Economics of hematopoietic cell transplantation

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Given the rapidly rising healthcare costs, it is important to understand the economic costs of hematopoietic cell transplantation (HCT), a procedure that is being used more frequently in the treatment of various hematologic disorders. Studies have reported a wide range of costs for HCT, from $36 000 to $88 000 (USD) for a single autologous transplantation for the initial hospitalization, to $200 000 (USD) or more for a myeloablative allogeneic procedure involving an unrelated donor. Common posttransplantation complications, such as infections and GVHD, have been shown to be significant cost drivers. Comparisons across studies are limited by differences in patient populations, cost ascertainment methods, and length of follow-up. This article summarizes the current state of knowledge about costs and cost-effectiveness of HCT, highlighting the challenges in conducting these studies and identifying important areas for future research. We discuss the need for more value-based assessments of HCT using high-quality approaches to measuring costs and outcomes so that potential future efforts to contain costs are well informed and appropriate. (*Blood*. 2012;120(8):1545-1551)

Introduction

Hematopoietic cell transplantation (HCT) is an important treatment modality for many benign and malignant hematologic disorders. There has been a dramatic increase in the number of autologous and allogeneic procedures performed worldwide.[1] However, an increasing use of this expensive treatment modality has economic consequences. According to an Agency for Health Care Research and Quality report, HCT generated the most rapid increase in total hospital costs from 2004 to 2007 with a growth rate of 84.9% and $1.3 billion spent in 2007.[2] It was estimated that 25.6% of this increase was the result of an increase in mean cost of hospital stays, and 59.3% was the result of an increase in the number of hospital days.

As advances in HCT allow the procedure to be offered to more patients, it is critical not only to assess clinical outcomes but also to carefully monitor financial costs. Increased attention to value for money can assist in the development of clinical practice guidelines and ensure that insurers and other agencies make appropriate coverage decisions. Accurate knowledge about clinical benefits and economic consequences can also help inform discussions between physicians and patients about treatment decisions that can affect costs of care, especially if treatment choices cause financial hardship for the patient without increasing the chance of a successful outcome.

Methods

Search strategy

The Medline database was searched using the following terms: "stem cell transplantation" or "hematopoietic cell transplantation" or "bone marrow transplantation" and "economics" or "cost analysis." Only articles published in English between January 1, 1986 and December 31, 2011 were considered. The reference lists from publications were reviewed to identify other relevant papers. Abstracts were reviewed and full text articles were retrieved if the study reported any information about costs as a primary or secondary outcome.

Each published cost study was reviewed and assessed for 3 important components: general study design, the type of cost data collected, and the analytic methods used by the authors in analyzing the cost data. These components have been highlighted as critical considerations for evaluating the quality and robustness of economic evaluations in healthcare.[3] Each study was summarized by N.K. with secondary review by S.B.Z. and S.J.L. if a component of the study was not clearly described in the original manuscript.

Why do costs matter?

The societal burden of cancer care is substantial and likely to increase with the newer treatment modalities. The National Cancer Institute estimated 13.8 and 18.1 million cancer survivors in 2010 and 2020, respectively, with associated costs of cancer care of $125 billion and $158 billion (2010 US) assuming constant incidence, survival, and cost.[4] Taken together, leukemia andlymphoma are the third most expensive cancer in females and second most expensive cancer in males. The rapidly evolving field of HCT is a key cost driver in treatment of these hematologic malignancies and other disorders. It lends itself to incorporation of economic evidence when evaluating the impact of advances in the field and understanding their cost consequences.[5,6]

In clinical practice, a common dilemma is how to factor in the concern for healthcare expenses into the clinical decision-making process (eg, when recommending a third line treatment for steroid refractory GVHD, considering options for a patient who relapses with acute leukemia within the first month after HCT or managing a patient with chronic GVHD who cannot afford medications/tests because of lack of insurance). This adds to the daily struggle between delivering care and considering the downstream effects on resource use for the healthcare system as well as the consequences on patient quality of life and financial burden. We no longer live in a world where we can ignore the costs of treatments we are recommending, even if a patient has insurance. Financial hardship from rising premiums, increased deductibles, copayments, and coinsurances for the patient can decrease their compliance with the recommended management and potentially undermine treatment success, especially if they choose to limit their medical care because of concerns about medical costs.[7,8] Having better information about the costs and outcomes can help them and their caregivers develop a financial plan at the outset, which may help avoid potentially deleterious health behaviors.

