A Clinic-Based, Comprehensive Care Model for Studying Late Effects in Long-Term Survivors of Pediatric Illnesses

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ABSTRACT. Objective. Long-term survivors of several childhood illnesses are at risk for multiple late effects of their illness or therapy, and children with documented toxic exposures may also experience long-term health consequences. Clinical studies of these effects are difficult to conduct. The Cardiovascular Status in Childhood Cancer Survivors Study is an established study that highlights the ability to perform comprehensive clinical investigations when patients are cared for in a formal, long-term follow-up clinic. This clinic model facilitates long-term retention and recruitment of patients, allowing comprehensive clinical studies of late effects of illness or exposures, in this case, of cardiovascular complications of cancer treatment during childhood.

Methods. The study is funded through the National Institute of Health Office of Cancer Survivorship. Participants are recruited from the Long-Term Survivors Clinic at the University of Rochester. The clinic provides care for all survivors of childhood cancer in the region. The Long-Term Survivors Clinic provides medical care and psychosocial and educational support to patients and facilitates coordination of care. Patients remain in close contact with clinic staff for extended periods.

Results. We recruited a representative sample of this long-term survivor population, with a wide range of ages, diagnoses, and time since diagnosis. Longitudinal collection of detailed clinical data will enable us to conduct cohort studies of late effects as well as case-control studies of toxic exposures.

Conclusions. The success of this study shows the advantages of formal programs for continued care of patients with chronic illnesses or treatment or toxic exposures. The Long-Term Survivors Clinic provides an excellent model for clinical care and research that is applicable to multiple pediatric and young adult populations. Pediatrics 2004;113:1141–1145; late effects, survivors, childhood cancer, clinic model.

Effecfiv models to study comprehensively the physiologic and psychosocial late effects of known toxic exposures during pediatrics that will lead to improved patient care and public health policy changes through research have not been well characterized. For children with exposure to drugs that are known to have late effects during the first few years after exposure, there is a strong need to continue to follow to understand the subsequent course of late toxicity. In this report, we describe a comprehensive multidisciplinary program for long-term survivors of childhood cancer that has served as the backbone to understand the impact of cancer and its treatment on individuals who live years beyond a cancer diagnosis. The challenges of survivorship have become a growing focus of attention as the number of cancer survivors is growing annually, and this should continue, making it even more important to understand the unique needs of this population and to identify those who are at increased risk for complications of treatment and might benefit from interventions to reduce that risk. There is a critical need among cancer survivors to understand survivorship issues, because what is clear is that most of our current treatments, although benefiting the patient overall, will produce some measure of adversity, such as cardiotoxicity, that may result in significant adverse psychosocial outcomes long after treatment ends. Most potentially life-threatening late cardiotoxic effects of cancer treatment have much longer latency periods and tend to occur during the extended survivorship years. Results from our inter-disciplinary team suggest that 1) there are long latalencies for potentially life-threatening late effects (eg, heart failure secondary to the cardiotoxic effects of cancer treatment), emphasizing the need for extended follow-up; 2) many disease- and treatment-related toxicities can be persistent, worsen over time, and carry significant potential to affect adversely the health and well-being of survivors; 3) the adverse sequelae of cancer and its treatment contributes to the ongoing burden of illness, costs, and decreased length/quality of survival; and 4) early identification of and interventions among those who are at increased risk for problems hold the promise of reduc-
ing adverse outcomes. A comprehensive clinical and research program for a defined cohort with a defined exposure during pediatric life that is targeted toward understanding a toxic drug exposure during childhood can provide important guidelines for providers to enable identification of patients who are at the highest risk for serious cardiovascular abnormalities, with higher morbidity and mortality rates. We hope that knowledge of risk factors for cardiovascular abnormalities may enable practitioners to selectively intervene earlier to prevent or reduce additional morbidity and mortality in these patients. This type of program can facilitate the determination of who is at risk for late and long-term cardiotoxicity and give some insight as to whether they can be protected. This type of program can lead to studies to determine whether there are specific, modifiable risk factors other than exposure to treatment for the development of late effects. The results of these studies may point to which subgroups of survivors are at elevated risk for declines in functional status. In addition, studies using this infrastructure can determine how common late physiologic sequelae, in this example cardiotoxicity of malignancy and its treatment, are and their effect on physical and psychosocial health. A well-organized clinical program such as this can help to determine whether a pharmacologic or other intervention delivered years after treatment will control, reduce, or treat chronic or late cancer-related cardiac morbidity. The information that comes directly from studies that result from this type of clinical program will help patients to make decisions now about treatment options that will affect their future; allow care providers to tailor therapies to maximize cure while minimizing adverse treatment-related effects both during therapy and for the survivor population; allow care providers to develop and disseminate evidence-based interventions that reduce cancer morbidity as well as mortality and facilitate adaptation among cancer survivors; and improve quality of care, control costs, and equip the next generation of health care providers with the information needed to provide the patient with the most comprehensive cancer care.

