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STEM CELL TRANSPLANTATION (R MAZIARZ, SECTION EDITOR)

The Difficulties of Informed Consent in Stem Cell Transplant

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Abstract Informed consent is the process by which a competent patient is provided with a sufficient amount of relevant information to make an educated decision about a procedure. The process of informed consent is designed to prioritize patients' autonomy. Stem cell transplant (SCT) is a complicated process with many possible results and requirements for ongoing decision-making depending on outcomes and complications. While understanding basic theories of decision science will help the physician provide improved information at the time of consent, experiential learning by the patients as they proceed through SCT may have the strongest influence in continued patient decision-making that may or may not align with their initial informed consent.

Keywords Informed consent · Autonomy · Stem cell transplant

> "Information is not knowledge. The only source of knowledge is experience."
> Attributed to Albert Einstein

Introduction

Informed consent is the process by which a decisional patient is given adequate information to decide whether he or she wishes to proceed with the intervention in question. It is both a legal and ethical requirement. The need for informed consent was borne out of the atrocities that occurred during the Holocaust and the Syphilis Study in Tuskegee, Alabama. The necessity for informed consent was codified with the Nuremburg code in 1947 and brought to public attention with a 1966 New England Journal of Medicine article entitled "Ethics and Clinical Research," in which Henry Beecher concludes:

> The statement that consent has been obtained has little meaning unless the subject or his guardian is capable of understanding what is to be undertaken and the hazards are made clear [1].

More recent reviews have addressed the evolution of informed consent in the modern era [2•, 3]. The process of informed consent for standard clinical care is different than that for participation in medical research, where the goal is to improve care for a population of patients, not just the individual. Yet, many of the same ethical considerations apply, particularly in high-stakes decision-making. Ultimately, the goal is to assist the patient in making his or her best decision at that time point.

In the era before anesthesia was available, surgical consent was often limited to the moment when the patient agreed to surgery, and thereafter, the wishes, or frequently, screams, of the patient were ignored. If a patient had agreed, that agreement remained in effect for the entirety of the procedure and its aftermath. Surgeons were prized for their speed and assistants for their strength in restraining patients [4]. This is very

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different from a stem cell transplant (SCT) today where a patient may consent to the transplant procedure but upon the development of complications, may decline further interventions such as dialysis or intubation. In this setting, it is clear that both the process of becoming 'informed' and the process of 'consent' are ongoing and based firmly in the patient's autonomy. Patients considering a stem cell transplant are embarking on a life-changing process with highly variable, somewhat unpredictable outcomes, the consequences of which can be difficult to understand for an average person. Consequently, it is debatable whether the individual is "capable of understanding what is to be undertaken," therefore placing the entire validity of informed consent in doubt and leaving physicians in the unenviable position of trying to find a correct balance between paternalism, beneficence, and patient autonomy. This review will address the goals of the informed consent process in SCT, placing in perspective the challenges in the decision-making process inherent to SCT.

Informed Consent

In a perfect world, devoid of intellectual limitations, time restrictions, emotional barriers, interpersonal conflicts, and physiologic realities, the informed consent process would not only satisfy medico-legal requirements but would also uniformly prevent patients from proceeding with a procedure that is inconsistent with their goals. Though laws vary by state regarding whether 'reasonable information' or 'full and complete disclosure' is required, the information provided must be understood by the patient, and the patient must be free to choose what is best for him- or herself [5].

For patients with acute leukemia, stem cell transplant is often regarded as the only potentially curative option. Given this sometimes unilateral view of transplant as the only life raft for survival, it can be difficult for patients to comprehend the very high morbidity and mortality of the transplant process, the potential for significant financial toxicity, risk to quality of life, and significant psychosocial stressors. Because the perceived 'life raft' is expected to carry the patient to safe harbor, it is difficult to imagine that life on that raft might actually contain dangers more difficult than life with a blood cancer or even a life potentially worse than death. A careful decision is required to maximize the likelihood of a favorable outcome that addresses more than just the overall survival benefit. The financial, social, and emotional ordeal of surviving must be acknowledged as well.