Although a detailed discussion about the role of costs in decreasing access to HCT is beyond the scope of this article, increasing procedural

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Table 1. Characteristics of cost studies in HCT

Study	Publication year	No. of study patients	Types of transplants	Costs/charges (median)	Costs/charges adjusted to 2012 USD	Time horizon
Societal						
Frey et al[26]	2002	Inpatient (n = 26), Outpatient (n = 21)	Autologous	Inpatient: $40 985 USD Outpatient: $29 210 USD	Inpatient: $51 639 USD Outpatient: $36 803 USD	Beginning of HDT to discharge from the facility
Hospital/healthcare system						
Smith et al[33]	1997	58	Autologous	PB: $45 792 USD BMT: $59 314 USD	PB: $68 106 USD BM: $88 217 USD	Initial transplant hospitalization
Kline et al[19]	1998	46	Both autologous and allogeneic	Mean charges: $243 550 USD	Mean charges: $338 676 USD	Initial transplant hospitalization
Lee et al[21]	2000	236	Both autologous and allogeneic	Auto: $55 500 USD Allo: $105 300 USD	Auto: $78 379 USD Allo: $148 709 USD	Initial transplant hospitalization
Van Agthoven et al[62]	2002	97	Allogeneic	MRD BM: $98 334 USD MUD BM: $151 754 USD MRD PB: $98 977 USD	MRD BM: $179 987 USD MUD BM: $277 765 USD MRD PB: $181 163 USD	2 y
Lee et al[20]	2002	TCD (n = 47), IST (n = 98)	Allogeneic	TCD: $113 000 USD IST: $155 000 USD	TCD: $148 740 USD IST: $204 024 USD	1 y
Cordonnier et al[32]	2005	MA (n = 12), NMA (n = 11)	Allogeneic	MA: €64 600 NMA: €60 000	MA: $109 710 USD NMA: $101 898 USD	1 y
de Lissovoy et al[17]	2005	TCD (n = 194); NTCD (n = 202)	Allogeneic	TCD: $145 115 USD NTCD: $141 981 USD;	TCD: $185 728 USD NTCD: $181 717 USD	6 mo
Svahn et al[31]	2006	93	Allogeneic	€139 414	$214 703 USD	5 y
Saito et al[24]	2007	MA (n = 185), RIC (n = 90)	Allogeneic	MA:$128 253 USD RIC:$80 499 USD;	MA: $153 893 USD RIC: $96 592 USD;	1 y
Saito et al[23]	2008	315	Allogeneic	$128 800 USD	$154 549 USD	1 y
Majhail et al[35]	2009	UCB (n = 173) MRD (n = 121),	Allogeneic	UCB: $137 654 USD MRD: $83 583 USD	UCB: $145 435 USD MRD: $88 308 USD	100 d
Majhail et al[28]	2010	MRD (n = 27), MUD (n = 28), UCB (n = 91)	Allogeneic	Mean cost per day survived MRD: $3446 USD; MUD: $4050 USD; UCB: $4522 USD	Mean cost per day survived MRD: $3582 USD MUD: $4214 USD UCB: $4700 USD	100 d
Third-party payer						
Rizzo et al[25]	1999	Inpatient (n = 115), Outpatient (n = 17)	Both autologous and allogeneic	Charges inpatient: $157 698 USD Outpatient: $110 879 USD	Charges inpatient: $214 553 USD Outpatient: $150 854 USD	100 d

