IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A History of Cancer Chemotherapy

-Mrudula Shrikrishna Pachpande and Nandini Bhushan Patil

Gokhale educationsociety Sir Dr M.S Gosavi college of pharmacy, Nashik 422005,

Maharashtra, India.

Abstract

The use of chemotherapy to treat cancer began at the start of the 20th century with attempts to narrow the universe of chemicals that might affect the disease by developing methods to screen chemicals using transplantable tumors in rodents. It was, however, four World War II–related programs, and the effects of drugs that evolved from them, that provided the impetus to establish in 1955 the national drug development effort known as the Cancer Chemotherapy National Service Center. The ability of combination chemotherapy to cure acute childhood leukemia and advanced Hodgkin's disease in the 1960s and early 1970s overcame the prevailing pessimism about the ability of drugs to cure advanced cancers, facilitated the study of adjuvant chemotherapy, and helped foster the national cancer program. Today, chemotherapy has changed as important molecular abnormalities are being used to screen for potential new drugs as well as for targeted treatments.

Introduction

In the early 1900s, the famous German chemist Paul Ehrlich set about developing drugs to treat infectious diseases. He was the one who coined the term “chemotherapy” and defined it as the use of chemicals to treat disease. He was also the first person to document the effectiveness of animal models to screen a series of chemicals for their potential activity against diseases, an accomplishment that had major ramifications for cancer drug development. In 1908, his use of the rabbit model for syphilis led to the development of arsenicals to treat this disease. Ehrlich was also interested in drugs to treat cancer, including aniline dyes and the first primitive alkylating agents, but apparently was not optimistic about the chance for success. The laboratory where this work was done had a sign over the door that read, “Give up all hope oh ye who enter.”

Surgery and radiotherapy dominated the field of cancer therapy into the 1960s until it became clear that cure rates after ever more radical local treatments had plateaued at about 33% due to the presence of heretofore-unappreciated micrometastases and new data showed that combination chemotherapy could cure patients with various advanced cancers. The latter observation opened up the opportunity to apply drugs in conjunction with surgery and/or radiation treatments to deal with the issue of micrometastases, initially in breast cancer patients, and the field of adjuvant chemotherapy was born. Combined modality treatment, the tailoring of each of the three modalities so their antitumor effect could be maximized with minimal toxicity to normal tissues, then became standard clinical practice

The Early Period of Cancer Drug Development

A selected history and timeline of events related to the development of cancer chemotherapy . The first four decades of the 20th century were primarily devoted to model development. The major limitations

of drug discovery were two-fold: first, the development of models that could effectively be used to reduce the vast repertoire of chemicals to those few that might have activity against cancer in humans, and second, the access to clinical facilities to test such agents.
major breakthrough in model development occurred in the early 1910s when George Clowes of Roswell Park Memorial Institute (RPMI) in Buffalo, New York, Roswell Park Memorial Institute developed the first transplantable tumor systems in rodents. This advance allowed the standardization of model systems and the testing of larger numbers of chemicals. Significant efforts were subsequently focused on identifying the ideal model system for cancer drug testing, which then became a major thrust of research for the next several decades.
The early model systems that were developed included Sarcoma 37 (S37), Sarcoma 180 (S180), Walker 256, and Ehrlich's ascites tumor, all carcinogen-induced tumors in mice.

It was Murray Shear, at the Office of Cancer Investigations of the USPHS, a program that was later combined in 1937 with the NIH Laboratory of Pharmacology to become the National Cancer Institute (NCI), who in 1935 set up the most organized program that would became a model for cancer drug screening

The 1960s—The Concept of Cure

In the 1960s, medical oncology did not exist as a clinical specialty. Those who were given the task of administering chemotherapy at most medical centers were regarded as underachievers at best. 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. A few vignettes will illustrate this point rather graphically.

At the medical institution where Vince DeVita began his career, the “chemotherapist” was an endocrinologist, Louis K. Alpert, who had published one of the early reports on the use of nitrogen mustard in lymphomas and administered chemotherapy as a sideline. Because of his stern and pointed visage, and because he appeared when chemotherapy was to be administered, he was referred to by the house staff and the faculty as “Louis the Hawk and his poisons,” a designation he took gracefully. Unfortunately, poison was the term in general use for anticancer drugs.

