LATE EFFECTS OF HEMATOPOETIC STEM CELL TRANSPLANTATION

How can hematopoietic cell transplant centers and referring physicians help each other during long-term follow-up?

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Late complications after HCT

Success with the use of HCT for treatment of leukemia and other malignancies has improved considerably during the past three decades. Much of this success has resulted from the use of HCT earlier in the natural history of these diseases and from improvements in preventing GVHD and infections. This success has enhanced the importance of long-term complications in determining the outcome after HCT. For example, in an early study describing results of marrow transplantation for treatment of acute leukemia, only 23 (28%) of the 83 reported deaths occurred beyond the first 120 days after the transplant [1]. In contrast, a 1991–1997 survey of allogeneic HCT for treatment of acute leukemia, CML, lymphoma, CLL or myeloma showed that mortality from 3 months to 3 years after transplant was equivalent to or higher than the mortality during the first 3 months after transplant [2]. With a further reduction in acute toxicity brought about by the use of nonmyeloablative pretransplant conditioning regimens, late complications have assumed even more importance in assessing the outcome of treatment.

Late complications after HCT not only affect survival but also cause considerable morbidity [3]. Most of the late morbidity is related to regimen-related toxicity, chronic GVHD, immunodeficiency and infections. These complications can impair function of virtually all organ systems, including the skin, eyes, gastrointestinal tract, liver, lungs, muscles, connective tissues, bones, teeth, endocrine glands, gonads, bladder, kidneys and central nervous system. More recently, secondary malignancies have been recognized as an important complication after HCT [4].

Mechanisms of long-term follow-up in a referral transplant center

Because survivors of HCT are at risk of therapy-related complications, a coordinated program of long-term follow-up is needed both for individuals and for the overall patient population. Such follow-up supports research that could lead to the development of preventive strategies and other interventions to reduce morbidity and mortality. The integrity of follow-up poses a major challenge in assessing long-term outcomes after HCT. Loss of cohort participants reduces study power and causes selection bias. Patients who participate in long-term follow-up may differ in systematic and important ways from those who do not [5–7].

Our center may differ from many others in the way we manage follow-up after HCT. Patients are referred for evaluation before treatment and remain under the direct care of physicians at our center until approximately 3 months after HCT. Direct responsibility for clinical care is then returned to the referring physician, but we remain involved in patient management through consultative services provided by the long-term follow-up (LTFU) program. The need for these support services is typically highest during the first 3 months after patients leave the transplant center and then declines gradually, unless patients develop chronic GVHD or other major complications.

The LTFU program provides a variety of services for patients and referring physicians, including education, telephone consultations, and formal medical evaluation of patients who return to our center. For patients who have had an allogeneic transplant, these services are provided by a group of physicians who rotate monthly as “LTFU attending,” assisted by a mid-level nurse practitioner, a nurse, and a dedicated
support staff. Interactions between these individuals, the patients and the referring physicians generate a large volume of letters, faxes, e-mail, office notes, telephone notes, and copies of medical records. In addition, approximately 400 patients return to Seattle each year for on-site medical evaluation. We encourage close collaboration with referring physicians both to ensure the quality and consistency of patient care and to maximize the amount of information we receive in documenting the outcome of our treatment.

Major efforts are made to provide educational support for patients and referring physicians. All patients attend classes taught by nurses before returning home. These classes focus on management of medications, recognition of side effects, nutrition, guidelines for activities, and manifestations of chronic GVHD. Referring physicians are given both generic and patient-specific guidelines whenever they assume primary responsibility for patient management. We have also designed an LTFU consult form as a mechanism to request clinical assistance from LTFU, to facilitate record keeping and to improve standardization of care. Responses are be made by sending standard guidelines or by a phone call from a member of the LTFU staff or from the LTFU attending physician.

LTFU also provides training for fellows, visiting physicians and physician assistants who are interested in developing expertise in the management of late complications after treatment. The LTFU functions to procure specimens and samples for laboratory tests. Because community pathologists might not have the expertise or familiarity needed to make the diagnosis of chronic GVHD, we make arrangements to have biopsy specimens reviewed by our pathologists. The clinical LTFU also assists in the procurement of samples for research studies.