PB indicates peripheral blood; HDT, high-dose therapy; TCD, T-cell depletion; IST, immunosuppressive therapy; NTCD, non–T cell-depleted; MA, myeloablative; NMA, nonmyeloablative; RIC, reduced intensity conditioning; MRD, matched related donor; UCB, umbilical cord blood; MUD, matched unrelated donor; USD, United States dollar; and €, Euro.

costs also have the potential of worsening disparities. The inequitable distribution of a life-saving technology resulting from the constraints of infrastructure and financial resourcesis well illustrated by a study from Thailand.[9] This study found that a related HCT for patients younger than 10 years with thalassemia was the most cost-effective option in the Thai context, but because of the limited infrastructure, this could only be made available to a minority of patients. Medical possibility and economic reality are often in conflict.[10] For example, in the United States, HCT is not performed unless a means of paying for the procedure is secured, usually through insurance preapproval or patient prepayment. Physicians are less likely to refer patients lacking insurance for consideration of HCT.[11]

How much does HCT cost?

Table 1 shows the costs of HCT adjusted to 2012 US dollars using the Consumer Price Index, which historically observes 3% to 5% inflation in medical costs per year.[12] The year the study was published was used for adjustment when the time period for the cost data was not specified. Studies conducted using foreign currency were converted to US dollars for the original study period and then adjusted to current 2012 US dollars (USD).[13] Although accounting methods differ considerably, costs of autologous transplantation for the initial transplantation hospitalization have been reported to range from $36 000 to $88 000, whereas costs of allogeneic transplantation for the first year range from $96 000 to $204 000 in 2012 USD. Most studies report costs through the first 100 days, although some report costs within the first year or even up through 5 years.

Whereas most studies report "costs," which reflect the actual resources used to deliver a service, some report "charges." Charges are inflated from actual costs and may vary widely among institutions based on accounting methodology, payer mix, and unreimbursed care. Charges can be converted to costs using Medicare global cost-to-charge ratios or institutional ratios. There are newer approaches to assessing costs, including activity-based costing, which may provide a more accurate assessment of the true resources required for a service and help in controlling costs.[14] Although no studies have reported costs of HCT using these alternative approaches, pilot studies in other areas of medicine are ongoing and may provide a map for future studies of HCT costs.[15]

Most studies are performed from the perspective of the healthcare organization, although some take the perspective of the insurance company, or very rarely, society as a whole. The societal perspective includes all costs accrued in the treatment of disease, including direct medical, direct nonmedical (transportation, food, and lodging), and indirect nonmedical (lost wages and productivity from illness or premature death). The societal perspective is recommended by the Public Health Service's Panel on Cost Effectiveness in Health and Medicine,[16] but it is the hardest to report because of difficulty in measuring costs other than direct medical costs.

Certain costs are often excluded from consideration in many studies because they areinaccessible or difficult to collect, such as professional fees and costs to patients and families, including indirect costs.[17-20] Many studies exclude costs of donor identification/stem cell procurement and patient evaluation for transplantation eligibility.[21-24]

A few studies have looked at the out-of-pocket cost burden in HCT patients. Rizzo et al examined the unreimbursed direct

medical, direct nonmedical, and indirect costs along with perceived financial impact through a questionnaire in their study to determine whether the shift from inpatient to outpatient care affected the financial burden on the patients.[25] They did not find any significant differences in the out-of-pocket costs to the patients between the inpatient and outpatient treatment groups. A similar study that compared the profile of costs for inpatient and outpatient autologous transplants reported a median of $2520 incurred by the caregivers as out-of-pocket costs or lost opportunity costs.[26]

What factors are associated with higher HCT costs?