Advances in chemotherapy, radiation therapy, surgery, and supportive care have improved survival for children and adolescents who receive a diagnosis of cancer. Approximately 77% of children who receive a diagnosis of a malignancy when younger than 15 years survive 5 years.1 The majority of these patients will be long-term survivors, despite increased mortality relative to the general population.2,3 Unfortunately, many will also experience late effects from their cancer therapy.4,5 Subclinical cardiac abnormalities are common and often progressive in survivors who were treated with anthracycline chemotherapy or mediastinal irradiation.6–8 Other late effects include lipid abnormalities, obesity, cardiomyopathy, and symptomatic cardiovascular disease, and the relationships between these late effects and treatment warrant additional study.

A collaborative effort at the University of Rochester produced a study protocol to assess comprehensively the risk factors for premature symptomatic cardiovascular disease and related late effects. One goal of this study is to identify a comprehensive cardiac risk factor profile on all eligible long-term survivors of childhood cancer who are treated within our catchment area of upstate New York. Patients are identified through the Long-Term Survivors Clinic in the Division of Pediatric Hematology/Oncology at the Golisano Children’s Hospital at Strong. Another primary goal of the study is to document successful recruitment and retention of patients from the Long-Term Survivors Clinic, supporting this model as a forum for clinical studies. The clinical care and provider–patient relationship maintained by the study long beyond acute management have important implications for research.

**METHODS**

**Clinic Base**

The Long-Term Survivors Clinic in the Division of Pediatric Hematology/Oncology was established in 1987 and is one of the oldest, continually running, long-term clinics in the United States. It is the sole follow-up center for all children and adolescents with an oncologic diagnosis within an 11-county catchment area in New York, as well as some counties in northern Pennsylvania. Rather than routine primary care, this clinic provides scheduled follow-up visits for the oncologic diagnosis; visits for acute issues that may be treatment related; and coordination of care for cardiac, endocrine, and other late effects.

The clinic operates within the designated Pediatric Hematology/Oncology clinic space in the ambulatory care facility at the University of Rochester. The clinic has a full-time nurse coordinator who is a certified pediatric nurse practitioner. One physician serves as a medical director and sees the majority of patients in conjunction with the nurse practitioner. The radiation oncologist who treats all children and adolescents at the institution has been involved with the clinic since inception and continues as a medical director and consultant to the clinic. The clinic also employs an educational liaison and a social worker, thus widening the range of services and the usefulness of the clinic. In addition, the study collaborates with a statistician who has extensive experience analyzing cardiac complications in long-term survivors of childhood cancer. An organization chart shows how the Cardiovascular Status in Childhood Cancer Survivors Study and Long-Term Survivors Clinic are integrated into the medical center (Fig 1).

