First FDA-Approved Chemo Agent Turns 60

BY BETSY BATES

"The response of the first patient was as dramatic as that of the first mouse. ... Within 48 hours after the initiation of therapy, a softening of the tumor masses was detected. It soon became obvious that this was not just wishful thinking." —Alfred Gilman, Ph.D., "The Initial Clinical Trial of Nitrogen Mustard" (Amer. J. Surg. 1963;105:574-8).

The top-secret intravenous administration of 0.1 mg/kg "Compound X" to an "x-ray resistant patient in the terminal stages of lymphosarcoma" in early December 1942 marked the quiet birth of chemotherapy in America.

The clandestine, government-sanctioned treatment of an anonymous patient at Yale University, New Haven, Conn., signified the first therapeutic use of nitrogen mustard, a mysterious compound that had been under investigation since its devastating use as a chemical weapon during World War I.

Dr. Gilman, Dr. Louis S. Goodman, and their team watched in amazement as obstructive symptoms associated with tumor masses involving the patient's face, mediastinum, and submental regions were eased within 4 days, and cervical and axillary masses receded soon after.

Ultimately, the first patient's course proved to be less miraculous than it first seemed. The person's bone marrow "slowly recovered" from toxic effects of the new treatment, but—"a great disappointment"—the tumors returned concomitantly.

Thus began the wrenching ups and downs of patient response to mustard gas in quiet experimental protocols at Yale, the University of Chicago, and the then–Sloan-Kettering Institute of Memorial Hospital in New York.

Until 1946, government secrecy restrictions prevented publication of small case series, but the experiments continued, and on March 15, 1949, mechlorethamine (Mustargen) became the first chemical agent to receive Food and Drug Administration approval for the treatment of cancer, transforming an agent of death into one that held the promise of extended life and launching a revolution.

"It is actually quite remarkable that it has only been 60 years since the first chemotherapy approval, considering where the field has gone in that time," said Dr. Richard Schilsky, professor of medicine at the University of Chicago and president of the American Society of Clinical Oncology. "We now have probably 100 or more chemotherapy drugs for the treatment of a wide range of different malignancies."

The journey has been anything but smooth, with strong early opposition documented by Yale oncologists Vincent T. DeVita Jr. and Edward Chu in a recent article, "A History of Cancer Chemotherapy" (Cancer Res. 2008;68:8643-53). "Remissions turned out to be brief and incomplete, and this realization then created an air of pessimism that pervaded the subsequent literature of the 1950s," they noted. Some academic physicians "became harsh critics of a national drug development program and the effort to prove that drugs could cure advanced cancer."

By the 1960s, "the main issue of the day was whether cancer drugs caused more harm than good, and talk of curing cancer with drugs was not considered compatible with sanity. The prevailing attitude toward the use of chemotherapy can only be described as hostile," wrote Dr. DeVita and Dr. Chu.

In spite of it all, chemotherapy emerged as a trusted modality in the treatment of cancer. The drug that started it all, Mustargen, became a key element in the revolutionary MOPP (Mustargen, Oncovin, procarbazine, and prednisone) combination chemotherapy regimen pioneered by Dr. DeVita for advanced Hodgkin's disease in the mid-1960s. It still is used today for stage III and IV Hodgkin's disease and other hematologic cancers, including polycythemia vera and mycoses fungoides, and bronchogenic carcinoma.

Initial observations regarding Mustargen were made during World War I, "when thousands were gassed," leading to recognition of profound lymph and bone marrow suppression in exposed soldiers and speculation that the agent might have therapeutic utility in diseases characterized by lymphoid and myeloid proliferation, said Dr. DeVita, former director of the National Cancer Institute.

By early 1942, the government's Office of Scientific Research and Development entrusted Dr. Goodman and Dr. Gilman of Yale University to shepherd a highly classified investigation of the deadly agent. After preliminary work in mice, they persuaded Dr. Gustav E. Lindskog, then assistant professor of surgery at the university, to supervise the first human clinical trial.

Detractors objected to the empiric manner in which the early drugs were investigated; the research partnerships that evolved among government, academic, and contracted pharmaceutical companies; and perhaps, most important, the terrible burden of side effects exacted from patients not assured of a cure.