Patient characteristics. Lee et al did not find significant correlation between costs and patient age and sex, disease risk, or status in a study of 236 consecutive transplant recipients,[21] similar to findings by Griffiths et al.[27] However, in some more recent studies, advanced disease risk was shown to be a significant predictor of higher costs.[20,22,24,25] Rizzo et al reported that patients with standard risk disease treated as outpatients had hospital charges that were 34% lower than those treated as inpatients, whereas those with high-risk disease had similar total charges irrespective of inpatient versus outpatient status.[25] Performance status has not emerged as a significant predictor of costs in many adult studies, but in one pediatric study, costs per day survived were 30% more for patients with a Lansky score less than or equal to 80, than in those with a score of 90% to 100%.[28]

Transplant factors

Transplant center experience. Similar to the trends seen in the solid organ transplant literature, investigators have shown that higher costs are incurred when an HCT program is being established and that the costs and clinical outcomes improve with time and greater institutional experience. However, this economic advantage may be offset as the complexity of the patients treated increases or more aggressive supportive interventions are used, resulting in a plateau in the improvement curve.[21,29] Svahn et al looked at the pattern of treatment, costs, and survival for patients with grades 3 or 4 acute GVHD from 1977 to 2004 and found that both the survival and costs of treatment increased with time.[30]

Conditioning. Some investigators have compared the costs between reduced intensity and myeloablative regimens. The larger studies find that costs of reduced intensity procedures are less, with Saito et al reporting lower median costs ($80 499 vs $128 253 in 2004 USD) and fewer median hospital days (21 vs 39 days) within the first year of the transplantation in reduced intensity conditioning patients compared with high-dose regimens.[24] This finding was also reported by Svahn et al who showed a significantly lower cost with reduced intensity conditioning: median 109 206 Euros (range 52 100-217 170 in 2003 Euros) compared with full myeloablative conditioning with a median of 158 061 Euros (range, 57 880-345 640 in 2003 Euros; $P = .024$).[31] However, a smaller study from France did not find a significant difference in the mean cost for 1 year after HCT or in the number of hospital days over 1 year after transplantation.[32]

Graft type. In autologous HCT for lymphomas, mobilized peripheral blood was shown to be less costly because of lower graft collection costs, shorter hospital stays, and less need for supportive care in an analysis of resource use data from a multicentric randomized clinical trial.[33] In the allogeneic setting, stem cell source was not a significant predictor of costs when either high dose or reduced intensity conditioning was used.[23,24,34] However, a cost-effectiveness study in pediatric patients showed that a bone marrow graft was more cost-effective than peripheral blood stem cells for standard-risk acute leukemia.[22] In high-risk leukemia, the differences were less marked; therefore, neither option had a clear advantage.

URDs and T-cell depletion. Use of unrelated donors (URDs) has emerged as a significant cost driver, even if the costs of stem cell procurement are not included.[23,24,35] Among the URDs, there are conflicting data on whether T-cell depletion (TCD) decreases the overall costs. Lee et al reported significantly lower costs ($113 000 vs $155 000 in 2000 USD, $P < .001$) with T cell–depleted grafts in a single-center comparative analysis, but the economic substudy of the randomized TCD trial conducted by National Heart, Lung, and Blood Institute found comparable costs between the TCD and unmanipulated donor arms ($145 115 vs $141 981 in 2001 USD, respectively; $P = .63$).[17,20] The National Heart, Lung, and Blood Institute trial reported that, although TCD of the donor graft reduced the short-term costs, frequent hospitalizations and higher average number of hospital days resulting from infectious complications in the first 6 months after transplantation appeared to offset any savings seen with the initial transplantation stay.

Majhail et al compared costs of the first 100 days between matched related donor (MRD) transplantation and umbilical cord blood (UCB) transplantation in adults.[35] They reported that the highest median costs per day survived are for myeloablative UCB at $2082, followed by $1156 for nonmyeloablative UCB recipients, $1016 for myeloablative MRD, and $612 for nonmyeloablative MRD ($P < .001$). A subsequent analysis of 100-day costs in MRD, HLA-matched URD, and UCB transplants in a pediatric population showed equivalent costs in the UCB and HLA-matched URD group irrespective of whether costs of graft acquisition were considered but significantly lower costs in MRD.[28]