The Francis Delafield Hospital, although connected with Columbia University College of Physicians and Surgeons, was ultimately denied access to residents and interns from Columbia because two successive chairmen of medicine, Robert Loeb and Stanley Bradley, did not want their house staff exposed to cancer patients receiving these cancer poisons, although their mentor would have been the distinguished Alfred Gellhorn. As Alfred Gellhorn recently recounted to the authors, [1] the otherwise great clinician Loeb, a giant in the field at the time, had a blind spot when it came to caring for cancer patients and testing chemotherapy. He was fond of saying to Gellhorn, rather openly, “Alfred, you belong to the lunatic fringe.” The Delafield Hospital program, the first example of a university-based cancer center, with many illustrious graduates, including Bernard Weinstein, Elliot Osserman, John Ultmann, Jim Holland, Paul Marks, Franco Muggia, Helen Ranney, and Jack Davidson, was closed in 1971. The leaders at Delafield provided the nidus to create a new cancer center at Columbia in 1974, after the cancer act in 1971 provided a mandate to create new university-based cancer centers.
At Yale, the first institution to test chemotherapy in humans in the modern era, the chemotherapist Paul Calabresi, a distinguished professor and founding father in the field, was forced to leave because he was involved in too much early testing of new anticancer drugs, an exercise as unpopular with the faculty and house staff at Yale as it was at Columbia.

At the Clinical Center of the NCI, where so many of the early breakthroughs with chemotherapy occurred, the well-known hematologist George Brecher, who read all the bone marrow slides of the leukemic patients, routinely referred to the Leukemia Service as the “butcher shop” at rounds.

And these are only the stories that can be told. It took plain old courage to be a chemotherapist in the 1960s and certainly the courage of the conviction that cancer would eventually succumb to drugs. Clearly, proof was necessary, and that proof would come in the form of the cure of patients with childhood acute leukemia and in adults with advanced Hodgkin's disease.

By 1960, the L1210 leukemia system had been established as both the primary screen and the model for treating acute leukemia. Work on L1210, childhood acute leukemia, and Hodgkin's disease was going on in parallel. At the turn of the decade, complete remissions were occurring in about 25% of children with leukemia, but with single agents, they were brief, measured in months. Several institutions were cooperating in protocols with a design that hinted at cure, not palliation, as an end point. Such studies were in progress at RPMI in Buffalo under Jim Holland

The 1970s: The Age of Adjuvant Chemotherapy

The concept of cure had a remarkably permissive effect on the use of chemotherapy in earlier stages of cancers. For example, about 90% of patients with breast cancer present with locoregional disease. Yet, the majority will develop recurrences if only the best locoregional treatment is used. Similar circumstances existed for other solid tumors, such as colorectal cancers. But a significant fraction of patients with locoregional disease will also stay free of tumor after regional treatment alone. If chemotherapy were to be used as an adjunct to local treatments, many other patients would be unnecessarily exposed to the potential side effects of drugs, hence the dilemma. To use chemotherapy as an adjunct to surgery or radiotherapy, one needed evidence that the relapse rate was likely to be high in the treated population, the program to be used was effective in patients with the same tumor type in its advanced stages, and some confidence that chemotherapy might have the capacity to cure patients with micrometastases while not being excessively toxic. The demonstration that combination chemotherapy could cure some types of advanced cancer gave hope that the same results could be achieved under ideal circumstances for more common solid tumors. Moreover, Skipper's cell kill hypothesis, and the invariable inverse relation between cell number and curability, suggested that drugs effective against advanced disease might work better in the adjuvant situation with only micrometastases to deal with

The main problem was where to test these treatment regimens as adjuvants to surgery. Despite the excitement over the new chemotherapy data, most surgeons in the United States were still reluctant to participate in clinical trials testing its use postoperatively. The courageous Bernard Fisher was the first choice . He and his group, the National Surgical Adjuvant Breast Project (NSABP), had done an early adjuvant study, sponsored by the CCNSC, testing the use of the alkylating agent thiotepa postoperatively to kill cancer cells dislodged at surgery. Thus, another solid tumor in adults fell to the use of combination chemotherapy. Today, chemotherapy is used for all stages of this tumor and testicular cancer is curable in most patients.

