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Report to the Ranking Minority Member, Subcommittee on Health, Committee on Ways and Means, House of Representatives

March 1994

BONE MARROW TRANSPLANTATION

International Comparisons of Availability and Appropriateness of Use

GAO/PEMD-94-10

GAO
United States
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Program Evaluation and
Methodology Division

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The Honorable William M. Thomas
Ranking Minority Member
Subcommittee on Health
Committee on Ways and Means
House of Representatives

Dear Mr. Thomas:

Your predecessor as Ranking Minority Member, the Honorable Willis D. Gradison, Jr., asked us to examine differences in the availability of health services and outcomes across developed countries. This report, one of two prepared in response to that request, describes the variation among the United States and nine other medically advanced countries in the use of allogeneic bone marrow transplantation, an expensive and complex medical therapy. The other report, Cancer Survival: An International Comparison of Outcomes (GAO/PEMD-94-5), examines survival from four specific forms of cancer across two locations, the United States and the Canadian province of Ontario.

If you have any questions or would like additional information about this study, please call me at (202) 512-2900 or Robert L. York, Director of Program Evaluation in Human Services Areas, at (202) 512-5885. Other major contributors are listed in appendix IV.

Sincerely yours,

Eleanor Chelimsky
Assistant Comptroller General

Executive Summary

Purpose

The emergence of each new medical "breakthrough" challenges health care systems to contain the ever-growing cost of care while ensuring patient access to the most beneficial treatments that medical science has developed. As the United States considers revising its health care system, two very different perspectives on how our society utilizes medical advances have entered into the debate. On one side are those who believe that U.S. patients are afforded higher quality care largely because they have greater access to the most advanced medical technologies. Others argue that many of the ills of the health care system derive from the overuse of the newest and most expensive medical treatments. This report empirically examines utilization patterns for one complex, costly, high-technology medical treatment: allogeneic bone marrow transplantation. By comparing these patterns across 10 countries, GAO presents a comparative, international perspective on the use of a complex and expensive therapy in the United States.

This report responds to a request from the Ranking Minority Member on the Health Subcommittee of the House Committee on Ways and Means. It describes how medically advanced, industrialized countries allocate bone marrow transplants. The evaluation, concerned primarily with comparisons between the United States and the other countries, is based on two dimensions of quality in health care: availability and appropriateness. A study question addresses each of these dimensions: Do patients who need transplants get them? and Are transplants performed at a point that optimizes benefits while minimizing risks?

Background

Allogeneic bone marrow transplants treat diseases of the bone marrow by destroying the diseased marrow of the patient (with either radiation or chemotherapy) and then infusing healthy marrow from a suitable donor.[1] Bone marrow transplants are both complex (requiring advanced technologies) and expensive. In the United States, patient charges for allogeneic transplantation commonly exceed $125,000. Transplantation is recognized as a standard treatment option for patients with many different diseases but is most often used in the treatment of three types of leukemia: chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), and acute myeloid leukemia (AML). Although a transplant sometimes offers the only chance of cure for patients with these diseases, it often leads to serious complications and sometimes to death. Therefore, its use requires a careful weighing of potential benefits and harm to the patient.

[1]The other major type of bone marrow transplant involves marrow drawn from the patient, is referred to as an autologous transplant, and is generally used to treat different diseases than those treated by allogeneic transplants.

GAO obtained both incidence data for leukemia and the most recently available data on all allogeneic transplants conducted in the United States and nine other countries: Australia, Canada, Denmark, France, Germany, the Netherlands, New Zealand, Sweden, and the United Kingdom. The data on transplants came from the 208 centers that performed them during the period 1989-91 and covered approximately 10,000 patients.

Results in Brief

GAO found that for the years 1989-91, the observed patterns placed the United States near the middle of the 10 countries on both the availability of transplantation and the appropriateness of its use. Along the dimension of availability, the position of the United States varied, depending on the type of leukemia. U.S. patients with chronic myeloid leukemia, a disease that could be cured only with transplantation, were less likely to receive a transplant than patients with that disease in six other countries. U.S. patients with acute myeloid leukemia, however, were more likely to receive a transplant than patients in seven other countries. The relative standing of the United States also varied along the dimension of appropriateness. The time from diagnosis to transplantation for U.S. patients with acute leukemia was relatively short. Despite this fact, the United States still had relatively more patients (with any of the three leukemias) receiving transplants at less favorable stages of the diseases than was true in most of the other countries. In the case of chronic myeloid leukemia, five other countries were ahead of the United States in providing transplants in the early, most favorable stage. GAO found evidence that, relative to other countries, some U.S. patients for whom the treatment offers few likely benefits received transplants, while others who could benefit more did not.

Principal Findings

Overall, the most bone marrow transplants per capita were performed in France, where the concentration was unevenly divided between a high rate of transplants for the acute leukemias and a low rate for chronic myeloid leukemia. The patterns observed for Canada were consistently with or ahead of those for the United States on the dimensions of both availability and appropriateness, with a total number of bone marrow transplants per capita slightly greater than that of the United States. The patterns for Germany showed that availability was relatively low but that appropriateness measures were more varied.

The role of bone marrow transplantation in patient management differs for each of the three leukemias. Therefore, GAO's findings on availability and appropriateness are discussed in more detail for each disease.

Chronic Myeloid Leukemia

The only curative therapy for CML during the 1989-91 period was bone marrow transplantation, and this treatment was most likely to be effective in the early stage of the disease. Thus, allocating transplant resources well for CML required having relatively high availability (because transplantation was the only cure) and providing transplants during the early stage (chronic phase) of the disease.

The U.S. position for CML was roughly in the middle of the 10 countries for both availability and appropriateness. Approximately a third of recently diagnosed U.S. patients who were under the age of 55 received bone marrow transplants during 1989-91 and 70 percent received transplants while their disease was in the first chronic phase.[2] Canada, Sweden, and the United Kingdom were the countries that had both a higher rate of transplantation for CML than the United States and a larger percentage of transplants performed while patients were in first chronic phase.

Acute Lymphoid Leukemia

ALL, unlike CML, can often be cured with chemotherapy. This fact is reflected in the considerably lower transplantation rates that were observed for ALL than for CML. With the exception of France (which had a rate 50-percent higher than any other country), the rates for ALL patients generally fell along a continuum that ranged from 3 percent in Denmark to 15 percent in the United Kingdom.

The relative effectiveness of chemotherapy in treating ALL also makes it difficult to assess appropriateness for the full population of patients. Therefore, GAO focused on specific groups of transplant patients in its examination of appropriateness. One such group was adult ALL patients, who, because they are less likely than children to respond to chemotherapy, should be considered for transplantation at earlier stages of the disease. The United States, Germany, New Zealand, and Australia were the four countries where a relatively large proportion of adult ALL patients (approximately 20 percent) received their transplant later in the progress of their disease. This pattern of late-stage transplants suggests a

[2]Patients aged 55 and older were generally not considered to be suitable candidates for bone marrow transplants because the complications that often accompany the treatment become more severe with age.

reliance on chemotherapy beyond the point at which it is most likely to be effective.

Acute Myeloid Leukemia

The best approach for continuing therapy of AML patients who have achieved a first complete remission has not yet been clearly determined. Part of the uncertainty stems from the difficulty in identifying which patients will remain in remission with continued chemotherapy (and therefore do not need a transplant) and which patients will relapse and would benefit from a transplant. Although higher or lower rates do not, therefore, indicate which countries are doing better in treating AML, there are criteria for evaluating the observed patterns. For example, the longer patients continue in first remission, the more likely it is that they have been cured by conventional chemotherapy. Therefore, the greater the percentage of transplants performed late in first remission, the greater the likelihood that at least some patients who did not need them were receiving transplants. In addition, the prognosis for patients who receive transplants when their disease is advanced is much poorer than for patients receiving transplants at an earlier stage, so few patients should receive transplants at a stage later than second remission.

Transplantation rates for AML were consistently higher than for ALL and generally exhibited little variation. Again, however, patients in France were almost twice as likely to receive a transplant as were AML patients in any other country. For patients who received transplants in first remission, those in France and the United States were most likely to receive the treatment rapidly, though waiting times were generally short for all countries. As to appropriateness, relatively few AML patients received transplants at an advanced stage of their disease, although this occurred more frequently in the United States than elsewhere.

Implications

These findings on availability and appropriateness, presented for the first time in this report, apply specifically to allogeneic bone marrow transplantation in the management of three diseases. These findings are thus quite narrow; however, this report has two larger implications. First, the data allow the 10 countries, and the bone marrow transplant communities within each, to see how they compare with other medically advanced societies on two dimensions of health care quality. Such comparisons can serve as either the impetus for change (in situations where quality can be improved) or as evidence that current practices and policies should be maintained.

Second, GAO's findings raise questions about two prevalent views of health care quality in the United States. Both views, that high quality is achieved through an abundance of high-technology medicine or that the overuse of medical technology detracts from quality by exposing patients to unnecessary risks, rest on a common assumption: that the United States relies on the newest and most complex treatments more than do other economically advanced countries. The findings in this report challenge that assumption. The patterns GAO observed demonstrate that U.S. patients, for good or ill, have not been the most likely to receive a transplant for any of the clinical conditions examined.

Recommendations

This report contains no recommendations.

Advisory Board Comments

This report does not examine any agency program; thus, no agency comments were requested. However, the findings from the study were presented to a project advisory panel whose comments and suggestions have been incorporated into the report. (See appendix III for the list of advisers.)

Contents

Tables

Abbreviations

ALL	Acute lymphoid leukemia
AML	Acute myeloid leukemia
BMT	Bone marrow transplant
CLL	Chronic lymphoid leukemia
CML	Chronic myeloid leukemia
GVHD	Graft-versus-host disease
HLA	Human leukocyte antigen
IBMTR	International Bone Marrow Transplant Registry
IARC	International Agency for Research on Cancer
MSD	Matched sibling donor
OECD	Organization for Economic Cooperation and Development
SEER	Surveillance, Epidemiology, and End Results

Introduction

The emergence of each new and costly medical treatment challenges health care systems to contain the ever-growing cost of care and at the same time to ensure patient access to the most beneficial treatments that medical science has developed. In the United States, the question of whether a reformed health care system can meet the expectation of most Americans for ready access to the newest, costly, high-technology medical treatments looms large. In an effort to inform the ongoing debate on health care reform on the availability and appropriateness of care across health systems, we have examined patterns of care in 10 industrialized nations for one sophisticated therapy, bone marrow transplantation.

Our work was undertaken at the request of the Ranking Minority Member of the Subcommittee on Health of the House Ways and Means Committee. In the sections that follow, we describe bone marrow transplantation (BMT) generally and how it is used specifically in the treatment of leukemia. We then present the detailed objectives of our work, its scope, and the methodology used to carry out the research.

Background

The term "bone marrow transplant" refers to two distinct types of therapy. In one category are allogeneic transplants. These procedures are used primarily to treat diseases of the bone marrow and involve the collection of marrow from a donor other than the patient. Bone marrow is the spongy tissue in the cavities of the bones that produces the components of blood and the immune system. The intent of allogeneic transplants is to destroy the diseased marrow (with either chemicals or radiation), thereby curing the disease. After this, the donor's marrow is infused into the patient.

The other major class of transplants is autologous bone marrow transplants.[1] These transplants are directed at a wide variety of diseases and involve marrow obtained from the patient. Autologous transplants can involve therapy that is directed at many different types of cells, not necessarily diseased marrow. However, the intensity of therapy is such that the marrow cells are killed as a consequence of the therapy. Therefore, marrow from the patient is harvested before the start of therapy and then reinfused into the patient once therapy against the disease has been completed. That is why this form of therapy is sometimes referred to as "high-dose chemotherapy with bone marrow rescue." Also, autologous transplants are sometimes used as an alternative to allogeneic

[1]Bruce D. Cheson et al., "Autologous Bone Marrow Transplantation: Current Status and Future Directions," Annals of Internal Medicine, 110:1 (Jan. 1, 1989), 51-65.

transplants in situations where no suitable donor can be found. In those situations (that is, when autologous transplants are used to treat diseases of the marrow), after the marrow is collected from the patient, it is sometimes treated in a process called purging in an effort to remove or destroy any diseased cells before reinfusion.

Both forms of transplantation share a number of important characteristics: both are in a state of technological flux, with advances in the delivery of the therapy continuing to be made; both are complex procedures relying on many different types of medical expertise; and both are expensive. This report focuses on allogeneic transplants only. Compared with autologous transplants, allogeneic transplants are generally more established but more complex and more expensive. Therefore, they offer an opportunity to study how the allocation of "high-tech, high-cost" medicine varies under different health care systems.