The LTFU provides major support in guiding the diagnosis and treatment of chronic GVHD. This is accomplished by educating patients and referring physicians about the signs and symptoms that herald the onset of chronic GVHD, by recommending appropriate tests and biopsies to be obtained in patients who might have chronic GVHD, by recommending initial treatment after the diagnosis is made, and by guiding the subsequent management of immunosuppressive treatment. Whenever possible, patients are enrolled in prospective clinical trials for treatment of chronic GVHD. The LTFU plays a major role in the management of recurrent malignancy after HCT. Guidance and support services related to diagnosis, assessment of chimerism, follow-up monitoring and treatment are provided for patients and referring physicians.

Data collection for research studies

The LTFU was designed not only to serve the needs of patients and referring physicians but also to enable collection of data that could be used for research related to outcomes after HCT. Information about these outcomes originates from several sources. These sources included telephone notes from conversations with referring physicians or patients seeking medical advice, correspondence and medical records sent as part of a request for assistance, and records from evaluations of patients who have returned to Seattle. These sources of information are of particular value at early time-points after HCT when contacts between many referring physicians and the LTFU program are most frequent. As time from HCT lengthens, however, the information received becomes less structured and more selected. Other sources of information have included copies of medical records sent by referring physicians who were not requesting specific assistance.

To support research studies, all documents are made available as digitized images in a password-protected optical web library that is accessible to investigators via the Internet. Staff members in the LTFU also review all correspondence and medical records, and selected information is abstracted into a computer database. The LTFU database is organized into 14 sections and contains a total of 80 items addressing major complications after HCT. The list of 80 items was selected after extensive consultation with faculty members who were likely to use the information for research. The list includes sites affected by chronic GVHD, complications due to chronic GVHD, infections, selected respiratory, cardiovascular, gastrointestinal, renal, genitourinary, musculoskeletal, endocrine, neuropsychiatric and hematologic complications, pregnancy, organ transplantation, recurrent or secondary malignancy or myelodysplasia, administration of immunosuppressive medications and performance score.

Patient questionnaires

Because we cannot conduct detailed clinical evaluations at frequent intervals, and because we cannot always obtain the relevant medical records, we have used patient self-reported data as one important source of information for long-term follow-up studies. Self-reported disease-specific and generic measures of health and quality of life have been used in questionnaires and telephone interviews to evaluate outcome after HCT [8–20].

In one study, a combination of 7 instruments was used to evaluate quality of life and health status at 6–18 years after marrow transplantation in a cohort of
117 patients [8]. Only 5% of the cohort reported poor health or health-related quality of life. The most common types of morbidity involved emotional and sexual dysfunction, fatigue, eye problems, sleep disorders, pain, and cognitive difficulties. In a cohort of 212 patients who had a marrow transplant for treatment of aplastic anemia, the most common types of long-term morbidity were skin abnormalities, cataracts, lung disease, bone and joint dysfunction, secondary malignancies and depression [9]. Chronic GVHD was a major risk factor for these complications.

Some attempts have been made to determine the validity and reliability of self-report data in HCT patients. Wingard et al. [14] found good agreement between patient and physician-rated Karnofsky scores in a cohort of 171 marrow transplant recipients. The presence of clinically significant illness correlated with self-reported health assessment, global health, pain and Karnofsky scores. In a study of health-related quality of life in 82 pediatric transplant survivors, Parsons et al. [15] found good correlation between health assessments reported by school age children and the disease severity rating reported by their physicians. Assessments by the parents did not correlate with the physicians’ assessment, and parental ratings were consistently lower than ratings by the children. These results support the validity of self-reported data in children, when an appropriate instrument is utilized.

A more comprehensive validation study of self-reported medical complications in HCT survivors has been published [16]. One hundred survivors of bone marrow transplantation at the City of Hope National Medical Center were mailed a self-administered questionnaire that contained 225 items regarding medical health, reproductive function, health habits, physical activity, socio-demographic factors and family history. Validity and reliability of self-reported medical complications were assessed by comparing responses with data from medical records. High sensitivity, specificity, positive and negative predictive values and kappa statistics were found for musculoskeletal, cardiovascular, endocrine, gastrointestinal and pulmonary complications, and for GVHD. Overall accuracy in reporting new malignancies was low, mostly because skin cancers were included in the analysis and because recurrences were reported as new malignancies. Accuracy in reporting less well-defined ocular and neurological complications was also low, most likely because physicians did not address mild symptoms during routine follow-up visits. Data for poorly defined disorders with a fluctuating clinical course had the lowest validity and reliability.