A careful consent process should also mitigate the risk for decisional regret. Decisional regret is one of the causative forces behind the requirement for informed consent. It describes a patient's feeling that he or she would have made a different decision if they had received more information [6•]. The goal of an informed consent is to prevent decisional regret by supplying all the necessary information to make a well-informed decision. Unfortunately, the complexity of living with a foreign immune system in one's body introduces a large number of unpredictable complications that are difficult to describe. While informed consent is tailored to the individual patient to the extent possible and may include many of the predictive tools for outcomes (hematopoietic cell transplant-comorbidity index, pre-transplantation assessment of mortality, Disease Risk Index, European Group for Blood and Marrow Transplantation risk score) in addition to providing specific data to the patient about his or her own situation and the local treatment environment, there will still be doubt as to how well a patient can truly understand the transplant process prior to undertaking it [7–10].

The Reality of Informed Consent

The informed consent process focuses on ensuring that patients have adequate information to make decisions about their willingness to proceed with stem cell transplant. Both emotional and educational ability can interfere with comprehension of the available information about SCT. It can be difficult to reconcile a consent process as "voluntary" after presenting patients with data suggesting SCT as the dominant option for long-term survival. Aside from the difficulty of trying to perform an unbiased, thorough, informed consent conversation in the highly emotionally charged setting of SCT, physicians are faced with the prospect of explaining the likelihoods of various risks and benefits to a population that has documented poor health literacy and numeracy [11]. Numeracy is a subset of overall health literacy and refers to the ability to understand numbers. One study has shown that 16 % of highly educated individuals were unable to correctly answer questions about risk magnitude [12]. Given the inherent imbalance in the informed consent discussion, it is perhaps not surprising that physicians and patients have been shown to have different expectations from SCT. In one study performed by Lee and colleagues, despite physicians providing lower estimates of disease-free survival in cases of intermediate or advanced disease, patient expectations regarding the outcome of their disease remained high [13]. Patients do not have a way to apply a median survival statistic into their own anticipated outcome. Similar results were seen by Grulke and colleagues who found no agreement with physicians' and patients' assessment of prognosis, this despite the physicians sharing their views on prognosis with the patients. While the physicians' assessments correlated with actual survival, the patients' assessment did not. The authors postulated that "To assess one's own chances of being cured is a highly emotional task that triggers negative mood states and seems to be only vaguely grounded in hard facts," again, bringing into question whether patients can truly understand the information that is provided to them [14].

Most patients have relatively little experience with SCT and the description of potential complications provided in a consent conference may be difficult for a patient to assess and incorporate into the initial decision to proceed. While a patient may consent to proceed to SCT, the commitment to continue aggressive care toward a long-term and abstract goal of cure may wane in the face of a more immediate and tangible experience with sepsis, the intensive care unit, graft-versus-host disease, etc. This phenomenon has been studied in high-risk surgery, where surgeons demonstrate an expectation of patient 'buy-in' to post-operative life support based on informal contracting pre-operatively [15]. The expectation of a similar commitment to high-level aggressive care post-SCT has not been well studied.

In absence of comprehension of the data or first-hand experience with SCT, studies on the decision-making process in SCT identify positive outcome expectations and trust in the physician as primary drivers in the choice to proceed. Accordingly, the ethical principle of beneficence is of paramount importance as physicians must provide the emotional support to patients who often feel that they are selecting the only viable decision because prospects are otherwise so low [16].

Decision Science

Significant study of decision-making in diverse fields including medicine has developed formally into 'decision science.' Decision science is the study of decision-making with the goal of improving outcomes and satisfaction with decisions [17]. It can be applied to the process of obtaining informed consent for SCT, with the goal of improving physician and patient understanding of the drivers of and biases regarding presentation of information and incorporation of values and ongoing experience. Behavioral economics focuses more specifically on the ways in which people can be influenced to make beneficial decisions and has not been applied in SCT. In the setting of SCT, the issues of framing, decision support, and shared decision-making are critical for understanding how to improve patient choices.

