YALE JOURNAL OF BIOLOGY AND MEDICINE 84 (2011), pp.169-172.

FOCUS: YALE SCHOOL OF MEDICINE BICENTENNIAL

The Birth of Chemotherapy at Yale

Bicentennial Lecture Series: Surgery Grand Round

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Chemotherapy, one of the mainstays of cancer treatment today, was pioneered at Yale during World War II. Last year, two Yale surgeons, Drs. John Fenn and Robert Udelsman, sought to unearth the mystery surrounding the discovery of chemotherapy and its first use at Yale. The first chemotherapy patient is known only as JD in the literature, and without a name, date of birth, or medical record number, a search for his record seemed futile. However, persistence coupled with sheer fortune led them to JD's chart, where they found information that differed from previous accounts. The riveting personal story of JD, an immigrant patient with lymphosarcoma, was revealed for the first time by Drs. Fenn and Udelsman on January 19, 2011, at a special Surgical Grand Rounds celebrating the bicentennial of Yale School of Medicine.

INTRODUCTION

Cancer is the second most common cause of death in the United States, accounting for nearly 1 out of every 4 deaths [1]. In 2010, it was estimated that 1,529,560 Americans would be diagnosed with cancer and 569,490 would succumb to the disease at an overall cost to the health care system of $263.8 billion [1]. The lifetime risk of being diagnosed with cancer is 41 percent, and the five-year survival rate for all cancers diagnosed between 1999 and 2005 was 68 percent, a substantial increase from the 50 percent reported in 1975-1977 [2]. This improvement in survival can be attributed to earlier diagnosis and advancements in treatment.

One of the mainstays of cancer treatment is chemotherapy, which is increasingly being used by today's oncologists [3].

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†Abbreviations: OSRD, US Office of Scientific Research and Development; IRBs, Institutional Review Boards.

Keywords: antineoplastic agents; chemotherapy history; intravenous infusions; non-Hodgkin lymphoma; mechlorethamine

Historically, the origin of chemotherapy has been shrouded in secrecy due to the circumstances surrounding its discovery. Reports of its first use at a Yale hospital during World War II are scattered within the literature [4-6]. However, reference to the first patient treated with chemotherapy was based on personal recollection rather than medical facts, as the chart had been misplaced. Lost within this record was the personal and medical history of JD, a man whose illness sparked the birth of chemotherapy. The case of JD remained a mystery for more than 60 years, until Yale School of Medicine physicians Dr. John Fenn, clinical professor of surgery, and Dr. Robert Udelsman, professor and chair of the Department of Surgery, became curious and sought to uncover his story. Without a name, date of birth, medical record number or precise date of treatment, the search for JD's record seemed futile. However, in May 2010, persistence coupled with sheer fortune led them to an off-site storage facility that contained JD's medical chart. To their surprise, the facts contained therein differed from those that had been previously reported, including inaccuracies in the personal history of JD, the circumstances surrounding his treatment, and his clinical course.

JD's story was revealed for the first time at a Yale Bicentennial Lecture on January 19, 2011, when Drs. Fenn and Udelsman gave a captivating account of how chemotherapy was discovered and its first use at Yale. As Yale School of Medicine celebrates its 200th anniversary, we reflect on its pivotal contributions to the field of medicine. The discovery of chemotherapy at Yale serves as the quintessential model for scientific innovation: diligent basic scientists collaborating with translational researchers and dedicated clinicians to develop a novel therapy and offer hope to terminal patients.

JD'S HISTORY

JD was born in Poland in 1894 and immigrated to the United States at the age of 18. He lived in Connecticut and worked in a ball bearing factory until he became ill in August 1940. What began as tonsillar enlargement and right submandibular pain rapidly progressed to multiple enlarging masses that were biopsied and found to be lymphosarcoma. Before long, they occupied the entire right side of his neck, and he could barely open his mouth. He was referred to the Yale Medical Center in February 1941 for X-ray therapy and admitted to what is now Yale-New Haven Hospital. He underwent external beam radiation for 16 consecutive days with considerable reduction in tumor size and amelioration of his symptoms. However, his improvement was short lived, and by June 1941, he required additional surgery to remove cervical tumors. He underwent several more cycles of radiation to reduce the size of the tumors, but by the end of the year they became unresponsive and had spread to the axilla. By August 1942, two years after the initial onset of symptoms, he suffered from respiratory distress, dysphagia, and weight loss, and his prognosis appeared hopeless.