Posttransplantation factors

Duration of hospitalization. Inpatient hospital care has been shown to be the single most expensive category of healthcare expenditures.[36] In the HCT cost studies performed thus far, length of stay has been found to be a good proxy for short-term costs with correlation coefficients ranging from 0.39 to 0.9.[19-21,24] Bennett et al showed that most of the decrease in the cost of autologous transplant for lymphoid malignancies from 1987 to 1991 was the result of decrease in length of stay over time and not the result of changes in cost per day.[29] A novel approach by the Swedish group to help cut down the inpatient costs was to provide aggressive home care for patients undergoing HCT during their pancytopenic phase. Interestingly, in their case-control study, they reported better 2-year survival rates (70% vs 57%; $P < .03$) and lower costs (RR = 0.37; $P < .05$) for the home care group versus controls treated in the hospital.[37]

Transplantation complications. Posttransplantation complications have been reported in multiple studies to be major cost drivers in both the autologous and allogeneic setting.[21,32,35,38] In a multinational pilot study of a new oral mucositis scoring system, oral mucositis was found to be associated with worse clinical and economic outcomes.[39] WhereasMajhail et al reported dialysis, graft failure, and mechanical ventilation as factors associated with higher costs,[35] Lee et al found infection, veno-occlusive disease, acute GVHD, and death added between $15 300 and $28 100 each to allogeneic transplantation costs.[21] Similar findings were reported by Esperou et al who reported an addition of 20 000 Euros because of occurrence of GVHD and infections.[38] Svahn et al categorized the transplantation costs according to the initial transplantation period, first posttransplantation year and up to 5 years, and found that bacteremia and veno-occlusive disease continued to be significant predictors for higher costs in all 3 categories.[31] These data confirm that prevention and better management of these complications can improve clinical outcomes as well as reduce the associated costs and resource use.

Do drugs contribute substantially to costs of HCT?

Despite the substantial costs of drug therapy in HCT patients, the literature in this area is very sparse. Pharmacy costs are included in most studies evaluating hospital costs for the first 100 days or 1 year after HCT, and they range from 8% to 39% of the total costs of HCT.[19,40-42] Among the category of pharmacy charges, colony-stimulating factors and antibiotics appeared to be the major contributors in the study by Kline et al.[19] These analyses need to be updated given the changes in HCT practice in the last decade with increasing use of peripheral blood as a stem cell source and emergence of newer immunosuppressive regimens and anti-infective agents. In addition, little is known about the economic burden imposed by long-term pharmacy costs. Although HCT is different from solid organ transplantation because immunosuppression is not necessarily lifelong, it is still relevant to assess ongoing costs for patients with chronic GVHD who may require prolonged immunosuppressive treatment.[43]

In the area of supportive care in HCT patients, there are multiple studies looking at the economic consequences of antifungal agents for prevention and treatment of invasive fungal infections. A recent review evaluated the available pharmacoeconomic evidence for antifungal prophylaxis in patients with hematologic malignancies and reported that the newer antifungal agents may have a more favorable cost-effective profile than fluconazole, but because of wide heterogeneity in patient characteristics, underlying diseases, hospital settings, and the lack of "head-to-head" trials among the agents, definitive recommendations could not be made.[44]

How do you integrate comparative effectiveness with cost considerations to chose between different treatment options?