We have had mixed success with the use of questionnaires as a method of obtaining self-report data from LTFU patients. The questionnaire that we have used during the past 5 years contained approximately 250 items organized into 6 sections. These sections included a self-assessed performance score, a symptom inventory, a list of complications procedures or medical interventions, a list of medications, a brief quality of life instrument, and a page for comments. Patients have been asked to complete the questionnaire when they return to the care of the referring physician, at 6 months and 1 year after HCT, and then at annual intervals. A postage paid return envelope is included with all mailings, and reminders are sent to patients who do not respond within 2 months.

One problem with the use of questionnaires is that not all patients respond. The overall response rate for our questionnaires has been approximately 50%. We have found that two variables influence the probability of response: age of the patient at the time of questionnaire and length of time from HCT. Older patients had much higher response rates than younger patients. Approximately 65% of patients respond to the questionnaire at 6 months after HCT, but only 50% respond to the questionnaire at 3 years. On the other hand, approximately 80% of patients responded to at least one of the questionnaires during the first 3 years after HCT. Patterns of response were highly variable for patients who were more than 5 years from HCT. Approximately 30% never responded to any of the first 4 questionnaires that they received, and approximately equal proportions of the remaining patients responded once, twice, three times or four times during the first 4 years.

Data from the patient questionnaires confirmed information from published reports, especially with regard to symptoms and attitudes about their experience after HCT. Shortness of breath with exertion, fatigue, muscle cramps, difficulty sleeping at night, and problems with memory and concentration were frequently acknowledged as problems for patients who had survived for more than 5 years after HCT. Comments from patients provided insights into the highly variable experiences of patients. As a way of improving response rates to the questionnaires, we have included a selection of anonymous quotations from interesting or eloquent comments with the questionnaire each year. We have also provided patients with summary data from the questionnaires. Many patients have found it useful to know that their problems are not unique.

**Physician questionnaires**

As part of our effort to collect LTFU data after HCT, we designed questionnaires and special notification forms to be completed by referring physicians. The questionnaire was designed to capture the same medical complications that are routinely abstracted into the database from medical records. The ques-
Conclusions and future directions

We are continuing our efforts to improve the quality of services to LTFU patients and their physicians, while at the same time enabling the collection of data for research purposes. We have found that the use of a single patient questionnaire for both clinical care and research purposes does not ideally suit both goals. In the future, we plan to use separate instruments for these different purposes. Two questionnaires will be sent to patients, one primarily for clinical care, and the other primarily for research.

The clinical care questionnaire will contain items related to activity level, review of symptoms, health habits, infections, hospitalization, diagnostic procedures, transfusions, medications and transfusions. Patients will be instructed that this questionnaire should be completed only if they are continuing to have problems related to HCT and if they anticipate that the transplant center might be involved in their care at some time in the foreseeable future. Patients who are not having problems related to HCT will be told that they should not complete this health care questionnaire. All completed questionnaires will be converted to digitized images and made available in the optical web library for use by providers when they are called upon to assist in the clinical care patients who have medical problems related to HCT.

A smaller research questionnaire will contain items related to self-assessed performance score, employment or school activity, marital status, some simple measures of health care utilization, such as number of hospitalizations, number of office or clinic visits, number of medications, and availability of insurance, together with a brief quality of life instrument such as the SF-12. All patients will be asked to complete this brief questionnaire. With a major decrease in the number of items in the questionnaire, we hope that the response rates will improve.

We hope that a similar decrease in the number of items will improve response rates to physician questionnaires. Items of greatest interest to transplant centers include vital status with the date of last contact or death, presence or absence of chronic GVHD and immunosuppressive treatment at the date of last contact, dates of onset for any recurrent malignancy, secondary malignancy or myelodysplasia, involvement of the physician in care of the patient, and any change of physician or patient contact information.

For both the patient and physician questionnaire, we might find higher response rate though the use of a web-based system. Security and protection of privacy are major considerations in the development of such a system. Regardless of whether we use a paper-based system or an Internet-based system, it will be necessary to find the appropriate balance between too little and too much information, and we need to ensure that we are collecting the most useful information and making this information easily available to medical providers and research investigators.

References