Passage of the Cancer Act of 1971 and Beyond

One unanticipated benefit of the report of the curability of choriocarcinoma, lymphomas, and acute leukemias with combination chemotherapy was the passage of the National Cancer Act in 1971. One of the patients with non–Hodgkin's lymphoma initially treated with the C-MOPP program at the NCI Clinical Center in 1969 was a lobbyist for the American Cancer Society who had been hired at the request of Mary Lasker to be her eyes and ears on Capital Hill. His complete response to combination chemotherapy caught Mary Lasker's attention, and she became convinced that the data on the lymphomas and leukemias were the missing link in treatment needed to eradicate cancer

It is still too early to know the full effect of all these changes in the screening program because the lag time between discovery of activity and ultimate proof of usefulness is quite long, sometimes measured in decades. However, something else has happened to change the landscape of drug development. As information about the molecular aberrations that occur in cancer cells has become available, random screening is being replaced by screening against specific critical molecular targets. As the market for cancer drugs has grown, so has the willingness of the industry to invest in new drugs, and discovery and development are now largely in the hands of a segment of the pharmaceutical industry that did not

exist before the advent of the CCNSC. As a consequence, many new drugs and new classes of anticancer drugs have been introduced since the 1980s, too many to discuss here, and are now available to clinicians.

The advent of monoclonal antibodies has enhanced the effects of chemotherapy. Hybridomas were described in 1975, and monoclonal antibodies were proven clinically useful starting in the mid-1990s. Although they are not chemotherapy per se, they seem to work best when they are used in conjunction with chemotherapy, as is the case for trastuzumab in breast cancer, cetuximab and bevacizumab in colorectal cancer, and rituximab in non–Hodgkin's lymphoma, and each are an integral part of chemotherapy regimens for these common tumors.

Chemotherapy has, in fact, transitioned to the age of “targeted therapy.” The story of how we got to the point of identifying many molecular targets takes us back again to the 1960s to a seemingly unrelated program—the Special Virus Cancer Program (SVCP). It was established in 1964 with another $5 million from the Senate Appropriations Committee, again at the urging of the ubiquitous and visionary Mary Lasker. It was also supported by research contracts and was conceived as a crash program to find viruses reported to be associated with cancer. When it failed to identify actual viruses, it morphed into a Program of Molecular Biology to study genes that were coopted by tumor viruses. The SVCP was often criticized because of the use of research contracts, but work in this program identified oncogenes, suppressor oncogenes, and signaling pathways essential for developmental biology itself

Cancer chemotherapy is curative in subsets of patients who present with advanced disease, including Hodgkin's and non–Hodgkin's lymphoma, acute lymphoblastic and acute myelogenous leukemia, germ cell cancer, small cell lung cancer, ovarian cancer, and choriocarcinoma. In pediatric patients, the curable cancers include acute leukemias, Burkitt's lymphoma, Wilm's tumor, and embryonal rhabdomyosarcoma. There is now an expanding role of chemotherapy to treat a wide range of solid tumors. Finally, in 1990, the national incidence and mortality of cancer began to decline. Mortality has continued to decline each year since 1990, and in 2005, overall deaths from cancer have declined despite the larger and older U.S. population. In 2007, the rate of decline actually doubled. Whereas half of this decline is due to prevention and early diagnosis, the other half is largely due to advances in cancer treatment, much of it due to the inclusion of chemotherapy in most treatment programs. Finally, in 1990, the national incidence and mortality of cancer began to decline. Mortality has continued to decline each year since 1990, and in 2005, overall deaths from cancer have declined despite the larger and older U.S. population. In 2007, the rate of decline actually doubled. Whereas half of this decline is due to prevention and early diagnosis, the other half is largely due to advances in cancer treatment, much of it due to the inclusion of chemotherapy in most treatment programs.

CONCLUSION:-

A plan for the diagnosis and treatment of cancer is a key component of any overall cancer control plan. Its main goal is to cure cancer patients or prolong their life considerably, ensuring a good quality of life. In order for a diagnosis and treatment programme to be effective, it must never be developed in isolation. It needs to be linked to an early detection programme so that cases are detected at an early stage, when treatment is more effective and there is a greater chance of cure. It also needs to be integrated with a palliative care programme, so that patients with advanced cancers, who can no longer benefit from treatment, will get adequate relief from their physical, psychosocial and spiritual suffering. Furthermore, programmes should include a awareness-raising component, to educate patients, family and community members about the cancer risk factors and the need for taking preventive measures to avoid developing cancer.

Where resources are limited, diagnosis and treatment services should initially target all patients presenting with curable cancers, such as breast, cervical and oral cancers that can be detected early. They could also include childhood acute lymphatic leukaemia, which has a high potential for cure although it cannot be detected early. Above all, services need to be provided in an equitable and sustainable manner. As and when more resources become available, the programme can be extended to include other curable cancers as well as cancers for which treatment can prolong survival considerably.

References

1.Brested JH. The Edwin Smith surgical papyrus. Translated for The New York Historical Society. Chicago (IL): University of Chicago Press; 1930.