There are 4 main types of economic evaluations that provide information intended to guide decision making on the basis of value for money: cost minimization, cost benefit, cost effectiveness, and cost utility. Cost minimization is commonly practiced in HCT whenever lower cost, equally effective treatment is chosen over more expensive treatments. For example, financial considerations have led the transplantation centers in developing countries to modify their transplantation procedures, resulting in lower costs without affecting outcomes adversely, thereby increasing the number of people who can be treated.[45] Cost-benefit analysis is almost never used in HCT because it requires assignment of monetary costs to measure clinical benefits. Several cost-effectiveness analyses, which compare 2 or more interventions by assessing both the difference in average costs and the difference in clinical outcomes (eg, life-years gained, symptom-free days) have been reported in HCT. Cost utility analysis is a specific type of cost-effectiveness analysis where outcomes are adjusted to consider health-related quality of life, so that a cure without treatment sequelae is considered more valuable than a cure that results in permanent disability. Although there is considerable controversy about what threshold is appropriate to designate an intervention as "cost-effective," in general, interventions that cost less than $50 000 per quality adjusted life-year gained relative to available alternatives are considered good value for the money.[46] Table 2 gives some examples of cost-effectiveness and cost-utility studies of HCT versus non-HCT treatments for hematologic malignancies.

The literature about whether HCT has a favorable economic profile in chronic myeloid leukemia with the advent of tyrosine kinase inhibitors is conflicting. Most investigators comment that the results of these studies are sensitive to the pricing of imatinib. More broadly, Gratwohl et al have analyzed the impact of cost consideration for HCT for chronic myeloid leukemia in Europe.[47] They estimated the median ratio between 1 year of tyrosine kinase inhibitors and allogeneic HCT at 2.0 (range, 0.9-5.9). These considerations are even more important in developing countries, where lifelong treatment with an expensive drug may consume more resources than a "once only" HCT procedure. Investigators from Mexico found a nonmyeloablative allograft with a median cost of USD $18 000 in their practice, a more attractive option for patients with newly diagnosed chronic myeloid leukemia because that amount would be enough to cover only 180 days of treatment with imatinib 400 mg/day.[48]

What are important areas for more research in the economic issues in HCT?

Longer-term costs. As the survival after HCT improves, it is vital to look at the cost burden of posttransplantation complications and downstream effects because survivorship costs are anticipated to contribute the largest increase in cancer care costs projected by 2020.[4]

Patient financial burden. A better understanding of the financial burden and inter-related factors, such as return to work/insurance coverage for the survivor population, can improve counseling before transplantation so that patients can plan for the future. HCT survivors, especially those with chronic GVHD who require long-term medications and use of multiple services to maintain optimal health, may be especially vulnerable to increasing out-of-pocket medical expenses.[49,50] Cancer is a risk factor for personal bankruptcy,[51] and little attention has been paid to the physician's responsibility to explain the financial risks of HCT.

Evolving transplantation technologies. Reduced-intensity conditioning has been increasingly used in the last decade, mainly for patients 50 years and older or those with significant comorbidities. Comorbidities have been shown to be a predictor of resource use and cost of care in primary care and cancer studies, but no studies have been performed in HCT to validate this observation.[52,53]

Relapse. Another area that would benefit from economic evaluation is prevention and management of posttransplantation relapse because relapse is the leading cause of death after HCT. Efforts to prevent relapse with maintenance treatment (eg, bortezomib and lenalidomide in myeloma, hypomethylating agents for acute myeloid leukemia/myelodysplasticsyndrome, or tyrosine kinase inhibitors in Philadelphia$^+$ malignancies) may have far-reaching clinical and economic consequences if routinely applied.[47,54]

Is there enough information about costs to factor them into individual or societal medical decision making?

Although there is an expanding knowledge base about the costs and cost-effectiveness of HCT, there is not yet sufficient information to integrate cost considerations into personal or societal decision making in a meaningful way. We think that this situation is not unique to HCT but reflects the challenges in conducting and interpreting these studies (Table 3), and the nation's reluctance thus far to be transparent about whether costs are a legitimate consideration in the practice of medicine. We can begin to provide the basis for a dialogue about costs if we encourage authors to include information about the estimated costs of the interventions in their publications, so that readers can have the efficacy, toxicity, and cost data available in the same report. Such analyses can also provide information about areas where costs could be decreased without compromising efficacy.