**Study Funding**

The study protocol and grant proposal were developed through a collaborative effort among the Long-Term Survivors Clinic in the Division of Pediatric Hematology/Oncology and the Divisions of Pediatric Cardiology and Pediatric Gastroenterology/Nutrition at Golisano Children’s Hospital at Strong, and the Departments of Radiation Oncology and Preventive Cardiology, University of Rochester School of Medicine and Dentistry. The University’s commitment to the study was an important factor in securing funding.

After the grant was developed and submitted, the National Institutes of Health funded a 5-year study through its Office for Cancer Survivorship. On receipt of funding, the team was completed with the addition of a study coordinator and an information analyst. Personnel, testing, and data support are provided by the participating departments and divisions, as well as the General Clinical Research Center and laboratory of the University of Rochester Medical Center and reference laboratories and an off-site Holter scanning facility.

**Study Population**

The Research Subjects Review Board approved the protocol and documentation immediately after the grant award. During the first 12 months of the protocol, the subcohort of patients were designed; the database was developed; and General Clinical Research Center support was obtained for nursing, physical facil-
ities, laboratory services, and database development. The first patient was recruited within 6 months of the award.

Patients for the study are recruited from the Long-Term Survivors Clinic. All efforts are made to enroll all patients regardless of gender or ethnicity. Eligible patients and control subjects are identified from patient lists and from monthly visit reminder postcards. All oncology patient charts were reviewed to identify inactive patients (patients who did not come back for follow-up visits or who had missed appointments) and eligible patients who had not been transferred to the Long-Term Survivors Clinic, which is rare but may occur if a patient prefers to see their treating oncologist for long-term care. The providers from the Long-Term Survivors Clinic serve as consultants to the primary oncologist in this situation. The study is discussed with patients during their visit to the Long-Term Survivors Clinic to introduce the protocol, encourage participation, and answer questions.

All eligible patients receive a letter from the investigators explaining the study in detail and inviting them to join. The nurse practitioner adds personal notes to each letter. Patients are offered the opportunity to schedule the study visit on the day of their annual Long-Term Survivors Clinic visit. If the patient does not respond within 6 months, then a follow-up invitation is sent. A newsletter about the study was sent to all patients, including those who participated, those who did not respond to the invitation, and those who declined to participate.

For patients who agree to participate, study appointments are confirmed by letters and reminder telephone calls, and patients are sent thank-you letters after the appointment. The study visit takes most of a day, so patients are given breakfast and lunch. A letter summarizing the cardiology and metabolic results is sent to the patient and to his or her primary care physician. The nurse practitioner or oncology physician telephones the patient to review the data in the letter. Participants are invited for a second study visit approximately 2 years after their first visit.

Participants in the study are representative of the Long-Term Survivors Clinic population in terms of diagnoses and treatments received (Table 1). Review of participants also demonstrates an appropriate sample by gender and age.

Data Management and Quality Assurance Procedures

All data are entered into an Access (Microsoft Corporation, Redmond, WA) database. Each paper worksheet used to collect data is designed to match the Access data entry screen, except for questionnaires, which are scanned into the database.

Quality assurance procedures include education and careful review of the protocol with the nurse managers and senior nurses, pediatric cardiology nursing staff and office manager, and orthopedic personnel. All questionnaires are checked for completeness before the patient leaves. Laboratory reports are checked as soon as they come in, in case any specimen must be retrieved and retested.

Data entry tables are scanned for aberrant entries. Full completion of forms and test result reports is monitored by recording all data when the data forms are received and by following up immediately if results for tests ordered are not tallied.

DISCUSSION

The existence of a well-established Long-Term Survivors Clinic provides access to a study popula-
tion for a comprehensive evaluation of cardiac risk factors in survivors of pediatric malignancy. With the clinic as a backbone, we have been able to recruit patients to this study. Other studies of long-term survivors have succeeded in contacting substantial numbers of patients, but these studies have used only questionnaires and telephone interviews. In contrast, our study requires patients to undergo multiple tests and to commit a substantial amount of time, but we have nonetheless recruited a large number of long-term survivors from a single center.