Bone Marrow Transplantation

Allogeneic bone marrow transplantation is a standard treatment option for some patients with certain types of cancer and for some fatal noncancerous disorders. As successful experience with BMT has accumulated, the list of established indications has broadened. Today there are several diseases or groups of diseases for which BMT is a standard therapy: chronic myeloid leukemia, acute leukemia, Hodgkin's disease and non-Hodgkin's lymphoma, multiple myeloma, neuroblastoma, myelodysplasia, aplastic anemia, transfusion dependent thalassemia, and severe combined immune deficiency.[2] Bone marrow transplantation is also being evaluated and increasingly applied in the treatment of other types of cancer, metabolic disorders, and immunodeficiencies, but its effectiveness in treating these diseases is not yet clearly established.

A Resource-Intensive Medical Technology

Allogeneic transplantation is an aggressive, complex therapy that includes many separate procedures and encompasses four phases: (1) identification of a donor, (2) pretransplant conditioning, (3) transplantation, and (4) prevention and treatment of complications.[3] Each is discussed in turn.

[2]Testimony of Claude Lenfant, Director, National Heart, Lung, and Blood Institute before the Subcommittee on Labor, Health and Human Services, and Education of the House Committee on Appropriations, U.S. Congress, Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations for 1993, Part 3 (Washington, D.C.: U.S. Government Printing Office, 1992) p. 657.

[3]Alfred A. Rimm et al., "Use of a Clinical Data Registry to Evaluate Medical Technologies: Experience for the International Bone Marrow Transplant Registry," International Journal of Technology Assessment in Health Care, 7:2 (1991), 182-93.

Finding a donor. Central to allogeneic transplantation is the availability of a suitable donor. Suitability is determined by the compatibility of the donor's tissues with the patient's tissues. This determination is made by comparing human leukocyte antigens (HLA), located on the white blood cells of both donor and recipient. The best chance for a match is among siblings; the likelihood of a match decreases as one moves to more distant family members and then to non-family members. Importantly, the poorer the HLA match, the higher the likelihood of complications and the poorer the prognosis for the transplant.

In the United States, one estimate is that 30-40 percent of candidates for a bone marrow transplant have a relative who would be a suitable donor.[4] In cases where no relatives are suitable, other donors are typically sought through national donor registries. Locating a suitably matched unrelated donor is often difficult and time-consuming, and the cost is high. In the United States, in the period 1987-91 only about 20 percent of searches for an unrelated donor through the National Marrow Donor Program, the largest U.S. donor registry, were successful. The search for a donor on the registry generally required 5-6 months.[5]

Pretransplant conditioning. In preparation for transplantation, the patient undergoes extensive laboratory and diagnostic tests followed by intensive doses of chemotherapy or radiation to kill diseased marrow. A patient also receives drugs to suppress the immune system so that the body will not reject the transplanted marrow. During this phase of the treatment, side effects almost always occur because chemotherapy and radiation are toxic to normal cells as well as to diseased cells. Side effects can include nausea, vomiting, diarrhea, lowered blood counts, and damage to vital organs. Other drugs are used to prevent or treat these side effects. Because the patient's immune system is severely weakened, the patient is susceptible to infections from bacteria, fungi, viruses, parasites, or other foreign matter. For this reason, the patient is usually placed in protective isolation, given antibiotics to fight infection, and sometimes provided with hematopoietic growth factors to stimulate cell growth. Throughout the conditioning period, the patient is monitored daily and receives periodic blood and platelet transfusions.

[4]Mortimer M. Bortin, Mary M. Horowitz, and Alfred A. Rimm, "Increasing Utilization of Allogeneic Bone Marrow Transplantation: Results of the 1988-1990 Survey," Annals of Internal Medicine, 116:6 (Mar. 15, 1992), 505-12.

[5]U.S. General Accounting Office, Bone Marrow Transplants: National Program Has Greatly Increased Pool of Potential Donors (GAO/HRD-93-11; Nov. 4, 1992), pp. 9-10.

Transplantation. Soon after chemotherapy or radiation therapy is completed, the patient receives the donated marrow through an intravenous catheter. This marrow travels through the bloodstream to the bone marrow cavities, where, in a process called engraftment, the transplanted marrow begins to manufacture new blood cells. Engraftment usually occurs within 14 to 30 days after transplantation.

Prevention and treatment of complications. In the months immediately following the marrow infusion, life-threatening complications may follow, with the four most common being graft rejection or failure, graft-versus-host disease (GVHD), infection, and recurrence of the original disease. Just as whatever remains of the patient's original immune system may reject the marrow graft, in GVHD the newly transplanted marrow may attack the patient's body. GVHD can be either temporary or chronic and can vary from a mild to a life-threatening disease. Drugs are used to reduce the risk and severity of GVHD and to treat it when it occurs. Similarly, drugs are also used to prevent and treat any infections, which are likely during this period because of the patient's weakened immune system. Additionally, direct toxicities from the conditioning regimen can continue to cause complications and can lead to death. The severity of these reactions to BMT generally increases with age; thus, transplants are rarely performed on older patients. Those aged 55 and older are not generally considered suitable candidates.

Because it usually involves expensive drugs, blood products, continual laboratory testing, special environmentally protective isolation hospital rooms, intensive nursing care, and often extensive use of radiotherapy equipment, BMT is a very expensive therapy. In the United States, patient charges for allogeneic transplantation commonly exceed $125,000. However, charges vary considerably depending on the initial response of the patient to the treatment, the extent of any subsequent complications, and the length of the patient's hospital stay.

Transplantation in the Treatment of Leukemia

Allogeneic transplantation is a standard treatment option for several of the most common types of leukemia. Leukemia is a collective term for several distinct malignancies that originate in the blood-forming cells, arising mostly in bone marrow. The presence of leukemic cells interferes with the production of normal red and white blood cells and platelets.

Leukemias are classified by cell type as either lymphoid or myeloid and by clinical behavior as either acute or chronic. Acute leukemia usually begins abruptly and progresses rapidly; symptoms develop quickly and are

intense. Chronic leukemia usually develops more slowly, often over a period of many years. The four basic forms of leukemia are chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), and chronic lymphoid leukemia (CLL).[6] Table 1.1 shows some distinctive features associated with specific leukemias.

Table 1.1: Features of Specific Types of Leukemia

	Cell type	
Clinical behavior	**Lymphoid**	**Myeloid**
Acute	Predominant childhood type; peak in children under 5	Predominant acute type in old age; most common type in mid-adulthood
Chronic	Predominant type in old age; uncommon before mid-adulthood	Predominant chronic type in mid-adulthood

Source: Moyses Szklo, "Are Further Epidemiologic Studies of Leukemia Needed?" American Journal of Epidemiology, 112:2 (1980), 228.

We found that 77 percent of all allogeneic transplants in 1989-91 in the 10 countries we studied were performed to treat either CML, ALL, or AML.[7] Yet, the role of BMT in the treatment of each disease differs, and these differences are critical for interpreting patterns of BMT use.

Stages of Leukemia and Therapy

All three types of leukemia that are treated with BMT progress through different "stages" or "phases," and these are crucial in determining the appropriateness of a bone marrow transplant.[8] In general, the earlier in the progression of a disease that a transplant is performed, the better the prognosis for the patient. However, in the early stages of acute leukemia, it is often difficult to distinguish between patients who will be cured by conventional chemotherapy and those who will eventually require a bone marrow transplant. Given that BMT is a dangerous procedure, exactly when the risks of the procedure outweigh the dangers from the disease is difficult to determine. Further, this point will differ for each of the diseases. The specific stages of each disease and the implications for defining when transplantation is most appropriate are discussed in greater detail in the respective chapters on CML, ALL, and AML (chapters 3-5).

[6]Lymphoid leukemia is also called lymphocytic, lymphatic, and lymphoblastic. Myeloid leukemia is also called granulocytic, myelocytic, myelogenic, and myelogenous. Acute nonlymphocytic leukemia is a broader term that includes AML as well as several rarer forms of leukemia.

[7]BMT is not a common therapy for CLL because the disease almost always occurs after middle age, and transplantation is rarely done for patients aged 55 and older.

[8]Mortimer M. Bortin et al., "Changing Trends in Allogeneic Bone Marrow Transplantation for Leukemia in the 1980s," Journal of the American Medical Association, 268:5 (Aug. 5, 1992), 607-12.

Objectives

The central objective of this report is to evaluate the use of bone marrow transplantation in different national health systems. Specifically, our interest is in answering two questions:

- Do patients who need transplants get them? and
- Are transplants performed at a point that optimizes benefits while minimizing risks?

Each of these questions relates to a dimension of health care quality. The first addresses the availability of transplant services and provides information on how likely it is that patients in each country who could benefit from a transplant would receive one. The second question is directed at the issue of appropriateness. Given that there are better and worse times to perform a transplant, we examine when in the progression of disease transplants are typically performed. The criteria used in assessing appropriateness, therefore, involve the stage of the patients' diseases at the time of transplant.

Each question is answered by examining how patterns of BMT use compare across national health care systems.[9] The focus on patterns rather than on individual cases has two implications. One is that our conclusions are general rather than specific. When we say that the likelihood of transplantation is higher in one country than another, this refers to the population of patients, not to individuals (whose likelihood may vary considerably within countries). Similarly, when we conclude, for example, that a pattern of early transplants is "appropriate," this does not mean that each case of early transplantation represents appropriate care or that any later transplant would be inappropriate. Rather, the conclusion is that one pattern is generally more consistent than others with the clinical criteria that define appropriate care.

The focus on patterns also means that our study is descriptive; that is, our intent is to provide evidence on where a patient is most likely to receive a transplant or to receive it at an optimal time. We do not set out to explain why one health care system "does better" in these patterns than the others. Numerous factors (including clinical philosophy, patient behavior, total resources, system capacity, payment mechanisms, and practice controls, to name but a few) may play some role in answering "why," but that question is beyond the scope of this report.

[9]Throughout this report we use the terms country and health care system interchangeably.

Scope

This report examines the availability and appropriateness of allogeneic bone marrow transplantation in the United States and nine other countries: Australia, Canada, Denmark, France, Germany, the Netherlands, New Zealand, Sweden, and the United Kingdom.[10] All are economically advanced democracies whose health systems vary in many ways including their organization, basic incentive structures, and how much each spends on health care.[11] In some, nearly all physicians are salaried; in others, only hospital-based physicians are; and in still others, such as the United States, most inpatient as well as ambulatory care is paid for on a fee-for-service basis. Similarly, the large majority of hospitals are publicly owned and administered in some countries and privately in others, while in a third set, neither type predominates. Independent of ownership and control, these hospitals may be paid by the service provided, by number of days from admission to discharge, through a fixed annual budget, or in some complex combination. In some cases, the national government manages the whole health care system; in others, subnational governments are dominant; and sometimes, different levels of government control different parts of the system. Nongovernmental or quasi-governmental organizations, such as sickness funds, also play an important role in some systems in both creating the physical capacity to offer different types of services and allocating the financial resources to pay for those services. The one element that the other nine systems have in common, in contrast to the United States, is that they all have put in place some type of financing mechanism that ensures that access to health care services does not depend on the patient's ability to pay for them.

For each of the systems, we reviewed the 3-year period 1989-91, the most recent years for which comprehensive BMT data could be obtained. We did not examine how the transplants were performed (that is, such factors as drugs used, length of hospital stay, type and frequency of irradiation), nor did we gather data on patient outcomes (for example, recurrence of disease or survival).

[10]Germany refers to western Germany only, and the designation United Kingdom refers to England, Wales, and Scotland.

[11]In 1991, the United States spent $2,868 per person on health care, exceeding spending in Canada, the next-highest spender, by 50 percent. At the other end of the range, New Zealand spent $1,047 and the United Kingdom $1,043 per person. For these and other data comparing health care expenditures in the 10 countries as well as in 14 others, see George J. Schieber, Jean-Pierre Poullier, and Leslie M. Greenwald, "Health Spending, Delivery, and Outcomes in OECD Countries," Health Affairs, 12:2 (Summer 1993), 120-29.

Methodology

Data Needs

To assess the availability of BMT in each of the countries, we needed complete counts of the number of transplants performed in each country and indication of the diseases for which those transplants were performed. To estimate rates of transplantation, taking account of variations in the population of the countries and the incidence of disease, we needed to know the size of the population and the annual number of cases of CML, ALL, and AML. To examine the appropriateness of the transplants, we sought data on the stage of disease at time of transplant. Finally, to measure timeliness of transplantation, we needed to know the date of diagnosis and the date of transplant.