Discussion

Our review shows that cost studies in HCT have been heterogeneous in terms of study populations, diagnoses, perspectives of the

Table 2.Cost-effectiveness and costutility studies of HCT versus chemotherapy

Study/disease	Category	Chemotherapy/ no transplant	HCT	Difference	Incremental cost-effectiveness ratio	Interpretation
Dufoir et al[42]/AML	Costs	304 486 FF	424 696 FF	120 210 FF	122 421 FF/year	Allo-HCT cost-effective in AML-CR1
	Survival	2.806 years	3.785 years	0.979 years		
Welch et al[63]/AML	Costs	$136 000 USD	$193 000 USD	$57 000 USD	$52 777 USD/year	Allo-HCT cost-effective for acute nonlymphocytic leukemia
	Survival	2.24 years	3.32 years	1.08 years		
Barr et al[40]/AML	Costs	$51 800 CAN	$100 600 CAN	$48 800 CAN	$29 221 CAN/year	Allo-HCT cost-effective for AML in CR2
	Survival	0.57 life-years	2.24 life-years	1.67 life-years		
Barr et al[40]/ALL	Costs	$102 800 CAN	$92 000 CAN	$10 800 CAN		Cost savings with HCT for ALL in CR1
	Survival	3.32 life-years	3.69 life-years	0.37 life-years		
Lee et al[18]/CML	Costs	$61 800 USD (IFN) $31 400 USD (Hydrea)	$333 600 USD	$271 800 USD (IFN) $302 200 USD (Hydrea)	$51 771 USD/QALY (IFN), $55 449 USD/QALY (Hydrea)	URD transplant is cost-effective for CML-CP compared with IFN or Hydrea
	Survival	4.7 QALY (IFN)/4.5 QALY (Hydrea)	9.95 QALY	5.25 QALY (IFN) 5.45 QALY (Hydrea)		
Costa et al[64]/acute leukemia	Costs	$20 702 USD (no transplant)	$69 830 USD (URD BM/PBSC) $92 330 USD (cord)	$49 693 USD (URD BM/PBSC) $72 157 USD (cord)	$16 346 USD/life-year (URD BM/PBSC) $34 360 USD/life-year (cord)	Both URD BM/PBSC and cords are cost-effective compared with no transplants
	Survival	0.75 life-years (no transplant)		3.04 life-years (BM/PBSC) 2.10 life-years (cord)		
Skrepnek et al[65]/CML-CP (Ph^+): 2-y cost-efficacy	Costs	$78 000 USD (imatinib)	$114 000 USD(MUD BMT)	$36 000 USD		MUD BMT is more costly and less efficacious than imatinib for CML during the first 2 y
	Survival	0.91 (imatinib)	0.44 (MUD BMT)	−0.47		
Breitscheidel[66]/CML-CP	Costs	€196 836 (imatinib)	€133 403 (MUD HCT)	€63 433	€77 410/QALY	MUD HCT is less costly and less effective than imatinib over a 5-year time horizon
	Survival	4.17 QALY	3.35 QALY	0.82 QALY		
Kouroukis et al[67]/multiple myeloma	Costs	$1803 CAN (melphalan/ prednisone)	$32 320 CAN (autologous HCT)	$30 517 CAN	$18 974 CAN	Autologous HCT cost-effective in patients < 65 years old with myeloma
	Survival	2.85 life-years	4.46 life-years	1.61 life-years		
Messori et al[68]/acute leukemia relapse	Costs	$60 000 USD (chemotherapy)	$150 000 USD (2nd HCT)	$90 000 USD	$52 215 USD/ life-year	2nd HCT cost-effective for posttransplant relapse of acute leukemia
	Survival	0.6 life-years	2.2 life-years	1.6 life-years		

FF indicates French franc; USD, United States dollars; CAN, Canadian; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; CML, chronic myeloid leukemia; CR, clinical remission; CML-CP (Ph^+), chronic myeloid leukemia-chronic phase (Ph^+); MUD, matched unrelated donor; QALY, quality-adjusted life-years; and MUD SCT, matched unrelated donor stem cell transplant.