The Long-Term Survivors Clinic follows patients through childhood and adolescence and into adulthood. This model provides optimal care for long-term survivors and also provides an opportunity to maintain a relationship with survivors that allows the comprehensive study of this population. We believe that this model is applicable to other populations of children with chronic illnesses or toxic exposures. With improving therapies and supportive care, children are surviving illnesses that were previously fatal, and they are surviving longer with chronic diseases and late effects of therapies. In addition, as the potential health consequences of prenatal, environmental, or other toxic exposure are identified, follow-up clinics within the appropriate pediatric setting or specialty clinic may serve as a source of studies to define and quantify the impact of these exposures. Established follow-up clinics, which maintain visits and contact into adulthood, have the potential to be valuable research settings, as well as provide important clinical care. In addition, the existence of these clinics in a university setting promotes collaborations between clinical care providers and researchers in the design, execution, and application of comprehensive studies.

Study design emphasizes basic courtesy, such as thank-you notes, and efforts to keep the participants informed, including telephone calls and summary letters of results as well as a newsletter. For a patient population that has embraced self-advocacy, these are important components of the study.

The results of this study have the potential to form the basis for large multicenter protocols in preventive cardiology. An example of such a protocol is the ongoing placebo-controlled study of afterload reduction therapy with enalapril in long-term survivors with asymptomatic left ventricular dysfunction, conducted through the Children’s Oncology Group.

The comprehensive nature of our cardiac risk factor profile study will provide additional information about commonly used monitoring tools, such as electrocardiograms and echocardiograms and add to the data on the role of laboratory tools, such as C-reactive proteins and natriuretic peptides for monitoring cardiotoxicity. Such data could improve clinical care and create a research base for additional studies.

Although we are studying a specific subpopulation, we are including many risk factors that are applicable to the general population, such as family history, obesity, and hyperlipidemia. Some of what is learned may be beneficial in terms of preventive cardiology for all children and young adults.