Data Sources

The patient-level data to address all three objectives were collected from one of three sources: the International Bone Marrow Transplant Registry (IBMTR), the Société Française de Greffe de Moëlle, and a survey of BMT centers in the 10 study countries not routinely contributing to the IBMTR database.

IBMTR, based at the Medical College of Wisconsin, collects and analyzes clinical data on allogeneic bone marrow transplantation from approximately 200 transplant centers around the world. The Société Française de Greffe de Moëlle maintains a database on all bone marrow transplants performed in French BMT centers. Not all BMT centers regularly submit data to IBMTR; thus, we arranged for IBMTR to survey all nonparticipating BMT centers to ensure that we had comprehensive data for this report. The response rate to the survey was 84 percent. For the small number of centers that did not respond, we obtained data on the number of transplants performed from two earlier surveys.[12] Overall, we assembled data on approximately 10,000 transplants performed in the 3 years at 208 transplant centers in the 10 countries. In compiling these data, we did not independently verify data supplied by any of the sources. Appendix I provides a detailed description of the sources and construction of our BMT databases.

[12]For a description of one survey, limited to European centers, see A. Gratwohl et al., "Bone Marrow Transplantation in Europe: Major Geographical Differences," Journal of Internal Medicine, 233:4 (Apr. 1993), 333-41, and A. Gratwohl, "Bone Marrow Transplantation Activity in Europe 1990," Bone Marrow Transplantation, 8:3 (Sept. 1991), 197-201. An IBMTR survey of centers worldwide is described in Bortin, Horowitz, and Rimm (1992).

National population data for calculating BMT per capita ratios were provided by the Center for International Research of the U.S. Bureau of the Census and by British Information Services. Data on leukemia incidence rates for the period 1983-87 (the most recent period for which comparable data were available) came from cancer registries in each of the countries other than Germany. For Germany, we assumed that its leukemia incidence rates were equal to the average incidence rates of the nine other countries. We have confidence in this assumption for three reasons. First, international variation in disease incidence for the leukemias is considerably less than it is for other cancers.[13] Second, the number of cases of disease estimated by using average incidence approximates estimates of incidence provided by German oncologists. Additionally, the ranking of German transplant rates relative to other countries remains the same whether one uses transplant rates computed using population as the denominator (for which we have precise data) or using disease incidence (with the average leukemia incidence assumption for Germany) as the denominator.

Analysis

The analysis plan for this study consisted of two general components. One primarily involved calculating rates and ratios. Some complexities in this component of the work were introduced by the need to estimate the cancer incidence rates for countries where there were no national registries. For those countries, we estimated national incidence rates from subnational registries. Additionally, we had to convert incidence rates to estimates of the actual number of leukemia cases in each country. Appendix II provides a full explanation of our sources and estimation methods for the computation of the disease incidence rates.

The other analytic task involved establishing criteria for each disease that could be used to define when a transplant was appropriate, including the time perspective on benefits and risks. We relied on the published literature on BMT to establish these criteria and then had the criteria reviewed by a panel of medical scientists expert in the treatment of leukemia.[14] (See appendix III for the list of advisers.)

Additional background information was obtained from interviews with medical directors at 24 transplant centers in the United States and 40

[13]Clark W. Heath, Jr., "The Leukemias," in Cancer Epidemiology and Prevention, eds. David Schottenfeld and Joseph F. Fraumeni, Jr. (Philadelphia: W.B. Saunders, 1982), p. 730.

[14]Because our focus was on BMT during 1989-91, this report relies primarily on the clinical literature that was published before 1992.

transplant centers in nine other countries. Our medical panel advised us in the conduct of the research and reviewed this report.

Organization of the Report

Chapter 2 presents data addressing the overall patterns of BMT utilization in each of the 10 countries. Chapters 3-5 contain our findings on each of the three leukemias: CML, ALL, and AML. Each chapter presents data on the availability and appropriateness of BMT for one of these leukemias. Our general conclusions and their implications are presented in chapter 6.

Chapter 2

Patterns of Transplantation

This chapter describes variation in the overall patterns of bone marrow transplantation for the populations of 10 countries. Across health care systems, the utilization of this therapy provides one example of relative access to medical technology. We measured such utilization in two ways. First, we determined overall rates of transplantation in each of the countries, taking into account the size of national populations. Then, in chapters 3-5, to capture national utilization differences taking account of variation in disease, we estimated the likelihood of transplantation for patients with each of three types of leukemia.

Rates of Transplantation

The most basic measure of treatment frequency is a simple count of the number or incidence of treatments during a given year. However, to draw meaningful conclusions from comparisons of incidence across national populations, it is necessary to account for differences in population size. Incidence rates are computed by dividing the total number of treatments occurring in a country during a given year by the national population in that year. For ease of comparison, incidence rates are expressed in this report as cases per million persons.

Because allogeneic transplantation was rarely used for patients aged 55 and older, we calculated rates for the age range 0-54.[1] Table 2.1 presents the number of transplants performed during 1989-91 in each of the 10 countries.[2] The table also presents the annual incidence rates of BMT—the number of people receiving allogeneic transplants per year per million people under age 55 for each country. Table 2.1 and all subsequent tables in this report order the countries by their ranks in the column of principal interest, usually the last column.

[1]During 1989-91, only 1.2 percent of transplant patients in the 10 countries were aged 55 or older. No patients aged 50 and over were transplanted in Denmark and New Zealand, and no patients aged 55 and over in Australia and Sweden. Patients aged 55 and over constituted one-half of 1 percent of transplants in Canada, the United Kingdom, France, Germany, and the Netherlands, and 1.6 percent of transplants in the United States.

[2]Data on patient's country-of-residence were not available. All tables in this report indicate the country where therapy was performed, not where patients resided, so the transplant figures include any patients referred from other countries.

Table 2.1: Annual Rates of Allogeneic Bone Marrow Transplantation

Country	Transplants[a]	Population aged 0-54[b]	Transplants per million per year
France	1,708	42.6	13.4
Sweden	168	6.3	9.0
Canada	576	21.5	8.9
Australia	369	13.9	8.8
United Kingdom	1,000	40.4	8.2
United States	4,873	199.9	8.1
Denmark	90	3.9	7.8
New Zealand	59	2.7	7.4
Netherlands	232	11.7	6.6
Germany[c]	757	44.9	5.6

[a]For the period 1989-91.

[b]In millions, for 1991.

[c]The population figure for western Germany is for 1990, the latest available.

Table 2.1 shows that the rate in France was distinctly higher than that in the other countries. While there was more than a two-fold difference in national rates between the highest and lowest countries, most national rates lay on an evenly spread continuum with the United States near the middle.

The rates in table 2.1 are one indication of how resources are distributed in health care systems. For example, more resources per capita were allocated to BMT in France than in the United States. Germany used the fewest resources per capita for transplants among the 10 countries.

Transplantation for Leukemias

Across the 10 countries, 77 percent of allogeneic transplants during the period were for CML, ALL, or AML. The remainder were for lymphoma and other malignancies, severe aplastic anemia, and other nonmalignant diseases. Table 2.2 displays the distribution of allogeneic transplants by disease.

Table 2.2: Distribution of Allogeneic Bone Marrow Transplantation by Disease[a]

Country	Transplants	Type of leukemia			Other disease
		CML	ALL	AML	
New Zealand	59	41%	24%	30%	6%
United Kingdom	1,000	31	28	22	18
United States	4,873	34	20	28	19
Canada	576	34	13	32	21
Germany	757	33	18	26	22
Australia	369	30	20	27	23
Netherlands	232	20	23	27	30
Denmark	90	33	16	20	31
Sweden	168	26	18	22	35
France	1,708	18	25	21	36

[a]For the period 1989-91; percentages may not add to 100 because of rounding.

From table 2.2, we can see that the proportion of all transplants for the three leukemias varied from 65 percent in France and Sweden to 94 percent in New Zealand, with the United States and four other countries clustered around 80 percent. Consequently, France and Sweden used a larger proportion of transplant resources for other diseases.

The next three chapters report our findings on the availability and appropriateness of bone marrow transplants for each of three leukemias.

Chronic Myeloid Leukemia

Chronic myeloid leukemia is a disease of particular interest for assessing the availability and appropriateness of bone marrow transplantation. This is because it is both a relatively common form of leukemia and one for which BMT is the only established curative therapy. The next section examines in detail the basis for assessing the availability and appropriateness of bone marrow transplantation given the specific clinical characteristics of CML. Drawing on both the medical literature and our panel of expert advisers, we developed four specific measures of availability and appropriateness. We then applied these criteria to the 10 health care systems under study. We describe the position of the United States relative to the other systems on each measure individually and on all four taken together.

Evaluation Criteria

As the term "chronic" implies, CML is a disease that typically develops over an extended period of time. In the initial stage of the disease, the symptoms are generally mild and the patient's quality of life is high. This stage will often last several years; however, at some point, the disease will progress from this "chronic phase" to a transitional stage (accelerated phase) and from there to the terminal stage of the disease, called "blast crisis."

Chemotherapy may minimize symptoms during the chronic phase but does not stop progression to the advanced stages of the disease and death.[1] In one study, approximately half the patients treated with conventional chemotherapy died within 5 years of diagnosis, increasing to over 80 percent after 7 years.[2] Interferon, a naturally occurring biological agent, has recently been shown to delay this progression for some patients.[3] However, during the 1989-91 period covered in this study, interferon's use in the treatment of CML was investigational and it was not generally available to patients as an alternative to chemotherapy.[4]

Bone marrow transplantation, by contrast, offered patients during this period the potential for long-term cure from the disease. IBMTR data collected from transplant centers around the world showed that

[1]Philip McGlave, "Bone Marrow Transplants in Chronic Myelogenous Leukemia: An Overview of Determinants of Survival," Seminars in Hematology, 27:3, Supp. 4 (July 1990), 23-30.

[2]E. Donnall Thomas and Reginald A. Clift, "Indications for Marrow Transplantation in Chronic Myelogenous Leukemia," Blood, 73:4 (Mar. 1989), 861-64.

[3]Moshe Talpaz et al., "Interferon-Alpha Produces Sustained Cytogenetic Responses in Chronic Myelogenous Leukemia," Annals of Internal Medicine, 114:7 (Apr. 1, 1991), 532-38.

[4]McGlave (1990), p. 23.

53 percent of patients receiving transplants in chronic phase were alive 6 years later.[5] Most of those who died did so in the 12 months following the procedure, almost all from complications of the treatment such as infections or graft-versus-host disease.[6] Many of these patients would probably have lived somewhat longer had they not received a transplant. However, the larger number of patients who survived the procedure obtained a much greater increase in overall survival through eradication of the disease.

Given the risks associated with the treatment, it might seem reasonable to wait to transplant until the chronic phase was over. Unfortunately, the probability of success decreases the longer one waits and, in particular, once the disease has progressed to the accelerated or blast crisis stage.[7] While that transformation takes place, on average, 3 years after diagnosis, for many patients it occurs sooner and without warning.[8] Therefore, it is recommended that CML patients who are eligible for a BMT (that is, have a suitable donor and meet the age and health status requirements) undergo the treatment within a year of diagnosis.[9]

Measures of Availability

As noted, bone marrow transplantation represents the only established curative therapy for CML; thus, our advisory panel recommended that we assess the availability of bone marrow transplants in the 10 countries through a comparison of the proportion of patients with CML who received transplants. To do this, we needed to relate the number of transplants for CML patients to the frequency of the disease in each country.

The lack of effective alternative therapies meant that we did not have to account for patients cured by other treatments. Nevertheless, we did not assume that a transplant would be justified in every case. For many patients, the risks associated with the procedure may well outweigh the likely benefits. As noted above, older patients are typically not eligible for a transplant; many patients die from the effects of the procedure; and some patients who undergo a transplant will not be cured of the disease.

[5]McGlave (1990), p. 24.

[6]McGlave (1990), p. 25.

[7]Thomas and Clift (1989), p. 862; McGlave (1990), p. 24. Even patients who go into accelerated phase and then are brought back into chronic phase with chemotherapy do significantly less well than those who are in their first chronic phase.

[8]McGlave (1990), p. 25.

[9]Thomas and Clift (1989), p. 862.