2.Papac RJ. Origins ofsf cancer therapy. Yale J Biol Med 2001; **74**: 391–8. **PubMedGoogle Scholar**

3.DeVita VT. The evolution of therapeutic research in cancer. N Engl J Med 1978; **298**: 907–**PubMedGoogle Scholar**

4.Osler W. The principles and practice of medicine. New York: D. Appleton and Company; 1893. p. 708.

5.Goldin A, Schepartz SA, Venditti JM, DeVita VT. Historical development and current strategy of the National Cancer Institute Drug Development Program. In: Busch H, DeVita VT, editors. Methods in cancer research, V16 (A). New York: Academic Press; 1979. p. 165–245.

6.Hirschberg E. Patterns of response of animal tumors to anticancer agents. Cancer Res 1963; **23**: 521 980.**PubMedGoogle Scholar**

7.Shear MJ, Hartwell JL, Peters VB, et al. Some aspects of a joint institutional research program on chemotherapy of cancer: current laboratory and clinical experiments with bacterial polysaccharide and with synthetic organic compounds. In: Moulton FR, editor. Approaches to tumor chemotherapy. Washington (DC): American Association for the Advancement of Science; 1947. p. 236–84.

8.Zubrod CG, Schepartz S, Leiter J, Endicott JM, Carrese LM, Baker CG. The chemotherapy program of the National Cancer Institute: History, analysis, and plans. Cancer Chemother. Rep 1966; **50**: 349–540.

Google Scholar

9.Zubrod CG, Schepartz SA, Carter SK. Historical background for the National Cancer Institute's drug development thrust. Natl Cancer Inst Monogr 1977; **45**: 7–11.

Google Scholar

10. Boyland E. Experiments on the chemotherapy of cancer. I. The effects of certain antibacterial substances and related compounds. Biochem J 1938; **32**: 1207–13.

FREE Full TextGoogle Scholar

11. Yoshida T. The Yoshida sarcoma, an ascites tumor. Gann 1949; **40**: 1–20.

Google Scholar

12. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet 1896; **2**: 104–7;162–165.

Google Scholar

13. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effects of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. Cancer Res 1941; **1**: 293–7.

FREE Full TextGoogle Scholar

14. Marshall EKJR. Historical perspectives in chemotherapy. In: Golding A, Hawking IF, editors. Advances in chemotherapy, vol. 1. New York: Academic Press; 1964. p. 1–8.

15. Krumbhaar EB, Krumbhaar HD. The blood and bone marrow in yellow gas (mustard gas) poisoning. Changes produced in bone marrow in fatal cases. J Med Res 1919; **40**: 497–508.

Google Scholar

16. Gilman A. Symposium on advances in pharmacology resulting from war research: therapeutic applications of chemical warfare agents. Fed Proc 1946; **5**: 285–292.

PubMedGoogle Scholar

17. Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, McLennan MT. Nitrogen mustard therapy: use of methyl-bis (β-chloroethyl) amine hydrochloride and tris (β-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia, and certain allied and miscellaneous disorders. JAMA 1946; **132**: 126–32.
CrossRefPubMedGoogle Scholar

18. Gilman A, Philips FS. The biological actions and therapeutic applications of the β-chloroethylamines and sulfides. Science 1946; **103**: 409–15.
FREE Full TextGoogle Scholar

19. Karnofsky DA, Burchenal JH, Ormsler RA, Corman I, Rhoads CP. Experimental observations on the use of nitrogen mustard in the treatment of neoplastic diseases. In: Moulton FR, editor. Approaches to tumor chemotherapy. Washington (DC): American Association for the Advancement of Science; 1947. p. 298–305.
20. Gilman A. The initial clinical trial of nitrogen mustard. Am J Surg 1963; **105**: 574–8.
CrossRefPubMedGoogle Scholar

21. Farber S. Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer. Blood 1949; **4**: 160–7.
PubMedGoogle Scholar

22. Farber S, Diamond LK, Mercer RD, et al. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). N Engl J Med 1948; **238**: 787–93.
CrossRefPubMedGoogle Scholar

23. Pinkel D. Actinomycin D in childhood cancer; a preliminary report. Pediatrics 1959; **23**: 342–7.
Abstract/FREE Full TextGoogle Scholar

24. Hitchings GH, Elion GB. The chemistry and biochemistry of purine analogs. Ann NY Acad Sci 1954; **60**: 195–9.
CrossRefPubMedGoogle Scholar

25. Elion GB, Singer S, Hitchings GH. Antagonists of nucleic acid derivatives. VIII. Synergism in combinations of biochemically related antimetabolites. J Biol Chem 1954; **208**: 477–88.
FREE Full TextGoogle Scholar