Framing

The way in which choices are presented by the physician and the context in which they are presented exert an extraordinarily powerful and potentially distorting influence upon the patient's resulting decision. This structure is described as choice architecture [18]. In SCT, the physician is typically the 'choice architect' who structures the discussion and ultimately decides to offer the option of stem cell transplant. Consents include discussions of risks, benefits and alternatives, and often a number of statistics including transplant-related mortality, risk of GVHD, overall survival, and likelihood of long-term survival without transplant. Many patients find it difficult to achieve a proper balance between dichotomous obvious outcomes (living vs. dying) and continuous variables (quality of life, financial burden) and are known to show a distinct bias toward the dichotomous outcome as it is simpler to understand [19]. When the discussion is framed around choosing a greater chance of living than dying, the option of life may overwhelm the importance of quality of life and in fact eliminate the possibility of a "choice." The difficulty of framing and establishing a context when performing an informed consent discussion is compounded by the difficulties with innumeracy. When presented with statistical information about the results of treatment with radiation therapy versus surgery for lung cancer, volunteer patients, students, and physicians were all shown to vary their preference depending on whether or not the data was presented in terms of probability of living (positive framing) versus probability of dying (negative framing). Additionally, choices varied depending on whether treatments were identified or de-identified, suggesting, perhaps not surprisingly, that individuals often rely on pre-existing beliefs more so than actual data when making decisions [20]. In combination with framing, the use of simplification of complicated choice and the assignment of value represent a simplified version of Daniel Kahneman and Amos Tversky's prospect theory. Each of these practices represents an opportunity for clarification and education about the decision process, by reframing using positive and negative frames avoiding incorrect oversimplification and the clarification of likelihoods and importance of outcomes.

Decision Support

Decision support tools are interventions that are intended to provide patients and physicians with support for making difficult decisions. These tools come in a multitude of forms, online videos, paper diagrams, and computer-based models, and are used to improve the quality of outcomes after interventions both for the patient and the healthcare system. In SCT, patients are often provided with written literature and on-line recommendations to obtain additional information. The presence of support and referral groups can also increase the patient's exposure to 'real' life patients who can provide real-life perspective. Decision support tools have been extensively studied in breast and prostate cancer, but less so in fields such as SCT with smaller patient numbers, where the development and validation of tools is more difficult, though arguably more critical.

Shared Decision-Making

Shared decision making is the process by which patients, along with their families and physicians, try to merge these varied interests as they discuss medical options. This approach is endorsed by the Institute of Medicine in its report "Crossing the Quality Chasm" and reflects the goal of increasingly patient-centered care [21]. Ideally, patients can become more active participants in the decisions about treatment and in their subsequent care with the greater understanding derived from a more engaged decision-making process.

It is clear that a SCT is not an appropriate therapy for every patient with a transplantable disease. Often, the most important decision is made by the physician who decides whether to refer the patient to a transplant physician. This is not a trivial matter given the known inconsistency of practice variation in physician referral [22]. Once a patient and transplant physician meet, however, each participant brings a number of factors to the table. The patient's decision process involves a number of identified factors including income, education, disease specifics, desire to survive, and familial obligations [23, 24]. The physician is also constantly gathering not only disease- and donor-related information but extended information about the patient's social structure and value system in order to help inform his or her recommendation.

One of the difficulties with shared decision-making is being able to incorporate patient wishes that are not always obvious or even known to the patient. Though there are competing theories on the development of preferences, the constructive preference theory suggests that people construct a preference in a given situation based on the information that they are provided, rather than resorting to deeply seeded values that would inform a decision in a new situation [25]. Preferences may therefore be influenced by familiarity and previous experience, whereas an absence of these may lead to an arbitrary decision influenced by unexpected factors. Because stem cell transplant is still a relatively uncommon procedure as compared to chemotherapy or surgery, patients often have little or no knowledge of the process prior to being diagnosed with a hematologic condition. Halpern et al. demonstrated the flexibility of beliefs in a study of thoracic oncology patients that utilized manipulation of default options on advance directives to demonstrate that the pre-set default option was a powerful influence on the patient's stated preference. By starting with a pre-selected option on the advance directive, patient choices regarding their end-of-life wishes (comfort care vs. life-extension) were strongly influenced by the default option suggesting that even with a decision as fundamental as end of life preferences, patients may not have deeply held preferences that will help guide their decision [26•].

Conclusions

The process of informed consent will benefit from starting earlier and continuing later through the SCT process. While resources for physician education and development are available through national programs such as the NMDP and ASBMT/CIBMTR, there is not a standardized curriculum for patients. Consideration could be given to development of a standardized education program, with accompanying studies to demonstrate impact on patient decision-making and decisional regret. The continued study of how to improve decision-making for patients who are undergoing the process will assist in the least regret, the best utilization of resources, and the fewest unpredictable reversals in goals of care. SCT is not an emergency procedure requiring immediate consent; rather, it is a complex process for patients who have often been ill for several months. The early referral of patients to discuss the process and begin to gather information will enhance the selection of appropriate patients and the provision of appropriate treatment recommendations.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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