"These drugs were highly experimental and used as a last resort. At first, they didn't work very well and made people who were already sick much sicker," said Dr. Franco Muggia, director of medical oncology at New York University and chairman and medical director of the Chemotherapy Foundation.

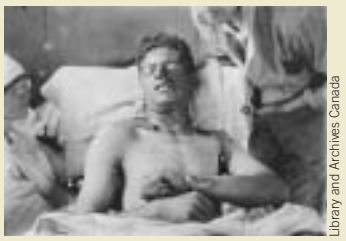
But early believers pressed on, confident that the regimens could be fine-tuned, the toxicities tamed. In time, dramatic advances were made in dosages and treatment regimens, in combining chemotherapeutic agents and in using them in various ways with surgery, radiation, and biologic therapies. A better biologic understanding of cancer led to more precise targeting of chemotherapy. And progress was made in treating the side effects that once seemed to be chemotherapy's death knell, a point illustrated by Dr. Schilsky.

The experts consulted for this article have conducted research for pharmaceutical companies that manufacture various forms of chemotherapy. ■

History of Chemotherapy: A Time Line

2nd Lt. T.L. Aitken
United Kingdom Government

1917 First use of mustard gas on the battlefield, WWI.



Library and Archives Canada

1942 Secret contract signed between U.S. Office of Scientific Research and Yale University to study chemical warfare agents; animal research begins.

December: First patient injected with "Compound X."

1943 Bari Incident: Mustard gas released during bombing of U.S. cargo ship in Italy.

National Cancer Institute

1949 Mechlorethamine (first approved chemotherapeutic drug) approved by FDA.

1955 Cancer Chemotherapy National Service Center (drug development program at NCI) established.

National Cancer Institute

1959 Methotrexate (antifolate) approved by FDA.

1962 5-Fluorouracil (antimetabolite) approved by FDA.

1963 Vincristine (vinca alkaloid) approved by FDA.

1965 POMP (methotrexate, vincristine, 6-mercaptopurine, prednisone) used to treat pediatric ALL.

1967 MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) used in lymphoma.

MOMP (nitrogen mustard, vincristine, methotrexate, prednisone) used in Hodgkin's disease.

1970s Adjuvant therapy era.

1978 Cisplatin (first platinum derivative) approved.

1992 Paclitaxel approved.

1996 Irinotecan approved.

Elsevier Global Medical News

Future of Cancer Treatment Includes Chemotherapy

People have been trying to write the epitaph for chemotherapy virtually since nitrogen mustard was approved in 1949. But the naysayers were shortsighted then, and still are today, a number of leading oncologists maintain.

For all the talk of "targeted" therapy taking center stage in cancer therapy, "chemotherapy is likely to be an important part of cancer treatment for some time to come," Dr. Schilsky said.

The belief that chemotherapy is too toxic, and therefore should be replaced by "targeted therapy," negates several truths; one, that chemotherapy isn't "targeted," and two, that molecular-targeted therapies such as biologics and immunotherapy are capable of curing the solid tumors that afflict most patients with cancer.

"Methotrexate and 5-fluorouracil are among the most targeted drugs we've ever had," Dr. Schilsky said. "They're more than 50 years old and have not been replaced."

Although agents designed to target characteristics unique to tumor cells may be the hope of the future, to date they have matched chemotherapy's success only in a few rare tumor types, he added.

Empiric studies of early chemotherapeutic drugs may look "pretty unsophisticated" today, but the signals that resulted were strong, Dr. Muggia agreed. "There's no one way," he said, predicting that chemotherapy will long play a key role in combination regimens that also may include molecular-targeted agents.

"As we get into targeted therapy, there are some problems with that as well," he added.

Dr. DeVita echoed the notion that "targeted therapy is chemotherapy."

"We always hoped, over time, that chemotherapy would become more specific and it has," he said. "Nitrogen mustard was the first use of systemic therapy based on the premise that treatment failure was due to circulating cancer cells. All subsequent systemic therapy, including biologics, is based on that premise."

Progress in cancer therapy, then, is likely to build on lessons of the past and encounter hurdles not foreseen, Dr. DeVita said.