The treatment of lymphosarcoma at the time was surgical resection and radiation therapy, which had been shown to improve symptoms and prolong life [7]. However, relapse and death were common, and cases arising from the tonsils were reported to be most malignant [7]. Now refractory to radiation therapy and having exhausted all surgical options, JD's doctors turned to an experimental therapy whose origins can be traced back to World War I. JD's physicians believed that nitrogen mustard, a related compound of the poison gases responsible for 1,205,655 non-fatal casualties and 91,198 deaths during the war, was his only chance for survival [8]. The leukopenic effect of mustard gas on blood and bone marrow was first reported by Dr. Edward Krumbhaar in 1919 after treating exposed soldiers at a hospital in France [9]. He noticed a peculiar change in the hematological profile in these soldiers: an initial increase in erythrocyte and leukocyte count, followed by a profound decrease in circulating leukocytes attributed to "exhaustion of the leukocyte forming centers" in the bone marrow.

Reports of severe toxicity prompted the U.S. Office of Scientific Research and Development (OSRD†), an agency of the War Department, to fund research investigating potential antidotes [10].

A contract was signed with Yale School of Medicine to fund a research team led by Dr. Alfred Gilman, a pharmacologist, and Dr. Louis Goodman, a physician and pharmacologist [6]. They used a rabbit model to evaluate the toxicity of nitrogen mustard and observed a similar decrease in the number of circulating lymphocytes and granulocytes. It occurred to them that this might have potential as a treatment for patients with lymphoid malignancies, and they initiated trials on mice with transplanted lymphomas in collaboration with anatomist and colleague Dr. Thomas Dougherty. The results were promising, and a marked decrease in tumor size was observed in the mice receiving treatment, corresponding to a prolongation of life. The researchers presented these results to Dr. Gustaf Lindskog, then an assistant professor of surgery at Yale, as a potential treatment for humans with refractory lymphoma. Having exhausted all other treatment modalities, the medical team offered experimental nitrogen mustard chemotherapy to JD. Despite having already experienced numerous relapses, physical suffering, and emotional anguish, JD maintained the will to survive and agreed to undergo experimental chemotherapy. Concurrently, the Chemical Warfare Service began controversial research testing of mustard gas on human subjects [11] and started investigating other chemical agents as countermeasures should they become necessary. As a result of censoring by the War Department, nowhere in JD's record do the words "nitrogen mustard" appear; rather, the substance was referred to as "a lymphocidal" or "substance X." Although both human trials preceded the Nuremberg Code, Belmont Report, and establishment of Institutional Review Boards (IRBs), a distinction must be made between the therapeutic use of nitrogen mustard on JD and its experimental use on military volunteers.

At 10 a.m. on August 27, 1942, JD received his first dose of chemotherapy recorded as 0.1 mg/kg of synthetic lymphocidal chemical. This dosage was based on toxicology studies performed in rabbits. He received 10 daily intravenous injections, with symptomatic improvement noted after the fifth treatment. Biopsy following completion of the treatment course remarkably revealed no tumor tissue, and he was able to eat and move his head without difficulty. However, by the following week, his white blood cell count and platelet count began to decrease, resulting in gingival bleeding and requiring blood transfusions. One week later, he was noted to have considerable sputum production with recurrence of petechiae, necessitating an additional transfusion. By day 49, his tumors had recurred, and chemotherapy was resumed with a 3-day course of "lymphocidin." The response was short-lived, and he was administered another 6-day course of substance "X." Unfortunately, he began experiencing intraoral bleeding and multiple peripheral hematomas and died peacefully on December 1, 1942 (day 96). Autopsy revealed erosion and hemorrhage of the buccal mucosa, emaciation, and extreme aplasia of the bone marrow with replacement by fat.

CONCLUSION

The riveting account of JD shared by Drs. Fenn and Udelsman on the first use of chemotherapy at Yale illustrates a monumental event in modern medicine. The multidisciplinary team of Yale pharmacologists and physicians was able to characterize the mechanism of action of nitrogen mustard and translate their findings from animal studies to the first human trial as a treatment for refractory lymphosarcoma. In administering the first dose of nitrogen mustard, they provided proof of concept that intravenous chemotherapy resulted in tumor regression, but that resistance occurred after multiple dosages. They also observed the profound bone marrow suppression resulting from chemotherapy use, which puts patients at a high risk of infection and death. This crucial discovery founded the field of

medical oncology and would not have been possible without the courage of JD. The full details of JD's life, medical history, and treatment course, as well as a historical account of the origin of chemotherapy, have been published by Drs. Fenn and Udelsman in the *Journal of the American College of Surgeons* [12].

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