However, for patients under 55 years of age, the proportion for whom the risks outweigh the benefits should be fairly small and of roughly comparable magnitude in each country. Therefore, the relative frequency of transplantation for CML across the 10 countries should provide an indication of the relative likelihood that those patients who would benefit from a transplant could actually receive one. For this measure, the higher the proportion of patients receiving transplants, the greater the apparent availability.

We also measured the availability of transplants for CML by examining how long it took for a system to provide them. If, for example, a country lacked sufficient capacity to perform transplants, resulting in queues or delays in referring patients to transplant centers, then it would generally take longer to provide patients with transplants than it would in a country that had sufficient capacity. This may especially be an issue for CML patients, since they tend to be the ones whose procedure is delayed if a more urgent case (such as an acute leukemia patient) needs a transplant. On this measure, then, shorter waits for a transplant may be taken as an indicator of greater availability.

Measures of Appropriateness

We addressed the appropriateness of treatment through two indicators: (1) the proportion of patients transplanted in first chronic phase, and (2) the proportion transplanted within a year of diagnosis. Here, the presumption was that if a transplant is to be performed, the procedure should be done when it is most likely to have a positive outcome for the patient. Appropriate care would thus be indicated by a higher proportion of patients receiving their transplants in the first chronic phase, since the outcomes for such patients are much better than for patients receiving transplants in accelerated phase or blast crisis.

The time from diagnosis to transplant is of interest for two reasons. First, it indicates the relative degree of risk tolerated in each system that patients might progress to a later stage before their transplant is performed. Second, some evidence suggests that even among patients in first chronic phase, those transplanted with less delay will have better results.[10] Therefore, a higher proportion of patients receiving transplants within 1 year of diagnosis is probably indicative of more appropriate care.

Of the two indicators, the first is more definitive, as numerous studies have shown that substantially worse outcomes are experienced by

[10]Thomas and Clift (1989), p. 862.

patients who received transplants in stages other than first chronic phase.[11] The two measures of appropriateness should be related, but not perfectly, since the chronic phase extends well beyond a year for many patients, while for a minority, the disease may progress more rapidly.

Likelihood, Timing, and Stage of Transplants

In the following sections, we present our findings on the likelihood, timing, and stage of transplants for CML patients in the 10 countries.

The Likelihood of Receiving a Transplant

To assess the likelihood that patients would receive a transplant, we first needed to determine how many potential candidates for transplantation there were in each country between 1989 and 1991. Using a range of data sources described in appendix II, we estimated for each country the annual number of new CML cases for persons under the age of 55. We then related this number to the number of transplants performed in that country over the study period to construct a national disease-specific BMT ratio. (The calculations are described in more detail in appendix II.) This ratio represents the rate of tranplantation; that is, the likelihood that CML patients under age 55 in each country would receive BMT as part of their leukemia treatment by the end of the second calendar year following the year of diagnosis of their disease. The rates also describe the relative likelihood of receiving a BMT across countries. For example, a rate twice another would indicate that a patient in one country was twice as likely to receive a transplant as a patient in another country within the specified time.

Table 3.1 presents the tranplantation rates for CML in the 10 countries. For some countries, such as Sweden, Denmark, and New Zealand, the number of transplants is small. That means that random fluctuation from year to year by even a few cases could significantly affect the rates and thus the rankings of these countries.

[11]In addition to McGlave (1990) and Thomas and Clift (1989), see Joseph E. Sokal et al., "Prognostic Discrimination Among Younger Patients With Chronic Granulocytic Leukemia: Relevance to Bone Marrow Transplantation," Blood, 66:6 (Dec. 1985), 1352-57; John M. Goldman, "Bone marrow transplantation for chronic myelogenous leukemia," Current Opinion in Oncology, 4 (1992), 259-63; and Jeffrey S. Miller and Philip B. McGlave, "Therapy for chronic myelogenous leukemia with marrow transplantation," Current Opinion in Oncology, 5 (1993), 262-69.

Table 3.1: Transplantation Rates for CML

Country	Rate[a]
Sweden	.54
United Kingdom	.48
New Zealand	.46
Denmark	.41
Canada	.39
Australia	.38
United States	.35
Netherlands	.33
France	.32
Germany	.26

[a]Ratio of the incidence of allogeneic bone marrow transplantation performed within 2 calendar years following the year of diagnosis to estimated annual incidence of CML; for transplants performed in 1989-91 on patients aged 0-54.

Table 3.1 shows that from one-quarter to one-half of CML patients in the countries received a bone marrow transplant within the specified period, a two-fold difference between least and most. The countries were fairly evenly distributed over the range.[12] The United States was below the middle of the range, in a cluster of countries where about one-third of CML patients were transplanted. German patients had the lowest likelihood of transplantation, while those in Sweden had the highest.

The Timing of Transplants

The time from diagnosis to transplantation for CML patients is shown in table 3.2. We restricted this analysis to those patients whose donor was a member of the patient's family (ranging from 67 percent of all CML transplants in Denmark to 96 percent in Australia). This largely reduces variations in timing caused by having to search for suitable unrelated donors.

[12]Because the rate is calculated using the annual incidence of the disease in each country, it can be affected to some degree by patient travel between countries to receive a transplant. Data on country-of-residence were not available.

Table 3.2: Months From Diagnosis to Transplantation for CML Patients[a]

Country	Percent of cases					Total cases
	5%	25%	50%	75%	95%	
New Zealand	1.8	5.9	**6.8**	8.8	69.7	10
Netherlands	3.0	6.5	**8.1**	12.3	58.6	38
Sweden	4.0	6.1	**8.6**	11.9	24.8	41
United States	2.8	5.2	**9.0**	21.6	72.4	972
Canada	3.3	6.2	**10.0**	20.5	63.6	146
France	4.0	6.8	**11.2**	22.2	70.3	177
United Kingdom	2.9	7.3	**11.8**	17.2	36.4	164
Australia	4.9	9.4	**13.8**	25.6	81.4	91
Denmark	7.0	14.0	**15.2**	22.3	42.3	19
Germany	4.9	9.9	**15.4**	24.4	59.4	145

[a]For related-donor transplants performed in 1989-91.

As can be seen in table 3.2, the median time from diagnosis to transplant—the point at which 50 percent of the patients who were treated with BMT had received their transplants—varied from a low of 6.8 months in New Zealand to a high of 15.4 months, or more than twice as long, in Germany. The United States was the fourth most rapid in terms of the median time-to-transplant. In Australia, Denmark, and Germany, the median occurred more than a year following diagnosis. In looking at the 75th percentile, it can be seen that the bulk of patients had received their transplants within 12 months in New Zealand, the Netherlands, and Sweden; whereas in the remainder of the countries, this point occurred from a year-and-a-half to two years following diagnosis. The United States had one of the broadest ranges, with relatively more patients transplanted both very quickly (in less than 3 months) and very late (more than 6 years following diagnosis).

Table 3.3 presents the percentage of CML patients transplanted within 1 year of diagnosis, the time period associated with better outcomes. We again limited this analysis to patients whose donor was related.

Table 3.3: CML Patients Transplanted Within 1 Year of Diagnosis[a]

Country	Total cases	Percent
New Zealand	10	80%
Sweden	41	76
Netherlands	38	74
United States	972	61
Canada	146	58
France	177	52
United Kingdom	164	52
Australia	91	42
Germany	145	36
Denmark	19	11

[a]For related-donor transplants performed in 1989-91.

Table 3.3 shows that patients had longer waits in some countries than in others. Within 12 months, one-half or more transplant patients in all of the countries except Denmark, Germany, and Australia had been treated.

Stage of Disease at Transplantation

Table 3.4 presents, for each country, the percentage of transplants for CML that were performed in the first chronic phase of the disease. As with the prior examination of time, the analysis is limited to transplants with related donors.

Table 3.4: CML Transplants Performed in Chronic Phase[a]

Country	Total cases	Percent
Netherlands	38	82%
Canada	155	79
Sweden	41	78
United Kingdom	198	78
Germany	188	73
Denmark	20	70
United States	975	70
Australia	88	67
France	190	65
New Zealand	12	50

[a]For related-donor transplants performed in 1989-91.

Table 3.4 shows a 32-percentage-point difference (50 percent to 82 percent) across countries in the proportion of related-donor transplants performed in the initial stage of the disease—when the therapy offered the best curative potential. In systems wherea high proportion of patients were transplanted in first chronic phase, physicians may have referred appropriate candidates quickly and had services available. Alternatively, systems providing transplants to a high proportion of patients in first chronic phase may simply not have performed transplants on patients whose disease was advanced at the time of diagnosis or had progressed before a transplant could be performed.

Four-fifths or more of Canadian and Dutch transplant patients received transplants in first chronic phase, compared to about two-thirds of patients in France and Australia and just half of patients in New Zealand.[13] However, this variation is substantially smaller than that observed in median time-to-transplant and in the proportion transplanted within 1 year. Moreover, in the systems where the smallest percentage of CML patients were transplanted within a year of diagnosis (Germany and Denmark), the proportion of patients receiving transplants in the most favorable stage of the disease was comparable to that in the United States and several other systems that tended to transplant their patients more quickly.

Conclusions

Variation in the use of bone marrow transplantation for CML provides considerable insight concerning the relative performance of these 10 health care systems in providing this complex and expensive procedure. CML is the diagnosis where bone marrow transplants are most clearly the curative therapy of choice and where treatment in the early stage of the disease is most certainly advantageous. However, the disease progresses relatively slowly for most patients, and they can be kept waiting if the resources available to perform transplants are relatively scarce (though with increasing risk that the disease will convert to a less treatable stage). Thus, we assessed these systems on two measures of availability—the proportion of CML cases that received transplants and the time from diagnosis to transplantation—and two measures of appropriateness—the proportion of patients receiving transplants in first chronic phase and the proportion transplanted within 1 year.

[13]The small number of cases in Denmark and New Zealand, however, make their rates more uncertain than those of the other countries.

Availability

In terms of the two measures of availability, the United States fell roughly in the middle of the 10 countries. The overall likelihood of transplantation was moderate. On the measure of time-to-transplant, the United States started rapidly, transplanting the highest percentage of BMT patients within 6 months of diagnosis. This implies readily available transplant capacity. However, the United States also was very slow to provide transplants to some. This could reflect any of a number of factors, including regional shortages of capacity, limitations in the ability of some patients to pay for the procedure, patient willingness, physician referral patterns, or differences in treatment philosophy.

Appropriateness

U.S. performance also fell roughly in the middle for the two measures of appropriateness. Both on the percentage of CML patients receiving transplants within 12 months and the percentage receiving them in first chronic phase, a number of other countries appear to have a more appropriate pattern of utilization of transplant resources. In the United States, along with Australia, France, and New Zealand, patients with advanced disease (and therefore poorer prognoses) had greater access to this expensive, high-technology, potentially life-saving treatment. This implies that a larger proportion of resources was spent on patients for whom the expectation of benefit was lower.

Overall

In general, different systems outperformed the United States on different measures of availability and appropriateness. Sweden ranked high on all four measures. The Netherlands and New Zealand ranked high on three of the four, including both indicators involving time-to-transplant. However, the Dutch performed transplants on a relatively small proportion of their CML patients, while in New Zealand, a low percentage of patients were transplanted in first chronic phase. In all, six other systems (Sweden, United Kingdom, New Zealand, Denmark, Canada, and Australia) transplanted a higher proportion of their CML cases than did the United States, and five (Netherlands, Canada, Sweden, United Kingdom, and Germany) performed transplants on a higher percentage of patients in first chronic phase.

The United States, however, was not distinctly worse than average on any of the four measures. This was also true for Sweden, Canada, and the United Kingdom. Germany, by contrast, was at or near the bottom on three dimensions (all but stage of disease at transplantation) and Denmark on two (both timing dimensions).

Acute Lymphoid Leukemia

The use of bone marrow transplantation in the treatment of acute lymphoid leukemia is well established, but its role differs from that for chronic myeloid leukemia, discussed in the preceding chapter. In treating ALL, BMT primarily serves as salvage therapy when chemotherapy has failed to provide a cure. In this chapter, we explain our basis for examining the availability and appropriateness of bone marrow transplantation for ALL. We then describe our findings for the 10 health care systems under study, with particular attention to the position of the United States relative to the other systems, and discuss the findings in terms of our measures of availability and appropriateness.

Evaluation Criteria

ALL begins in an acute phase, which rapidly advances. If the disease is untreated, life expectancy is less than 1 year.[1] However, treatment is available that can extend the life of the majority of patients, many of whom appear to be cured.[2] The goal of treatment is to achieve "remission," an eradication of any signs of disease. This is typically brought about by chemotherapy. ALL is highly responsive to chemotherapy, especially in children.[3] The patient in remission is followed to monitor any recurrence of the disease, or "relapse." If a relapse occurs, a second round of therapy is initiated.