Table 3. Challenges in designing and interpreting cost studies

Methodologic: study design/data collection elements
Difficult to capture all societal costs
For studies with patient perspective: out-of pocket costs may vary based on insurance schemes and income levels
Heterogeneity between accounting methods and cost estimation among different institutions or even the same institution over time
Difficulty accounting for costs outside the hospital system, especially for long-term survivors resulting from fragmentation of care, unless using claims-based system
Estimation of costs related only to the transplant process in patients with multiple comorbidities that need medical management
Analysis and interpretative elements
Costs in the context of clinical trials may be inflated because of trial-specific requirements
Modeling-based methods for cost-effectiveness analysis rely on assumptions that may not reflect real-world decisions
Complexity of medical science and rapid pace of therapeutic innovation makes constant reevaluation of benefits and costs essential
Cost-effectiveness thresholds vary over time and from country to country

analyses,time horizons, and study methods, as has been reported by prior reviews of literature in this area.[55,56] Most studies have focused on the early costs after transplantation until 100 days or 1 year; cost studies beyond 1 year are rare. Investigators have shown that, similar to the clinical outcomes, the costs of procedures are influenced by patient- and disease-related factors, transplantation-related factors, and external factors. This review also identifies areas for more research, as it is clear that the contribution of economic analysis to HCT should continue to evolve with advances in therapeutics to ensure high quality but low cost care.

Sullivan et al recently identified the key cost drivers and possible solutions to the growing economic burden of cancer that called on all major stakeholders to work together to rein in spending.[57] Smith and Hillner have proposed 10 provocative solutions to address the problem of unsustainable trends in cost of cancer care.[58] They acknowledge the challenges in trying to change behaviors, attitudes, and practices but also point out that there is no other alternative because the growth of healthcare expenditures is unsustainable. The federal solution to rising costs may include more stringent eligibility criteria, greater cost sharing, or changes in the provider payment (eg, bundled payment system),[59] which may not be liked by physicians, patients, and society in general. The Oregon health plan was considered as an embodiment of rationing healthcare when it initially refused to cover HCT and other expensive treatments based on criteria of quality of life, cost-effectiveness, and so on. However, 7 years later, the coverage list was revised to include specific diagnosis-treatment pairs where the treatment had been proven to prevent death and lead to full recovery (including expensive therapies as long as they were clinically effective).[60] More recently, in 2011, Arizona Medicaid decided to stop covering certain transplants, including URD HCT, although the funding was restored later.

The balance between advocating for one's patient and considering the good of society often seems precarious, and cost information may accentuate this tension. The availability of high-quality comparative effectiveness and cost studies is vital to help ensure evidence based practice while systematically containing healthcare expenses. It is also very important to update these studies as new scientific data become available with time. Coverage with evidence development as proposed by the Center for Medicare and Medicaid services is one of the novel approaches to help collect enough data about efficacy of a treatment before making final coverage decisions while continuing to provide the service to those who need it. This can avoid the debacle that occurred with autologous transplants for metastatic breast cancer. Because of political and legal pressures, the health plans were forced to cover the procedure, which led to $3.4 billion in costs paid by the insurers that was eventually passed on to taxpayers and subscribers. Research was also impeded because 9 of 10 patients opted to receive their transplants outside of clinical trials.[61] The upcoming Blood and Marrow Transplant Clinical Trials Network randomized study comparing the clinical outcomes of cord blood versus haploidentical transplants will hopefully have an economic evaluation. Collection and use of this economic information are a testament to the fact that we are beginning to realize our fiscal responsibilities in patient care and to broaden the types of information we will consider in deciding which treatment is best. Integrating the goal of patient welfare with commitment to cost-effective care can help lower healthcare spending without having adverse effects on the health of our patients.

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Authorship

Contribution: N.K. designed the review, conducted the literature search, and wrote the manuscript; S.B.Z. offered critical review of the paper and contributed to analysis; S.J.L. designed the review, contributed to the analysis, and offered critical review; and all authors approved the final manuscript.

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