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Impact of Declining Fertility Rates in Canada on Donor Options in Blood and Marrow Transplantation

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An HLA-matched sibling remains the optimal donor for most patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Marked declines in total fertility rates in Canada over the past 50 years will lead to increasing numbers of patients without sibling donors well into the future. We retrieved transplantation data from a Canadian center and the Canadian Blood and Marrow Transplant Group and total fertility data from the United Nations Department of Economic and Social Affairs. The mean age of adults with acute myelogenous leukemia (AML), who underwent transplantation at The Ottawa Hospital between 1995 and 2004, was 41 ± 12 years (n = 87). The chance of finding 1 or more HLA-matched sibling donors for a patient with AML treated in 2002 is reflected by the total fertility rate in 1961 (average birth year for patients and sibling donors). The sibling rate for 1961 is the total fertility rate–1.0, or 2.68. The chance of having 1 or more HLA-matched sibling is 53.7% (1–chances of no matched sibling, or $1 - 0.75^{2.68}$). In 2009, the chance of identifying a matched sibling is only 37.1%, because of declining total fertility rates. Following this trend, this chance will be 24.6% in 2014 and 16.6% in 2024. Greater reliance on alternative donors, such as umbilical cord blood (UCB) and HLA-mismatched donors, can be anticipated. The issue of declining fertility rates appears to be regional, and the impact on transplantation will be more pronounced in Canada than in other developed nations.

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INTRODUCTION

An HLA-matched related sibling donor is the optimal donor for most patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) [1,2]. Recent results from several groups also have reported favorable outcomes for some patients using unrelated HLA-matched donors identified through international registries [3-5]. Alternative donors, such as haploidentical transplants, HLA-mismatched transplants, and umbilical cord blood (UCB), are emerging as potential options, but these are associated with greater risk and increased resource utilization [6-11]. Alternative donors are typically reserved for patients with more advanced disease or with particular high-risk features.

The likelihood of successfully identifying a suitable HLA-matched sibling donor increases with a greater number of siblings. With the marked decline in total fertility rates over the past 50 years in Canada [12], patients will have fewer siblings and thus have a lower chance of finding at least one matched sibling donor for many years into the future.

Acute myelogenous leukemia (AML) is currently the most common indication for allogeneic HSCT in Canada [13] and afflicts approximately 1 in 25,000 individuals [14]. Although many patients are older or have concomitant medical problems that preclude aggressive treatment, a significant proportion of patients are eligible for allogeneic HSCT and can be cured in part by the graft-versus-leukemia effect [1-3].

In this article, we provide a quantitative model for the anticipated increasing reliance on unrelated and alternative donors for patients with AML undergoing allogeneic transplantation as a direct result of the declining total fertility rates in the Canadian population. The problem appears to be uniquely Canadian among developed nations with active transplantation programs. We provide some discussion of potential strategies to preserve transplantation options for Canadian patients.

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METHODS

The database of the Blood & Marrow Transplant Program at The Ottawa Hospital was searched to retrieve basic demographic information about patients undergoing allogeneic transplantation for AML between 1995 and 2004. All patients provided consent in accordance with the institutional research ethics board guidelines on the anonymous use of patient information for research purposes. Data on average birth rates per female in Canada and other countries were retrieved from the Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat [12]. Information on transplantations performed in Canada was retrieved from the Canadian Blood and Marrow Transplant Group registry [13]. Information on the searches performed by the OneMatch Marrow and Stem Cell Network was provided by Canadian Blood Services.

RESULTS

The mean age (± SD) of adults with AML who underwent HSCT at our center between 1995 and 2004 was 41 ± 12 years (n = 87). We estimated the year of birth using the mean patient age. For patients undergoing transplantation in 2002, for example, the average year of birth was 1961. Based on the assumption that patients and their siblings are on average the same age, we were able to determine the number of siblings for patients undergoing transplantation in any given year. Because the birth rate in 1961 was 3.68 per female (Figure 1), the sibling rate was 2.68. Siblings have an approximately 25% chance of being HLA-identical based on principles of haplotype segregation, ignoring the minor contribution from DNA recombination events. Thus, the expected number of HLA-matched siblings for a patient undergoing transplantation in 2002 was $0.25 \times 2.68 = 0.67$. Within any given family, more than 1 sibling may be an appropriate match for a patient. The chance of finding at least 1 matched sibling is equal to 1 minus the chance of not finding any matched siblings, or 0.75^n, where n is the sibling rate. Thus, for a family of 4 siblings, the chance of finding at least 1 matched sibling would be $1 - 0.75^3$, or 58%. In 2002, the chance of finding at least 1 matched sibling donor was 53.7% (sibling rate, 2.68). For patients undergoing transplantation in 2009, the average year of birth for the donors is 1968 when the birth rate is 2.61 (sibling rate, 1.61), and the chance of having at least one matched sibling donor is on average 37.1%. By the year 2024, the expected chance of having at least 1 HLA-matched sibling declines to 16.6% (Table 1).