For most patients with ALL, cure rates using chemotherapy are so high that BMT is usually reserved as salvage therapy for this disease upon relapse.[4] Some risk, however, is associated with waiting to perform a transplant until after a relapse. Patients who receive transplants while they are in complete remission have the best prognosis; those with advanced disease (second relapse or beyond) have a poorer prognosis.[5] Thus, just as with

[1]Peter H. Wiernik, "Acute Leukemias of Adults," in Cancer: Principles and Practice of Oncology, 2nd ed., chap. 45, eds. Vincent T. DeVita, Jr., Samuel Hellman, and Steven A. Rosenberg (Philadelphia: J.B. Lippincott, 1985), pp. 1711-37.

[2]Clinicians are hesitant to pronounce a leukemia patient as "cured" since there is always some chance that the disease may recur, but a patient is typically considered to be cured if there has been no recurrence of the disease within 5 years.

[3]Stephen J. Forman and Karl G. Blume, "Allogeneic Bone Marrow Transplantation for Acute Leukemia," Hematology/Oncology Clinics of North America, 4:3 (June 1990), p. 521.

[4]Philip B. McGlave, "The Status of Bone Marrow Transplantation for Leukemia," Hospital Practice, 20 (Nov. 15, 1985), 97-110.

[5]Frederick R. Appelbaum and E. Donnall Thomas, "Treatment of Acute Leukemia in Adults With Chemoradiotherapy and Bone Marrow Transplantation," Cancer, 55:9 Supp. (May 1, 1985), 2202-09; Richard Champlin and Robert Peter Gale, "Bone Marrow Transplantation for Acute Leukemia: Recent Advances and Comparison With Alternative Therapies," Seminars in Hematology, 24:1 (Jan. 1987), 55-67.

CML, the chances of a transplant being successful become poorer as the disease progresses. This creates a tension in treating ALL in that the earlier in the progression of the disease, the less likely BMT is necessary but the more likely it will be successful. Additionally, the risks of the treatment are sufficiently high that a careful evaluation is required to avoid performing transplants on patients already cured by the chemotherapy.

Transplantation is not viewed as a salvage therapy for every ALL patient. Certain categories of patients are considered to have so high a risk of not responding to chemotherapy or of relapsing that BMT is seen as legitimate primary therapy. Included in this category are patients who have certain chromosomal abnormalities, who have a high leukocyte level at diagnosis, or who require more than 4-6 weeks of chemotherapy to achieve a remission.[6] In addition, some consider most adult patients with ALL to be high-risk patients because, in general, the older the patient, the poorer the prognosis. However, there is evidence that adult patients can be classified as standard risk or high risk on the basis of the above prognostic indicators.[7]

For high-risk patients, a BMT would be considered an appropriate treatment option even when they are in first remission. However, for standard-risk patients, a BMT would be less appropriate unless they have failed at least one round of conventional chemotherapy.

Measures of Availability

Given that bone marrow transplantation is a recommended therapy for the treatment of ALL patients who relapse and for those with "high-risk" disease, it needs to be available to appropriate candidates. We assessed the availability of bone marrow transplants in the 10 countries through computation of the proportion of patients with ALL who had received transplants by the end of the second calendar year following the year of diagnosis. This provided an estimate of the likelihood for each country that a patient with ALL would receive a transplant. To do this, we related the number of transplants for ALL to the estimated level of the disease in each country. As with our examination of CML, this analysis was limited to patients under age 55 because it is rare for BMTs to be performed on older patients.

[6]Nelson J. Chao and Karl G. Blume, "Bone Marrow Transplantation: What Is the Question?" Annals of Internal Medicine, 113:5 (Sept. 1, 1990), 340-41.

[7]McGlave (1985), p. 105.

Our analysis allows for an examination of the relative levels of use of the procedure across countries. Thus, a country with a ratio twice that of another performed transplants on twice the proportion of its ALL patients. However, we cannot say what level of transplantation is best. Many patients are cured by chemotherapy and do not need a transplant; thus, projecting the base level at which transplants for ALL should be performed is not possible. In addition, the 3-year time frame of our study may be insufficient to capture some patients whose disease remains in check for an extended period following diagnosis, but who will ultimately relapse and receive a transplant.

As an additional measure of the availability of the treatment, we examined the time from diagnosis to transplantation for that subset of patients who received their transplant in first remission. The "time-to-transplant" is not a meaningful measure of availability for patients transplanted at later stages of the disease because of variability among these patients in how long their disease was in remission before a relapse occurred. However, for patients who are recommended to receive a transplant in first remission (those who are considered high risk), the sooner the transplant is performed, the better, primarily because up to 5 percent of these patients will relapse every month. In this instance, delays in obtaining a transplant can indicate poor availability.[8]

Measures of Appropriateness

The time from diagnosis to transplantation for patients receiving a transplant in first remission is also an indicator of the appropriateness of care, because long waits for receiving a transplant increase the chances that high-risk patients will see their disease progress. A pattern of long waits for patients receiving transplants while in first remission also presents another concern about appropriateness. Because some proportion of even high-risk patients will have been cured by chemotherapy, at some point there will be a change in the probabilities favoring transplantation over waiting to see if a relapse occurs. That is, the longer a patient has waited without relapsing, the higher the probabilities become that the patient has been cured by chemotherapy. Thus, if the wait extends long enough, the risks of receiving a transplant may begin to

[8]The proportion of acute leukemia patients who fail to achieve even a first remission through chemotherapy (primary induction failure) that receive transplants would also provide insight on the relative availability of transplantation in different systems. This is because BMT offers these patients a small but real chance of cure when their prospects would otherwise be nil. However, our data, as reported in the following sections, can only describe the proportion of transplants that are provided to patients experiencing primary induction failure. We do not know what proportion of patients in this situation undergo BMT.

outweigh the risks of waiting. At this point, a transplant would be less appropriate because the patient may already have been cured.

In addition to examining time-to-transplant, we also examined the stage of disease as an indicator of appropriateness. The focus was on the percent of transplants performed on patients with advanced disease (that is, past second remission). However, just as with time, we restricted our examination of stage to a subgroup of ALL patients. Excluded from the analysis were pediatric patients. The focus on adults was based on research that showed that many adults respond relatively poorly to chemotherapy.[9] Therefore, continued rounds of chemotherapy would be less appropriate for these patients than they would be for children. Although uncertainty remains among clinicians as to whether adult patients should receive transplants in first remission or only after relapse, their relatively poor responsiveness to chemotherapy means that waiting until adult patients relapse a second time before providing a BMT would be less appropriate than providing the transplant in first or second remission.

Likelihood, Timing, and Stage of Transplants

The sections that follow present our analyses of the likelihood, timing, and stage of transplants for ALL patients in 10 countries.

The Likelihood of Receiving a Transplant

To assess the availability of BMT to treat ALL, we needed to determine how many potential candidates for transplantation there were in each country between 1989 and 1991. As discussed in the previous chapter, we used a range of data sources (described in appendix II) to construct a disease-specific transplantation rate. This rate represents the likelihood that ALL patients under age 55 in each country would receive BMT as part of their leukemia treatments by the end of the second calendar year following the year of diagnosis. The rates also describe the relative likelihood of receiving a BMT across countries.

Table 4.1 presents these rates for ALL in the 10 countries. As noted previously, for some countries, particularly Sweden, Denmark, and New Zealand, the number of transplants performed is small, which means that random fluctuations from year to year by even a few cases could significantly affect the rates and thus the rankings of these countries.

[9]Mary M. Horowitz et al. "Chemotherapy Compared with Bone Marrow Transplantation for Adults with Acute Lymphoblastic Leukemia in First Remission," Annals of Internal Medicine, 115:1 (July 1, 1991), 13-18.

Table 4.1: Transplantation Rates for ALL

Country	Rate[a]
France	.23
United Kingdom	.15
Netherlands	.11
Sweden	.09
Australia	.08
United States	.07
Germany	.06
Canada	.05
New Zealand	.04
Denmark	.03

[a]Ratio of the incidence of allogeneic bone marrow transplantation performed within 2 calendar years following the year of diagnosis to estimated annual incidence of ALL; for transplants performed in 1989-91 on patients aged 0-54.

Because the ALL cure rate with standard chemotherapy is high, especially in children, the transplantation rates for ALL were lower than those for CML. However, we still found variation in the use of BMT to treat ALL. Table 4.1 shows that ALL patients in France were considerably more likely to receive a BMT as part of their therapy than patients in any of the other countries.[10] Patients in Denmark and New Zealand had the lowest probabilities of transplantation. Transplantation rates in the other countries ranged from just above that minimum to about two-thirds of the French rate, with the United States near the middle of the range for the remaining countries.[11]

During the 3 years of interest to our study (1989-91), French physicians had in place several nationwide randomized clinical trials comparing transplantation and chemotherapy for acute leukemia. These large-scale trials may have resulted in more patients receiving transplants than would otherwise have been expected.[12]

[10]Because the time frame might not be sufficiently long to obtain an accurate picture of the proportion of ALL patients receiving BMTs, we also computed the ratio of all transplants performed for the disease in 1989-91 (irrespective of date of diagnosis) to the disease incidence. The relative rankings of the countries was essentially the same.

[11]In addition, just as for CML, the rates in some countries may be influenced by patient travel between countries to receive transplants.

[12]The transplant resources required for the acute leukemia trials (physicians, beds, staff, drugs, etc.) could conceivably have served to depress the rates of transplantation for CML or other conditions to some unknown extent.

The Timing of Transplants

The time from diagnosis to transplantation for those patients receiving a transplant in first remission is shown in table 4.2. This analysis was restricted to first remission transplants (those cases where BMT was used as primary therapy and not reserved as salvage therapy for patients who relapsed). For these patients, the sooner the transplant is performed, the better, to avoid the risk of relapse. In addition, the analysis was limited to patients whose donor was related, to eliminate any effects on timing from delays caused by the search for an unrelated donor.

Table 4.2: Months From Diagnosis to Transplantation for ALL Patients[a]

	Percent of cases					Total
Country[b]	5%	25%	50%	75%	95%	cases
France	2.6	3.2	**3.7**	4.4	6.6	117
Canada	3.1	3.9	**4.7**	5.9	11.5	26
United States	2.5	3.6	**4.7**	7.7	16.4	135
Germany	3.3	4.1	**5.2**	8.0	14.9	18
Sweden	3.7	4.1	**5.2**	6.0	8.8	8
United Kingdom	3.0	4.4	**5.2**	7.3	11.4	81
Netherlands	4.0	5.1	**6.2**	8.4	10.5	26
Australia	3.6	5.1	**7.2**	7.7	9.2	16

[a]For patients in first remission at time of transplant; related-donor transplants performed in 1989-91.

[b]Denmark and New Zealand are not included in this table; Denmark had no ALL patients transplanted in first remission, and New Zealand had only one.

If we look at the time frames in table 4.2, we see that all the countries made a rapid start on providing transplants to these patients. The median time from diagnosis to transplantation (that point at which 50 percent of patients had received their transplants) varied from a low of 3.7 months in France to a high of 7.2 months, or about twice as long, in Australia. The United States was the second most rapid, along with Canada, in terms of the median time-to-transplant. At the 75th percentile, variation across the countries was quite small, with seven systems bunched in a two-and-a-half-month range (France was the exception, with 95 percent of its cases receiving transplants by a similar point in time). Evidently, all these systems were able to offer transplants to ALL patients fairly quickly when BMT was chosen as the primary therapy.

Stage of Disease at Transplantation

Table 4.3 presents the number and percentage of adult patients receiving transplants for ALL by stage of disease the time of transplantation. Again,

we restricted this analysis to those patients whose donor was a member of the patient's family, to remove any possible effects on disease progression during the search for a suitable unrelated donor.

Table 4.3: Stage of Disease at Transplantation for Adult ALL Patients[a]

Country	Induction failure[b]	First complete remission	First relapse	Second complete remission	Advanced disease[c]	Total cases
Australia	3%	44%	15%	18%	21%	34
Canada	3	68	3	22	5	37
Denmark	0	0	0	100	0	2
France	4	72	4	20	1	164
Germany	5	33	7	37	19	43
Netherlands	3	63	3	22	9	32
New Zealand	0	25	0	25	50	4
Sweden	0	33	17	42	8	12
United Kingdom	2	72	4	17	6	85
United States	5	33	18	25	20	342

[a]For related-donor transplants performed in 1989-91. Adult is defined as patients aged 17 and older.