This study involves patients with a wide range of

| Diagnosis                        | Eligible Participants | Participants by Diagnosis | Patients Exposed to Anthracyclines Alone | Patients Exposed to Cardiac Irradiation Alone | Patients Exposed to Both Anthracyclines and Irradiation | Patients Exposed to Only Anthracyclines | Patients Exposed to Only Irradiation | Patients Who Received Cardiac Irradiation Alone | Patients Who Received Anthracyclines Alone | Patients Who Received Both Treatments | Patients Who Received Cardiac Irradiation | Patients Who Received Anthracyclines | Patients Who Received Both Treatments | Total |
|---------------------------------|-----------------------|---------------------------|----------------------------------------|---------------------------------------------|--------------------------------------------------------|----------------------------------------|----------------------------------------|------------------------------------------|----------------------------------------|----------------------------------------|------------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|--------|
| All                             | 144 (32.0%)           | 99 (68.5%)                | 46 (34.3%)                             | 59 (41.1%)                                 | 20 (31.3%)                                             | 1 (1.7%)                                | 7 (14.9%)                             | 27 (29.3%)                              | 11 (12.8%)                             | 13 (15.8%)                             | 40 (63.2%)                              | 31 (64.9%)                             | 15 (61.3%)                             | 3 (46.2%)                             | 450    |
| Hodgkin’s                       | 59 (31.4%)            | 51 (85.8%)                | 16 (27.1%)                             | 24 (41.4%)                                 | 7 (15.2%)                                              | 1 (1.7%)                                | 9 (15.5%)                             | 23 (40.7%)                              | 12 (20.4%)                             | 12 (22.2%)                             | 13 (23.1%)                              | 13 (23.1%)                             | 2 (15.4%)                             | 82     |
| Non-Hodgkin’s                   | 37 (62.7%)            | 36 (97.3%)                | 24 (66.7%)                             | 35 (97.2%)                                 | 12 (34.3%)                                             | 2 (5.6%)                                 | 7 (19.4%)                             | 20 (57.1%)                              | 14 (40.0%)                             | 10 (33.3%)                             | 6 (15.4%)                               | 8 (12.2%)                             | 1 (3.7%)                             | 45     |
| Wilms’/kidney                   | 48 (10.7%)            | 24 (50.0%)                | 15 (62.5%)                             | 13 (52.1%)                                 | 7 (29.2%)                                              | 2 (8.3%)                                 | 6 (25.0%)                             | 10 (41.7%)                              | 3 (12.5%)                              | 5 (20.0%)                              | 7 (29.2%)                               | 3 (12.5%)                             | 1 (3.7%)                             | 9 (2.0%)                             | 26     |
| RMS/STS                         | 38 (6.0%)             | 26 (68.4%)                | 13 (34.2%)                             | 13 (35.1%)                                 | 4 (11.1%)                                              | 2 (5.6%)                                 | 5 (15.6%)                             | 5 (15.6%)                              | 3 (15.8%)                              | 5 (25.0%)                              | 2 (6.8%)                                | 4 (23.5%)                             | 1 (3.7%)                             | 6     |
| Other                           | 82 (18.2%)            | 27 (32.9%)                | 13 (16.2%)                             | 27 (33.3%)                                 | 13 (16.2%)                                             | 2 (2.5%)                                 | 3 (4.2%)                              | 13 (16.2%)                              | 27 (33.3%)                             | 13 (16.2%)                             | 6 (7.5%)                                | 3 (3.7%)                              | 1 (1.2%)                             | 5     |
| Total                           | 450 (100.0%)          | 188 (41.8%)               | 206 (45.8%)                            | 206 (45.8%)                                 | 91 (19.8%)                                             | 11 (2.4%)                                | 35 (7.7%)                             | 35 (7.7%)                              | 35 (7.7%)                              | 35 (7.7%)                              | 35 (7.7%)                               | 35 (7.7%)                             | 35 (7.7%)                             | 450    |
diagnoses and treatment regimens. Participants to date provide a representative sample of long-term survivors. In addition, the large size of the study will make it possible to analyze certain specific populations, such as survivors of acute lymphoblastic leukemia. Study participants also represent a range of ages, both at the time of treatment and at the time of study. This range will be an important variable to consider in the analyses, but the range can also be beneficial in terms of determining future directions for study, monitoring, and intervention for long-term patients at different points off therapy.

Although participation is higher for patients who are considered to be at risk for cardiotoxicity, control patients have also been willing to participate. Participants have exhibited an interest in a comprehensive assessment of their own clinical status, as well as a desire to contribute to the care of fellow survivors. By combining a clinical care visit with the study procedures, we have reinforced our interest in accommodating patient needs, but we have also enrolled patients who have not had follow-up for many years but have been motivated to return both for the study and for a clinical visit. This response has provided additional information and data but has also allowed the opportunity to review the patient’s current health status and discuss appropriate individualized health care. The diversity of personnel involved has provided the essential coordination of patient participation, oversight of the diverse medical aspects of the study, and focus on patient care and communication that are critical to the success of the study.

We continue to enroll patients for initial visits and have started seeing patients for their second visits. With the completion of the database, statistical analysis will be initiated for initial visits. We hope and expect that our comprehensive study of cardiac risk factors in long-term survivors of childhood cancer, with the generous participation of our patients, will contribute substantially to improving the health of this population. The Long-Term Survivors Clinic and the Cardiovascular Status in Childhood Cancer Survivors Study serve as important examples of the benefit of establishing formal clinics for follow-up of patients who are at risk for long-term health sequelae and of the type of research study possible to provide this and related populations with appropriate, evidence-based recommendations for health maintenance and medical interventions.

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