Table 1. Calculating the Chance of Identifying an HLA-Matched Sibling Donor Depending on Donor's Year of Birth

Donor/Patient Birth Year	Average Birth Rate, Actual	Sibling Rate, Calculated	Chance of ≥ 1 HLA-Matched Sibling Donor, Calculated*
1951-1955	3.65	2.65	53.3%
1956-1960	3.88	2.88	56.3%
1961-1965	3.68	2.68	53.7%
1966-1970	2.61	1.61	37.1%
1971-1975	1.98	0.98	24.6%
1976-1980	1.73	0.73	18.9%
1981-1985	1.63	0.63	16.6%
1986-1990	1.62	0.62	16.3%
1991-1995	1.69	0.69	18.0%
1996-2000	1.56	0.56	14.9%
2001-2005	1.52	0.52	13.9%

*Formula: $1 - (0.75)^{\text{sibling rate}}$.

The reliance on unrelated and alternative donors will increase dramatically in Canada because of the marked drop in available matched sibling donors over the coming 15 years. If we assume that similar numbers of transplantations will be performed for AML over the next 15 years, then we can model the number of patients who will require an alternative strategy to matched-sibling transplantation (Figure 2).

In 2002, 107 allogeneic HSCTs were performed in Canada for adult AML using matched related donors

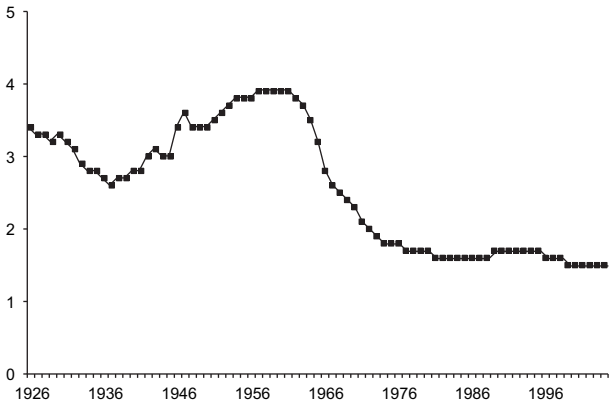

Figure 1. Total fertility rate in Canada, 1926-2004 (average children per female age 15-49 years in her lifetime). The 1926-1959 rates exclude Newfoundland, Yukon, and the Northwest Territories, and the 1960-1990 rates exclude Newfoundland. (Source: Statistics Canada, unpublished data.)

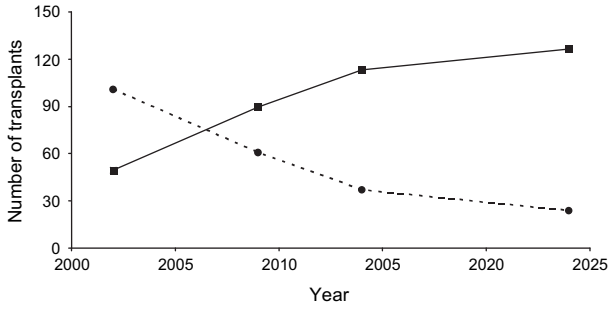

Figure 2. Projected decline in HLA-matched related transplantations in adults with AML in Canada (dashed line) and the increasing need for unrelated or alternative donors (solid line) if the number of adults undergoing transplantation for AML were to remain stable at 150 annually.

[13]. This number includes patients undergoing transplantation in first complete remission (CR1) or beyond, patients receiving peripheral blood stem cells (PBSCs) and/or bone marrow (BM), and patients undergoing a myeloablative (MA) or nonmyeloablative (NMA) conditioning regimen. From our previous calculations, the average chance of finding at least 1 matched sibling donor was 53.7% in 2002. If there were similar patients eligible for transplantation but without a sibling donor, then we estimate that an additional 92 patients were potential candidates for unrelated or alternative donor transplantation. A total of 43 transplantations were performed using unrelated donors and none were performed using CB in 2002, representing 47% of the predicted number of eligible patients. The gap between the number of patients potentially eligible for unrelated or alternative donor transplantation and those actually undergoing transplantation may reflect some patients for whom no donor could be identified, or patients who may have progressed during the longer period needed to identify and confirm an unrelated donor. Moreover, unrelated transplantation may have been deemed too risky for some patients, even if they were candidates for matched sibling transplantation. Details concerning the reasons why patients did not proceed to transplantation are not available. Based on the reduced numbers of patients who will have matched sibling donors, we expect that increasing numbers of patients will require alternative therapies, which could include matched unrelated, CB, and mismatched donors (Table 1).