[b]Induction failure refers to patients in whom chemotherapy has failed to induce a complete remission.

[c]Advanced disease refers to patients who are in their second relapse or beyond.

Transplantation by stage of disease appears to fall into two patterns for adult ALL patients. Well over half of Canadian, French, Dutch, and British transplant patients were treated in first remission while the majority of patients in other countries received their transplants at first relapse or later. Further, in the United States, Australia, and Germany, about 20 percent of patients with ALL who received a transplant were at an advanced stage of the disease, while in New Zealand half the patients were at this stage.

Conclusions

The comparative assessment of systems in their treatment of acute lymphoid leukemia is complicated because BMTs are not necessarily called for in the case of this disease. Many patients (especially children) are cured by chemotherapy alone, so lower rates of transplantation and transplantation at later stages of disease may be more consistent with proper care than higher rates at earlier stages. We examined the

availability of BMTs for ALL with two measures: the proportion of ALL patients who received transplants and the time from diagnosis to transplantation for patients transplanted in their first complete remission. We also used time-to-transplant as a measure of appropriateness of care, along with the stage of disease at which the transplant was provided.

Availability

We looked at two measures of availability. Overall, the United States was among the majority of countries that transplanted a fairly low proportion of its ALL patients. In terms of time-to-transplant, the United States was the fastest system to begin performing transplants, indicating a ready availability of BMTs for this disease. However, the United States was also the country with patients transplanted at the longest interval following diagnosis. Only the United States and Germany had more than 5 percent of their patients who would ultimately receive a first remission transplant still awaiting the procedure 1 year after diagnosis. Just as for CML, where a similar distribution was found, any of a number of factors, including regional shortages of capacity, limitations in the ability of some patients to pay for the procedure, patient willingness to undergo the treatment, physician referral patterns, or differences in treatment philosophy could explain this pattern.

France stood out from all the other countries on the measures of availability in that it transplanted ALL patients at a substantially higher rate than the others and was by far the fastest in providing transplants to its first remission patients. Thus, the French implemented a treatment policy for ALL that provided BMTs quickly and more extensively than we found in the other nine systems. This may be related to the large-scale clinical trials in France on transplantation for acute leukemia, among other factors.

Appropriateness

With regard to the measures of appropriateness, the United States appears to fall somewhat below the middle. For patients transplanted in their first complete remission, the issue of appropriateness of time-to-transplant is whether some patients waited so long for a transplant that the risks of disease progression no longer outweighed the risks of the procedure. This appeared to be a particular concern in the United States and, to a lesser extent, in Germany. In both these countries, more than 5 percent of these patients waited over a year following diagnosis before the procedure was performed.

Regarding stage of disease at transplantation, the United States is among four countries in which a substantial proportion of transplants were for patients with advanced disease. Among adults, transplantation at earlier stages of the disease is more appropriate than with advanced disease, when the prognosis is much poorer. The relatively high proportion of adult patients transplanted with advanced disease in the United States means that a higher proportion of the resources expended in the United States on transplantation for ALL were going to patients with relatively poorer prognoses.

Because the overall level of transplantation for the disease in the United States is moderate, the relatively high number of patients being transplanted with advanced disease points to a difference in the treatment pattern for the disease, not an overall higher level of use of the technology. In addition, the United States is alone in transplanting any of its ALL patients in first remission more than 18 months beyond diagnosis.[13] The experts who reviewed these data viewed such transplants as clearly outside the boundaries of appropriate treatment.

Looking at stage of disease in the other countries, four systems—Canada, France, the United Kingdom, and the Netherlands—distinguished themselves in that well over half of their ALL transplants were done in first complete remission. While France, the United Kingdom, and the Netherlands are the systems that transplanted the highest proportion of patients with ALL, Canada had a much lower rate. On the one hand, France, the United Kingdom, and the Netherlands appear to have used BMT as a primary therapy for a broader range of ALL patients than the other countries. The pattern in Canada, on the other hand, with its moderate overall rate of transplantation for ALL, was more consistent with an approach that concentrated transplant resources on the high-risk patients who benefit most from BMT in first complete remission.

Transplants performed for ALL represent a significant portion of the resources devoted to BMT in each system. However, currently, there are no clear lines where it can be stated that a system provides "enough" or "too many" transplants for ALL. The boundaries for appropriate and inappropriate care are much broader for this disease than for CML, and in almost all instances, the care patients received in all these countries fell within those boundaries.

[13]There were patients in United States receiving transplants more than 3 years following diagnosis.

Acute Myeloid Leukemia

Acute myeloid leukemia is the most common type of leukemia in young- and mid-adulthood and accounts for the great majority of adult acute leukemia cases. Bone marrow transplantation has been an established treatment for this disease for more than a decade.[1] To evaluate the availability and appropriateness of transplantation for AML in the 10 health care systems, we identified from the clinical literature specific criteria for this diagnosis. Below, we describe these criteria, and then we present data describing how patients in the 10 countries vary in their likelihood of receiving a transplant, the timing of transplants, and the stage of disease at the time of transplantation. The chapter concludes with an assessment of how the United States compares to the other countries on the availability and appropriateness of allogeneic transplantation for AML.

Evaluation Criteria

AML advances rapidly, and if untreated, the life expectancy for patients is less than 1 year.[2] Therefore, immediate treatment to bring the patient into remission is critical. Intensive chemotherapy (induction therapy) is often successful in the initial treatment of AML, and approximately 60-75 percent of patients achieve a remission. Once this occurs, patients are treated with several courses of intensive consolidation therapy and then followed closely with no further therapy. Unfortunately, many patients who achieve a first complete remission relapse within 12-18 months. Further chemotherapy, called reinduction therapy, can induce a second remission in one-third of patients and, occasionally, a third remission. However, each remission following the first relapse tends to be shorter than the one preceding it, and almost always a relapse eventually occurs that does not respond to chemotherapy. Long-term survival for AML patients, therefore, largely depends upon achieving and maintaining the first remission. Once a patient relapses, a bone marrow transplant offers the best prospect of a cure.

Some AML patients are cured by the initial round of chemotherapy but many are not; thus, whether continued chemotherapy alone or transplantation is the optimal therapy for patients who have achieved a

[1]Robert Dinsmore et al., "Allogeneic Bone Marrow Transplantation for Patients With Acute Nonlymphocytic Leukemia," Blood, 63:3 (Mar. 1984), 649-56.

[2]Peter H. Wiernik, "Acute Leukemias of Adults," in Cancer: Principles and Practice of Oncology, 2nd ed., chap. 45, eds. Vincent T. DeVita, Jr., Samual Hellman, and Steven A. Rosenberg (Philadelphia: J.B. Lippincott Co., 1985), pp. 1711-37.

first remission is still being debated.[3] Part of the uncertainty stems from the difference between short- and long-term results. With conventional chemotherapy, drug-associated mortality is low, but patient survival rates decline gradually over time owing to death from relapse. With transplantation, treatment-related mortality is higher in the first 2 years, but if the patient survives the therapy, the likelihood of cure is greater than it is with conventional chemotherapy.[4] Adding to the uncertainty is the difficulty in identifying which patients will relapse (and therefore might benefit from a transplant) and which patients will stay in remission (and therefore will do better if not subjected to the risks of a transplant). However, the longer a patient continues in first remission, the less likely it is that the patient will subsequently relapse. Thus, the relative risks and benefits between chemotherapy and transplantation change over time, even for the same patient.

Measures of Availability

Given that the best course of treatment is uncertain, rates of transplantation for patients with AML comparable to those for CML patients should not be expected. Continued chemotherapy may be the most appropriate treatment for patients for any of several reasons. First, because of the patient's age or the lack of a suitable donor, transplantation may not be a relevant consideration. Second, BMT itself is sometimes a cause of life-threatening complications and early mortality, while chemotherapy alone does cure some patients. Thus, physicians need to evaluate for each individual patient the risk of transplantation against the risk of conventional therapy in terms of survival and quality of life.

At the aggregate level, the relative likelihood of transplantation for AML tells us something about how available transplantation is in each of the countries for patients with this disease. However, all the uncertainties mentioned above make it inappropriate for us to conclude that countries that have higher (or lower) rates of transplantation are doing a better job of treating AML. The rates simply inform us about the relative distribution of resources for transplantation for this disease.

As an additional measure of the relative availability of transplants, we examined the time from diagnosis to transplantation for patients who

[3]As of 1992, after the period studied in this report, published trials suggested that transplantation is equivalent and possibly superior to chemotherapy, while no trials suggested the superiority of chemotherapy. Rajesh Chopra and Anthony H. Goldstone, "Modern Trends in Bone Marrow Transplantation for Acute Myeloid and Acute Lymphoblastic Leukemia," Current Opinion in Oncology, 4:2 (Apr. 1992), 247-58.

[4]Philip B. McGlave, "The Status of Bone Marrow Transplantation for Leukemia," Hospital Practice, 20 (Nov. 15, 1985), 97-110.

received the treatment in first remission. Time-to-transplant is not meaningful for patients who receive transplants at later stages of the disease because of the variability in how long these patients were in remission before a relapse occurred. However, as with ALL, for those patients who are recommended for transplantation in first remission, the sooner the transplant is performed, the better. In this instance, longer times to provide the treatment can indicate poorer availability.

Measures of Appropriateness

The uncertainties surrounding optimal therapy for AML patients also make it difficult to evaluate the appropriateness of care. Two criteria, however, can be used. One of these is time-to-transplant from the point of diagnosis for patients who receive transplants while they are in first remission. For these patients, it is clear that the earlier they are treated, the more likely they are to benefit from the procedure. This is true for two reasons. One is that the cumulative likelihood of relapse increases as time passes and transplantation is more likely to succeed when the disease is in the first complete remission, rather than in first relapse or in second remission.[5] Second, the longer a patient goes without a relapse, the more likely it is that the remission will continue without a transplant. Both these factors together indicate that if a patient is to receive a bone marrow transplant while in first remission, earlier is better.

The second criterion we used to measure appropriateness is the stage of the disease at time of transplantation. As mentioned above, it is difficult to discriminate between patients who will relapse (and, therefore, should be transplanted while in first remission) and patients who will be cured by chemotherapy alone (and, therefore, do not benefit from a transplant). However, research has demonstrated that after a patient has relapsed, it is best to transplant as soon as possible. For some patients, it is feasible to transplant immediately, rather than subject that patient to a second round of intensive chemotherapy.[6] In other cases, it is appropriate for the patient to be reinduced into a second complete remission and then transplanted. By this point, all AML patients considered eligible for transplantation should have the procedure performed. At any later stage (second relapse,

[5]R.A. Clift et al., "The Treatment of Acute Non-lymphoblastic Leukemia by Allogeneic Marrow Transplantation," Bone Marrow Transplantation, 2:3 (Oct. 1987), 243-58.

[6]Frederick R. Appelbaum and E. Donnall Thomas, "Treatment of Acute Leukemia in Adults With Chemoradiotherapy and Bone Marrow Transplantation," Cancer, 55:9 Supp. (May 1, 1985), 2202-09.

third remission, and so forth) their prospects for a positive outcome are notably diminished.[7]

Likelihood, Timing, and Stage of Transplants

We provide our analyses of the likelihood, timing, and stage of transplantation for AML in the sections that follow.

The Likelihood of Receiving a Transplant

As in previous chapters, we have constructed a disease-specific BMT utilization-to-incidence ratio to represent the rate of transplantation. The rates in table 5.1 represent the likelihood that AML patients under age 55 in each country would receive BMT as part of the their leukemia treatments by the end of the second calendar year following the year in which they were diagnosed. The rates also describe the relative likelihood, across countries, of receiving a transplant. As in previous tables, when the number of events is small—the situation for New Zealand, Denmark, and Sweden—random fluctuation from year to year in the number of patients, by even a few cases, could noticeably affect the rates and thus the rankings of countries.

Table 5.1: Transplantation Rates for AML

Country	Rate[a]
France	.50
Canada	.27
United States	.23
United Kingdom	.20
Australia	.20
New Zealand	.19
Netherlands	.18
Sweden	.17
Germany	.13
Denmark	.10

[a]Ratio of the incidence of allogeneic bone marrow transplantation performed within 2 calendar years following the year of diagnosis to estimated annual incidence of AML; for transplants performed in 1989-91 on patients aged 0-54.

