies based on the CD34\textsuperscript{+} enumeration, a practice that can lead to resource rationalization and a high rate of mobilization.\textsuperscript{27-29}

Transplant specialists indicated more frequent use of chemomobilization in NHL, partly because such patients are already receiving disease-specific chemotherapy and mobilization can often be performed during recovery from the previous cycle of chemotherapy. In MM, most transplant specialists who indicated a preference for chemomobilization believed that its use would offer better long-term disease control, which is an unconfirmed hypothesis.\textsuperscript{30,31}

A large proportion of transplant specialists indicated that they do not use plerixafor mobilization due to its high cost or reserve its use for a second attempt in patients who have failed initial mobilization. However, some studies suggest that, although plerixafor is costly, its judicious use based on individualized risk of poor mobilization avoids the expense of remobilization and medical care for the complications of chemotherapy mobilization, thereby neutralizing the cost difference and potentially allowing more patients to proceed to transplantation.\textsuperscript{27,32,33}

Conclusions

This survey suggests that several areas are in need of improvement. Oncologists may benefit from additional education on the importance of referring potential candidates for autologous hematopoietic stem cell transplantation early on as well as the implication of their therapy choices on the collection of hematopoietic stem cells. Because hematopoietic stem cell mobilization methods remain diverse, more education and broader discussions involving transplant specialists may improve patient outcomes. In addition, more prospective trials and clinical data are needed to further delineate mobilization practices. Oncologists and transplant specialists should be encouraged to work together to streamline processes that promote easy and fast access for referred patients.

References