We estimated the success rate of finding matched unrelated donors (MUD) for Canadian patients through international registries by calculating the total number of donor workups requested through the OneMatch Marrow and Stem Cell Network of Canadian Blood Services, which coordinates unrelated donor searches for all Canadian transplantation centers. The success rate in finding a suitable donor (as determined by the transplantation center) was used to estimate the combined utility of the international unrelated registries for Canadian patients. Between 2004 and 2009, a total of 2674 donor workups were requested for Canadian patients, and 1296 suitable donors were identified (48.5%). In terms of variation among ethnic groups, success in finding a suitable donor was most likely for patients of East Indian descent (59.6% of 47 requests) and the lowest rates were observed in patients who self-identified as black (24.5% of 53 requests) and Chinese origin (14.3% of 14 total requests). The most common ethnicity of patients requiring unrelated donor workups was Caucasian (2058 workups requested and 50.0% success in finding a suitable donor) and other/unknown (263 requests and 49.8% success). Of interest, the success rate in finding a suitable donor for aboriginal Canadians was only slightly lower than that of the overall group (42.4% success in 33 requests).

We addressed whether declining total fertility rates are particular to Canada by examining trends in several developing countries during the period 1970-2007. We found varying degrees of decline in total fertility rates over the past 40 years in most countries (Figure 3), although the United States has maintained a stable rate of approximately 2.0, whereas France and the United Kingdom have had stable total fertility rates of approximately 1.8 since 1990, and Germany and Italy have had stable fertility rates of approximately 1.5 since 1990. It appears that Canada and Japan are the only 2 developed nations that we examined that have a similar trend of declining fertility rates persisting beyond 1990.

DISCUSSION

Our findings highlight the important impact of declining fertility rates on the practice of allogeneic HSCT in Canada. As the number of cases without a matched sibling donor increases over the next 15 years, there will be an increasing number of patients relying on alternative donors, such as haploidentical, mismatched, and UCB donors.

Unrelated donor registries typically underrepresent certain ethnic and minority groups, as we observed in Canadian patients requiring donor searches through the OneMatch Marrow and Stem Cell Network. Overall, it appears that Canadian patients have reasonable success in finding appropriate donors through unrelated registries, although up to 50% of patients still may not have a suitable donor. The utilization rates of the National Marrow Donor Program were estimated to be approximately 33% in a recent report [15]. Moreover, donor registries must deal with attrition and change of donor status, which can hinder success in finding a matched donor in a timely manner. It is likely that rates of successfully searching unrelated donor registries will plateau and will remain challenged by rapid changes in global ethnic diversity. The rate of finding a matched donor for Canadian patients is substantially lower in specific population subgroups, related to cultural and ethnic-specific

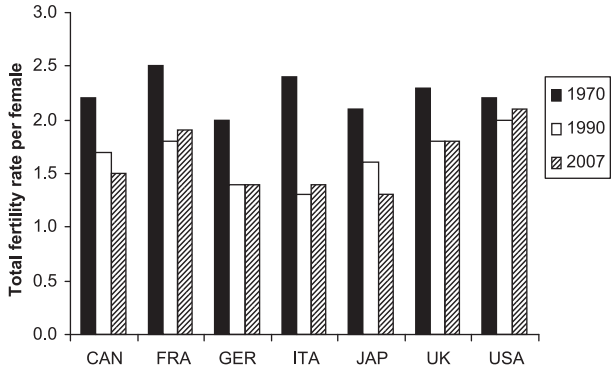

Figure 3. International trends in total fertility rates, 1970-2007.

factors. We did not address data on changing fertility rates in these subgroups of the Canadian population in this study.

It remains uncertain whether the median age of patients undergoing HSCT for AML will remain stable. As the use of reduced-intensity conditioning (RIC) regimens increases, we are likely to see an increase in the median age of transplantation-eligible patients. A separate analysis of the impact of changing fertility rates may be needed to better understand the future impact on this older population of patients with AML. It is likely that RUC transplantation may delay the impact of reduced total fertility rates.

Strategies that recognize the impact of changing fertility rates in allogeneic HSCT are needed. In addition, alternative therapies for AML and other diseases currently treated with blood and marrow transplantation will become even more essential. Interestingly, the importance of changing fertility rates varies in different countries [12], and different strategies may be required to ensure an adequate supply of matched donors in various jurisdictions. Other countries with well-developed HSCT programs may have different demographics in terms of aging, immigration, and ethnic minority populations. It appears that Canada faces challenges that are distinct from the United States and some European countries in this regard.

Potential strategies to ensure an adequate supply of donors for allogeneic HSCT include UCB banking, aggressive and novel recruitment strategies to unrelated donor registries, and successful development of improved transplantation practices and leukemia care reduce the need for HLA-matched donors.

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