[7]F.R. Appelbaum et al., "Timing of Bone Marrow Transplantation for Adults with Acute Nonlymphocytic Leukemia," Autologous Bone Marrow Transplantation: Proceedings of the Fourth International Symposium, eds. K.A. Dicke et al. (Houston: University of Texas M.D. Anderson Cancer Center, 1989), 21-26.

Table 5.1 shows that French patients, at 50 percent, had the highest probability of receiving a transplant.[8] The probability was almost twice that of patients in any of the other nine countries. In the United States, nearly one-fourth of AML patients received transplants as part of their therapy. That ratio was slightly lower than Canada's and slightly higher than in five other countries. Patients in Denmark and Germany had the lowest likelihood of transplantation. For each country, the likelihood of transplantation for patients with AML was greater than for patients with ALL and, except for France, less than for CML patients.

The Timing of Transplants

Table 5.2 presents data on time-to-transplant for patients who received a transplant while in first remission. To ensure that variations due to the availability of donors were not incorporated, the table includes data only on patients receiving related-donor transplants.

Table 5.2: Months From Diagnosis to Transplantation for AML Patients[a]

	Percent of all cases					Total
Country	5%	25%	50%	75%	95%	cases
France	2.5	3.0	**3.6**	4.7	7.4	143
United States	2.4	3.4	**4.4**	5.8	10.2	367
Canada	2.6	3.8	**5.3**	7.6	13.2	82
Netherlands	3.9	4.6	**5.4**	6.2	8.7	46
Sweden	3.0	4.6	**5.6**	7.1	9.1	25
Germany	3.3	4.9	**5.7**	7.2	9.9	75
Australia	3.3	4.5	**6.0**	8.7	12.2	38
Denmark	4.8	5.0	**6.4**	8.2	9.8	7
United Kingdom	3.9	5.3	**6.4**	7.6	10.8	102
New Zealand	3.8	6.3	**6.5**	6.8	7.1	8

[a]For patients in first remission at time of transplant; related-donor transplants performed in 1989-91.

The table shows that the median times from diagnosis to transplant—the time when 50 percent of BMT patients in each country had received a transplant—ranged from 3.6 months in France to 6.5 months in New Zealand. More than three-fourths of French and U.S. patients transplanted in first remission were treated within 6 months. In Denmark, the United

[8]As noted in the previous chapter, the high rate of transplantation in France for acute leukemias may have been related in part to nationwide clinical trials then ongoing to compare the efficacy of BMT to chemotherapy for treating AML and ALL.

Kingdom, and New Zealand, the corresponding figures were less than one of every two patients.

Stage of Disease at Transplantation

Table 5.3 presents the percentage of transplants for AML conducted in each stage of disease. Again, the data are restricted to related-donor transplants to eliminate the possibility that variation is caused by the search for a suitable donor.

Table 5.3: Stage of Disease at Transplantation for AML Patients[a]

Country	Induction failure[b]	First complete remission	First relapse	Second complete remission	Advanced disease[c]	Total cases
Australia	13%	46%	33%	5%	2%	82
Canada	8	68	11	10	2	134
Denmark	0	54	15	31	0	13
France	8	68	5	16	3	277
Germany	6	67	7	14	6	168
Netherlands	4	82	2	9	4	56
New Zealand	0	80	0	20	0	10
Sweden	9	66	9	11	6	35
United Kingdom	6	79	8	6	1	158
United States	8	47	21	17	7	974

[a]For related-donor transplants performed in 1989-91.

[b]Induction failure refers to patients for whom chemotherapy has failed to induce a complete remission.

[c]Advanced disease refers to patients who are in their second relapse or beyond.

In table 5.3, we see that the patterns for the United States were quite distinct from those for most other countries. Most obvious is the relatively low percentage of transplants that occurred while patients were in first remission. Here, the United States was joined only by Australia in transplanting less than half its BMT patients during this stage of the disease. Additionally, the United States provided transplants to relatively more patients with advanced disease than any other country, although the differences were small.

Conclusions

Just as for ALL, the comparative assessment of the 10 countries in their treatment of AML is complicated because transplants are not necessarily called for in caring for these patients. Some are cured by chemotherapy alone, so transplantation is not clearly indicated unless and until a patient relapses. However, if a transplant is to be performed, the prognosis is better if the patient receives the transplant in the first complete remission of the disease. In assessing how the 10 health care systems handled the treatment of AML, we examined the availability of BMTs using two measures: the proportion of patients who received transplants and the time from diagnosis to transplant for patients who received transplants in their first complete remission. We also used time-to-transplant as a measure of appropriateness of care, along with the stage of disease at which the transplant was provided.

Availability

Our data on availability cannot indicate which countries had the "right" amount of transplantation. The data simply show that France was unique in the level of transplantation, with a French AML patient almost twice as likely to receive a transplant as those in any other country. For the United States, the data show levels of transplantation on par or slightly higher than that of most other countries (besides France). The United States was among the quickest to begin providing transplants and second only to France in the time required to treat the bulk of its patients, indicating good availability of transplant services for patients with AML.

Appropriateness

The question of whether a transplant should be done remains open for many patients with AML. However, the benefits of acting quickly for those patients who do receive transplants are fairly well established.[9] Here, the patterns exhibited by patients in the United States and most of the other systems are largely positive. The United States was second only to France in the speed with which patients in first complete remission received transplants.[10] However, even the slowest systems transplanted half these patients within slightly more than 6 months of diagnosis and 95 percent within a little more than a year.

[9]Appelbaum and Thomas (1985), p. 2206.

[10]The only qualification is that, as with CML and ALL, a small group of patients seemed to wait a long time before receiving a transplant. While the United States was second fastest in providing transplants for 75 percent of the patients, the last 5 percent waited longer than their counterparts in six other countries.

In terms of stage of disease, the United States, Australia, and Denmark were least likely to transplant in first complete remission. Patients in these countries appear more likely to have been treated under an alternative strategy, in which BMT was reserved for those who relapse from their first complete remission. Since the reported outcomes of the two strategies are equivalent, neither is more appropriate. While the United States also led in the number of patients receiving transplants in still later stages, the overall frequency was low (only 7 percent of U.S. transplants for AML).

In short, U.S. patients with AML experienced similar levels of bone marrow transplantation availability and appropriateness relative to those in the other health care systems examined. The one major exception was the much higher rate of transplantation in France.

Conclusions and Implications

In the previous chapters, we have examined how the utilization of one costly, high-technology medical treatment varied across 10 national health care systems. We looked in particular at the patterns displayed in the use of bone marrow transplantation in the treatment of three prevalent forms of leukemia: chronic myeloid leukemia, acute lymphoid leukemia, and acute myeloid leukemia. This chapter summarizes the principal findings from our study. After presenting these, we discuss their implications.

Summary of Findings

Our objectives were to determine, from a comparative perspective, the availability of transplants (that is, the likelihood that patients who needed transplants would receive them) and the appropriateness of the observed patterns (the extent to which transplants occurred at a time when they optimize the risk-benefit ratio to the patient).

In terms of the first dimension, viewed across the three common types of leukemia for which transplantation is a standard treatment option, we found that the placement of the American health care system varied, but was never at either extreme of availability. For the two acute leukemias, alternative treatments may work as well as transplantation for many patients and pose less risk. For these conditions, the only conclusion that can be drawn is that the United States was not unique in using this expensive procedure when its relative advantages were less clear. However, for CML, a disease that could be cured only by transplantation, we found that U.S. patients were less likely to receive a transplant than were patients in some other countries.

The placement of the United States also varied along the dimension of appropriateness. The intervals from diagnosis to transplantation were among the shortest for the majority of U.S. transplant patients with acute leukemia. However, some patients in the United States waited longer for their transplants than patients in any other country. Further, higher proportions of U.S. patients (in the case of each of the leukemias) received transplants at a relatively late stage of the disease compared to patients in most of the other countries. The implications of this pattern are less clear for the acute leukemias (where the optimal stage of intervention is less well defined) than for the management of CML. In the latter case, the substantial number of U.S. CML patients who were transplanted with advanced disease has negative implications for the quality of care provided. This is especially true because the overall rate of transplantation for CML was not particularly high in the United States. Thus, the relatively large percentage of transplants performed on poor prognosis patients in

the U.S. means that relatively fewer good prognosis patients received transplants in this country than was the case elsewhere.

Implications

We have presented data for a single treatment and how it is used in the management of three diseases. Bone marrow transplantation is just one example of very expensive, complex, high-technology therapies. It cannot be assumed that our findings for BMT would necessarily hold true for other such procedures or for a wider range of medical interventions. In light of this uncertain generalizability beyond bone marrow transplantation, as well as the descriptive nature of our findings, what larger implications, if any, do our results suggest?

First, by presenting international data on utilization of BMT, this report informs members of the transplant community about how their treatment patterns compare to those of their colleagues in other countries. For other medical procedures, such as Caesarian section deliveries, hysterectomies, and prostatectomies, the presentation to practitioners of national and regional variations in practice patterns has led to a reconsideration of the indications for treatment, particularly among those who diverge most markedly from the others. Our international findings should facilitate and encourage a comparable discussion both within individual countries and across the international bone marrow transplant community. For example, the U.S. transplant community could consider why, to a greater extent than was true elsewhere, patients in the United States for whom the treatment offered fewer likely benefits (for example, those in advanced stages of leukemia) often received transplants, while others who could benefit more did not.

Second, our findings on bone marrow transplantation raise questions about two contrasting views of how the United States uses medical technology. One perspective sees higher utilization of costly, high-technology therapies as evidence of a greater availability of state-of-the-art medicine to the public. The other views higher utilization of these therapies in this country as indicative of wasteful and potentially harmful overuse of available technology.

Both views rest on the assumption that expensive, high-technology medicine is used to a far greater extent in the United States than in other economically advanced countries. However, the findings presented in this report challenge that assumption. Although the United States did better on some dimensions (time-to-transplant for acute leukemia) and less well on

others (stage of disease for CML transplants), on no measure did it surpass the other nine countries studied. Further, the data show that some countries that have been characterized in the public debate as much more restrictive in the provision of sophisticated health care treatments actually had levels of transplantation that were equivalent to, if not greater than, those of the United States.

Data Sources

To describe the patterns of utilization of bone marrow transplants in the 10 countries in the study, we needed to obtain data on patients receiving transplants from all the transplant centers in each country. This appendix discusses the data sources from which we derived the information on the number of transplants, the stage of disease at transplantation, and the time from diagnosis to transplant. These sources include the International Bone Marrow Transplant Registry based at the Medical College of Wisconsin, the Société Française de Greffe de Moëlle, and three surveys.

Our initial source of information was the IBMTR, which collects detailed information on all allogeneic bone marrow transplants performed at approximately 200 transplant centers worldwide, representing more than 50 percent of the transplant teams in the world. The primary database contains clinical information about each of more than 15,000 patients who have received bone marrow transplants since 1970.

The Société Française de Greffe de Moëlle is a professional society that collects data for research on bone marrow transplants performed at French institutions. A total of 35 centers contributed data to the society on allogeneic BMTs in 1989-91, while only 14 of these centers participate in the IBMTR. For France, we obtained data on transplants from the society rather than from IBMTR.[1]

Although most transplant centers contribute data to IBMTR, some centers do not participate, or at some hospitals with multiple transplant teams (e.g., pediatric and adult), one or more teams may not participate. Also, some centers only submit certain types of cases to the registry. We therefore surveyed all the transplant teams in the remaining nine countries, other than France, for which the IBMTR database could not provide comprehensive information.

We used the IBMTR Directory of Bone Marrow Transplant Teams to identify all the institutions at which allogeneic bone marrow transplantation was done. After cross-checking this directory with lists of transplant centers obtained in some of the countries and published lists from the European Bone Marrow Transplant Group, we identified transplant teams at more than 100 transplant centers from which we needed information.[2] This

[1]Data were obtained from the society and from a report of one of its predecessors, the Groupe d'Étude des Greffes de Moëlle Osseuse.

[2]A. Gratwohl et al., "Bone Marrow Transplantation in Europe: Major Geographical Differences," Journal of Internal Medicine, 233:4 (1993), 333-41. A. Gratwohl, "Bone Marrow Transplantation Activity in Europe 1990," Bone Marrow Transplantation, 8:3 (1991), 197-201.

included some teams that participate in IBMTR but whose data were not complete owing to lags in reporting. We arranged for IBMTR to send a questionnaire to each team, and to follow up by telephone or telefax with any who had not responded. Eighty-four percent of the transplant teams surveyed responded with information on their transplant activities.

