Introduction

Foundations of Clinical Cancer Research: Perspective for the 21st Century

Evan M. Hersh
Arizona Cancer Center, Tucson, Arizona 85724

We are pleased to present in this special issue of Clinical Cancer Research the papers that were delivered at the Foundations of Clinical Cancer Research international symposium held at M. D. Anderson Cancer Center (Houston, TX) on March 14–15, 1997. The purpose of the conference and this Festschrift is to honor one of the great pioneers of clinical cancer research and a founder of the field of medical oncology, Dr. Emil J Freireich, on the occasion of his 70th birthday. To do this we brought together his former and current colleagues and students who have played a key role in the development of therapeutic cancer research and who have promoted and/or carried forward the principles established by Dr. Freireich and his colleagues in the 1950s and early 1960s at the National Cancer Institute and, subsequently, at the M. D. Anderson Cancer Center.

The field of clinical cancer research had its beginnings in the early 1950s in the Medicine Branch of the National Cancer Institute, where Dr. Freireich and his colleagues, Drs. Emil Frei III, Gordon Zubrod, and James Holland, and later, Nathaniel Berlin, Paul Carbone, Edmund Gehan, Ti Li Loo, and the late Myron Karon, together with their clinical associates, came together at a unique crossroads in modern medicine. At that time, there were no effective treatments for leukemia or lymphoma or for metastatic solid tumors. In-patient services were established at the National Cancer Institute, where physicians could devote their full time to the in-patient treatment of individuals with leukemia and other malignancies in a setting of a very well supported and diverse laboratory research program, unfettered by the constraints placed on clinical research today. At that time, there were no fields of medical or pediatric oncology, and essentially all patients with leukemia, lymphoma, and disseminated solid tumors died of their disease. There was no adjuvant therapy for patients freed of disease by surgery and very limited supportive care to deal with the complications of disease or treatment.

In a 10-year period, from 1955 to 1965, acute leukemia, malignant lymphoma, and Hodgkin’s disease had become treatable entities (1–4). Platelet (5–6) and leukocyte (7) transfusion had been developed as therapeutic support modalities. Dr. Freireich played a pivotal role in these developments. The team he led did unique studies that defined the natural history and causes of death in acute leukemia (8) and the pathogenesis of leukostatic disease in the brain of leukemic patients (9). They did the first prospective randomized clinical trials of a therapeutic agent in malignant disease (2). Together with their colleagues Howard Skipper and Frank Schabel at the Southern Research Institute, they established the principles of combination chemotherapy with drugs having nonoverlapping toxicities (10). This quickly lead to combination regimens that induced a high percentage of remissions in both acute leukemia and Hodgkin’s disease (11).

Concurrently, the concept and principles of supportive care were established. Despite major obstacles, Dr. Freireich developed the technology for platelet transfusion (5, 6). Subsequently, his team showed that deaths from hemorrhage in acute leukemia declined dramatically with the advent of this therapy (8). A unique event that illustrates Dr. Freireich’s creativity and ability to exploit opportunity was the development of the blood cell separator (7). Mr. George Judson, an IBM engineer whose son was being treated for leukemia at the Medicine Branch, was given both the time and resources by IBM to join Dr. Freireich in cancer research. Mr. Judson translated into reality Dr. Freireich’s idea of an inline continuous-flow instrument to selectively harvest leukocytes, platelets, or plasma and return the remaining blood components to the patient. Within one year, this instrument had gone from a bench model to a clinical prototype and was being used in patients with leukemia. Leukapheresis with the blood cell separator is now a well-established clinical procedure useful in a variety of diseases.

In 1965, Dr. R. Lee Clark, president of the M. D. Anderson Hospital and Tumor Institute, recognizing that clinical cancer research was the pathway to the conquest of cancer, invited Drs. Frei and Freireich to establish the Department of Developmental Therapeutics at his institution. By 1966, the initial team of Drs. Frei, Freireich, Loo, Dah H. (Daisy) Ho, Grady Saunders, Priscilla Saunders, Edmund Gehan, Myron Karon, Gerald Bodey, Sr., Jules Harris, Evan Hersh, and James Luce was in place. In 1970, they were joined by Drs. Jeffrey Gottlieb and Ken McCre ide, who both died prematurely, and Jordon Gutterman. Over the next decade, this group grew in number and activity and ultimately developed and characterized many of the major therapeutics agents for malignant disease. M. D. Anderson was indeed a very fertile environment for their endeavors.

They developed original approaches to prognostic variable analysis and the design of therapeutics strategies based on that analysis (12–14). They and their trainees developed combination chemotherapy regimens for acute leukemia (15–17), lymphoma (CHOP; Ref. 18), breast cancer (FAC; Ref. 19), sarcoma (CYVADIC; Ref. 20), and testicular cancer (BEP; Ref. 21). More recently, they established the role of IFN-a in hairy cell leukemia (22) and chronic myelogenous leukemia (23) and of fludarabine in chronic lymphocytic leukemia (24). In each instance, an understanding of the biology of the disease and its prognostic variables and an understanding of the pharmacology of the therapeutic agents led to the establishment of the new...
therapy. In addition, over the years, critical studies of the cell biology, cytogenetics, and molecular biology of normal hematopoietic tissues and the leukemias were carried out (25–29). Much of this work was based on one of Dr. Freireich’s important principles, namely that the laboratory and the clinic are intimately related and that laboratory studies based on clinical observations are as important as the translation of laboratory observations to the clinic. It is evident from the papers in this issue that the principles established by Dr. Freireich and his colleagues are indeed being carried forward into the 21st century.

Not only is Dr. Freireich a clinical scientist, but he has been unique in understanding, confronting, and challenging the relationships of clinical science to preconceived ideas, rigidity of approach, bias, and politics as obstacles to progress. Dr. Freireich realized that clinical science does not exist in a vacuum. We are not in an ivory tower, but rather in a complex society. He addressed this in his 1976 Karnofsky lecture, published in this Festschrift for the first time (30).

This Festschrift celebrates Dr. Freireich’s contributions, leadership, and inspiration. It also calls attention to other key leaders in the field who were unable to attend or may no longer be with us, including Drs. Sydney Farber, David Karnofsky, Joseph Burchenal, Henry Kaplan, Gordon Zubrod, George Mathé, Howard Skipper, and Frank Schabel, whose contributions along with Freireich’s were critical to the development of the field.

In addition, this Festschrift celebrates the achievements of Dr. Freireich’s students, 19 of whose papers appear in this issue. Although there is much yet to be accomplished, we have come a long way. The decline in the mortality of leukemia and lymphoma seen in the 1960s and 1970s due to the advances outlined above is now being seen in solid tumors, including breast cancer and even lung cancer.

This Festschrift has five components: the scientific basis of clinical trials, developmental therapeutics, combined modality therapy, supportive care, and exploitable molecular mechanisms. The papers in this issue are designed to first identify the current status of disease and treatment, describe how we have gotten to the point at which we are, describe the current problems and obstacles to control the disease, and then describe strategies toward better therapies using the latest techniques and concepts of molecular biology. In addition, Dr. Frei has provided an analysis of Dr. Freireich’s achievements in relationship to his personality and character and to the tenor of the times in which they did their initial work. Finally, Dr. Freireich has outlined his views of the future of clinical cancer research in the next millennium. We hope that this Festschrift will serve as a pivotal landmark for the field of clinical cancer research, defining where we have come from, where we are at present, and where we are going in the future toward the ultimate conquest of malignant disease.

References


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