Each team surveyed was asked to provide data on the number of transplants performed, the stage of disease at the time of transplantation, and the interval from diagnosis to transplant for each patient. However, if a team's records did not allow for ready retrieval of this information, it was requested to supply summary information on the number of transplants performed, the type of disease, and stage at transplantation, but not on the interval from diagnosis to transplant.

For each of the transplant teams that did not respond to the survey or that provided only partial information, we obtained data from that older surveys: a worldwide survey that IBMTR had conducted in 1991 and an annual study of European transplant centers.[3] The data available on these centers were limited to the number of transplants performed and did not include information on the stage of disease or the interval from diagnosis to transplant. The IBMTR survey covered only the years 1988-90. We obtained the number of transplants performed in 1991 in two ways: either from the annual European Bone Marrow Transplant Group study, or (for non-European centers) by assuming that the number of transplants performed in 1991 at each center was equal to the average number performed there the preceding 2 years.

The number of transplant cases and transplant centers provided by each data source for each country are shown in table I.1.

[3]For a description of the IBMTR survey, see Mortimer M. Bortin, Mary M. Horowitz, and Alfred A. Rimm, "Increasing Utilization of Allogeneic Bone Marrow Transplantation: Results of the 1988-1990 Survey," Annals of Internal Medicine, 116:6 (Mar. 15, 1992), 505-12. For a description of the survey of European centers, see Gratwohl et al. (1993) and Gratwohl (1991).

Table I.1: Data Sources for Number of Allogeneic Bone Marrow Transplants[a]

	IBMTR[b]		GAO survey[c]		Other surveys[d]	
Country	**Cases**	**Centers**	**Cases**	**Centers**	**Cases**	**Centers**
Australia	306	12	18	1	45	1
Canada	223	5	347	6	6	1
Denmark	0	0	90	1	0	0
France	1,708[e]	35	0	0	0	0
Germany	184	3	521	9	52	1
Netherlands	138	3	94	2	0	0
New Zealand	32	2	0	0	27	1
Sweden	138	3	30	1	0	0
United Kingdom	390	10	381	15	229	5
United States	1,148	33	3,500	50	225	8
Total	**4,267**	**106**	**4,981**	**85**	**584**	**17**

[a]For transplants performed in 1989-91.

[b]International Bone Marrow Transplant Registry database of transplants performed worldwide.

[c]Survey conducted for this study of transplant centers for which the IBMTR data were not complete.

[d]For centers that did not respond to the GAO survey, a 1991 IBMTR survey of all transplant centers in the world was used as the source of information. For European centers, data from this survey were supplemented by data from the European Bone Marrow Transplant Group.

[e]Groupe d'Étude des Greffes de Moëlle Osseuse, Rapport D'activité 1991, p. 2, tableau 1.

In total, we obtained data on 9,832 transplants performed at 208 transplant centers. As noted above, this provided complete information on the number of transplants performed, but the data on stage of disease and interval from diagnosis to transplant were not complete for all cases. For those cases from the IBMTR survey, we had neither stage nor time information, and time data were also unavailable on cases from the centers responding to our survey who supplied only summary data tables.

Computation of Rates

We presented the rates for allogeneic bone marrow transplantation for CML, ALL, and AML in chapters 3, 4, and 5. This appendix describes how those rates were computed. We begin by describing how we estimated the number of cases of each of these three forms of cancer in each of the countries. We then show how we used our data on transplants in combination with the estimated incidence to determine the relative likelihood of transplant in each country. The final section of this appendix discusses the reasonableness of the estimates.

Computation of Disease Incidence

We used several sources of data on cancer incidence to estimate the number of cases of CML, ALL, and AML for each country. For most of the countries, we employed data assembled by the International Agency for Research on Cancer (IARC), an affiliate of the World Health Organization.[1] However, for the United States, we drew directly from data produced by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The SEER data cover approximately 10 percent of the population in the United States. We also obtained data on cancer incidence in Sweden from the Swedish National Cancer Registry and in the Netherlands from the Dutch Cancer Registry.

To use these data, we had to overcome two limitations. One was that some of the countries in our study do not have national cancer registries that collect data on the full national population. In France, population-based registries in six departments in the northern, eastern, and southern sections of the country represent about 7 percent of the national population. In Australia, the six available registries cover 84 percent of the population. In both cases, we derived estimates of national incidence rates for CML, ALL, and AML from an extrapolation of the data from the registries weighted by their relative populations. We also combined data for separate population groups to obtain an overall national rate for New Zealand (Maoris and non-Maoris) and the United Kingdom (England, Wales, and Scotland).[2]

The Saarland has the only cancer registry with population-based incidence data for the western portion of the recently reunited Germany. (Since the German Democratic Republic had a completely different health care system, we limited our analyses to the German länder (states) that belonged to the Federal Republic of Germany before 1990). Because the

[1]D.M. Parkin et al., eds., Cancer Incidence in Five Continents, Volume VI. IARC (Lyon, France, 1992).

[2]All of our analyses of the United Kingdom exclude Northern Ireland because its population is not covered by any cancer registry and so incidence data were unavailable.

Saarland represents just 1.7 percent of the population for western Germany, these cancer rates might not reflect those in other parts of the country. Therefore, we chose to compare Germany to the other countries based on an assumed incidence rate for each disease that was the average for the other nine countries. As noted in chapter 1, this approach seemed reasonable for three reasons: (1) it results in a ranking for Germany consistent with that obtained using total national populations, (2) leukemia incidence rates do not vary that much among countries overall, and (3) these incidence estimates are in line with those suggested independently by German oncologists.

The second obstacle in estimating incidence was that IARC reported incidence data for each leukemia in the form of single age-standardized rates for males and females in each registry. An age-standardized incidence rate removes the effect of differences in age distributions among countries. What it represents is the number of new leukemia cases per 100,000 population which would have occurred during 1 year if the actual rates observed in a country in specific age categories (0-4, 5-9, and so forth) had operated in the standard world population with an arbitrary proportion of people in each age group. While age-standardized incidence rates are preferred for many types of international comparisons, our analyses required an estimate of the actual number of leukemia cases experienced in each country. Moreover, we needed to estimate the number of cases of disease in the population eligible for transplantation, generally below age 55.

To convert national male and female age-standardized rates to an estimate of the number of cases diagnosed in this subset of the overall population, we did the following. We made the assumption that the relative distribution of cases across age groups would be fairly constant among countries. That is, if a country had an overall age-standardized rate that was 50-percent higher than another's, the incidence rate in each five-year age category would be 50-percent higher in the first country. SEER provided the age-specific rate for each 5-year age group from 0 to 54 in the United States for each of the three leukemias. Using the ratio of the age-standardized rates for males and females in the United States to those in each of the other countries, we derived an age and gender-specific rate for each country that was proportionately higher or lower than that of the United States for each age and gender category. This rate was then multiplied by the actual size of the male or female population of that country in that age group. Summing this result across all the age and sex categories 0 to 54 for males and females produced an estimated count of

leukemia cases that could have been candidates for BMT in each country. The estimates for each disease for each country are shown in table II.1.

Table II.1: Estimated Annual Incidence by Disease

	Type of leukemia		
Country	**CML**	**ALL**	**AML**
Australia	77	202	149
Canada	128	320	209
Denmark	19	54	52
France	247	459	208
Germany	256	528	474
Netherlands	42	114	109
New Zealand	13	47	31
Sweden	25	80	65
United Kingdom	163	450	346
United States	1,159	2,827	1,850

Likelihood of Transplant

To calculate the proportion of newly diagnosed patients that received transplants (and thereby remove the effect of cases that were "backlogged" from previous years), we stratified the cases according to the calendar year in which they were diagnosed. We calculated the proportion of cases transplanted in (1) the same year as the diagnosis, (2) the year following that of diagnosis, and (3) the second year following that of diagnosis. We then added the three proportions together to obtain the proportion transplanted by the end of the second full year following the year of diagnosis.

Each of the individual proportions (within the same year, the following year, and the second year after diagnosis) was itself calculated from 3 years of data. We computed the proportion of cases transplanted in the same year as the diagnosis by taking as the numerator the average of the number of cases (1) diagnosed in 1989 and transplanted in 1989, (2) diagnosed and transplanted in 1990, and (3) diagnosed and transplanted in 1991. As the denominator, we used our estimate for the annual incidence of the disease in question (CML, ALL, or AML).

For the proportion of cases transplanted in the year following diagnosis, we averaged the number of cases (1) diagnosed in 1988 and transplanted in 1989, (2) diagnosed in 1989 and transplanted in 1990, and (3) diagnosed in 1990 and transplanted in 1991. Again, this average number for the three

sets of cases was placed over the estimated annual incidence to calculate the proportion of cases transplanted in the year after diagnosis.

Finally, for the third component of the overall ratio (the proportion of cases transplanted in the second full year following that of diagnosis), we counted (1) cases diagnosed in 1987 and transplanted in 1989, (2) cases diagnosed in 1988 and transplanted in 1990, and (3) cases diagnosed in 1989 and transplanted in 1991 and placed their average over the same annual incidence figure. By adding all three proportions, we arrived at an estimated rate of transplantation for a 3-year period in which each component of the total was based on cases diagnosed in 3 different years.

Reasonableness of Estimates

The rate at which allogeneic bone marrow transplants can be performed is limited by the ability to find a suitable marrow donor. The most likely place to find donors is among the siblings of the patient, yet even here, the likelihood that any individual sibling will be an ideal donor (HLA-matched) is only one in four. In situations where a matched sibling donor (MSD) cannot be found, the search expands to include other family members, mismatched siblings, and HLA-matched unrelated donors (identified through donor registries). Although the likelihood of finding donors through any of these mechanisms is unknown, the inability to identify a donor occurs frequently enough to make one skeptical about national rates of allogeneic BMT that exceed 40 or 50 percent.

Because some of our rates were in this range, we reviewed our computations to verify that both the data and the algorithm were correct. Further, we examined what component of each rate was comprised of matched sibling donor transplants. In this way, we could determine whether the rates were higher than expected because the likelihood of finding a related donor is greater than what was assumed or because more matched unrelated, matched nonsibling-related, and mismatched related-donor transplants were performed than expected. Table II.2 shows the results of these computations, giving both the overall rate and the rate for matched sibling donor transplants.

Table II.2: Disease-Specific Transplant Rates for All Transplants and Matched Sibling Donor Transplants[a]

	Type of leukemia					
	CML		ALL		AML	
Country	Total	MSD[b]	Total	MSD[b]	Total	MSD[b]
Australia	37.8%	27.9%	7.6%	6.2%	20.2%	17.2%
Canada	38.5	30.6	5.4	4.2	27.2	23.4
Denmark	40.7	26.8	3.1	1.9	9.5	6.5
France	32.1	26.3	23.0	19.9	50.2	45.3
Germany	26.2	22.2	5.6	4.8	13.4	12.7
Netherlands	32.8	25.3	11.0	10.7	18.4	16.3
New Zealand	46.1	33.5	3.7	2.5	18.6	18.6
Sweden	54.2	51.2	8.8	8.2	17.3	14.7
United Kingdom	48.2	36.8	15.2	13.5	20.4	18.0
United States	35.2	22.1	6.8	4.6	22.5	17.4

[a]For transplants performed in 1989-91.

[b]MSD refers to percentage of all cases of the disease in which patients received a transplant from an HLA-matched sibling.

As can be seen from the table, in some instances the rate for matched sibling donor transplants was higher than what might be expected. For example, the rate for CML in Sweden and AML in France are particularly striking. Despite this divergence from expectations, however, we remain confident that the estimates are reasonable approximations. Whereas in the case of France we know that the incidence estimates may be somewhat imprecise because of the absence of a national registry, the same is not true for Sweden, where the incidence data are firm and still we find that one of every two cases with CML had an available sibling donor.

Advisory Panel

Frederick R. Appelbaum, M.D.
Professor of Medicine
University of Washington
Director, Division of Clinical Research
Fred Hutchinson Cancer Research Center
Seattle, Washington

Bruce Cheson, M.D.
Head of Medicine Section
Cancer Therapy Evaluation Program
National Cancer Institute
Bethesda, Maryland

Mary M. Horowitz, M.D., M.S.
Scientific Director
International Bone Marrow Transplant Registry
Associate Professor of Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin

Major Contributors to This Report

Program Evaluation and Methodology Division

Marcia G. Crosse
Eric A. Peterson
George Silberman
Richard C. Weston

European Office

Michelle Grgich

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