

# Chemotherapy over the Years

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## Abstract

At the beginning of the 20th century, attempts to use chemotherapy for the treatment of cancer were started, and the first four decades of the 20th century were mainly dedicated to model development. There existed a dominant doubt regarding the capacity of drugs to treat advanced cancers until the success of combination of chemotherapy in treatment of acute childhood leukemia and advanced Hodgkin's disease in the 1960s and the early 1970s. Chemotherapy has undergone a lot of changes until the date, and nowadays molecular abnormalities are intensely studied to screen for potential new drugs and targeted treatments as well. The article highlights the major milestones in chemotherapy through the years.

**Key Words**-Chemotherapy-cancer-leukemia-NCI-lymphoma-monoclonal antibodies-Rituximab- vinca alkaloids- breast cancer -targeted therapy- TKI- imatinib- Cisplatin- Carboplatin -mechlorethamine- vincristine- methotrexate- prednisone

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## INTRODUCTION

In 1910, the German chemist Paul Ehrlich started the age of chemotherapy by discovering the first antibacterial agent; a compound effective against spirochete that causes syphilis [1]. In addition, he recognized the efficacy of animal models in screening series of chemicals for their possible therapeutic effects, an achievement that had great implications on developing cancer therapy [2]. Aniline dyes were among the drugs –supposed to treat cancer- that Ehrlich was interested in, however, he was not hopeful about their success. The laboratory in which these experiments were carried out had a sign on its door that read "Give up all hope oh ye who enter" [3]. The field of cancer therapy was led by surgery and chemotherapy until 1960s. Afterwards, the new studies revealed that combination chemotherapy has the capacity to treat patients suffering many progressive cancers [4]. The combined efforts of the pediatric surgeons and the pediatric oncologists along with the radiation therapists in the 1960s and 1970s to enhance the treatment of Wilm's tumor in children represented the first fruitful application of a multifaceted tactic to treat cancer. The success of the combinations of chemotherapeutic agents in treatment of Hodgkin disease during the 1960s led to the extensive use of combination chemotherapy in treatment of nearly all types of cancers [5].

## The Use of Animal Models

A substantial advancement in the complexity and application of animal models in medical studies was seen during the first 4 decades of the 20th century and the years of the Great War [6]. In the early 1910s, George Clowes of Roswell Park Memorial Institute (RPMI) in Buffalo, New York, Roswell Park Memorial Institute established the first transplantable tumor systems in rodents. This was a significant advancement as it allowed the standardization of model systems, and the testing of larger numbers of chemicals as well. Afterwards, a lot of efforts were concerned with finding the ideal model system that suits cancer drug testing [7]. In 1937, the National Cancer Institute (NCI) was established through the combination of the Office of Cancer Investigations of the United States Public Health Service (USPHS), and the NIH Laboratory of Pharmacology becoming the National Cancer Institute (NCI) [8]. A manuscript by Furth et al. [9] was published in the same year unfolding the mechanism of leukemia transmission in mice from a single implanted cell that gave rise to death of the recipient. After 2 years, Charles Huggins and his team, began studying androgen levels and the occurrence of prostate cancer in dogs. Later in 1966, Huggins was awarded the Nobel Prize for medicine in gratitude of this work that showed the relationship between hormones and certain cancers [10].

## World War II and the immediate Post-War Period

Gases were not employed in the battleground during World War II (WWII), however, excessive research was carried out in order to study vesicant war gases [11]. In addition to the experience in WWI, the outcomes of an unintentional exposure to sulfur mustards in Italy in WWII led the way to noting that those men who were exposed to the mustard gas showed a significant depletion in bone marrow and lymph nodes as well [12]. The pharmacologists Alfred Gilman and Louis Goodman of Yale University did some research funded by the US Office of Scientific Research and Development (US OSRD) in order to study the possible therapeutic effects of Nitrogen mustard, and they found that it showed antitumor activity against murine lymphoma [13]. In 1943, the first use of a mustard compound to treat human cancer was recorded; a patient suffering from non-Hodgkin's lymphoma, and presenting with severe airway obstruction. Gilman and Goodman succeeded in persuading Gustaf Lindskog (The thoracic surgeon who was following up the non-Hodgkin's lymphoma patient at Yale) to give mustard to the patient. A significant, but transient regression was found in this patient and other lymphoma patients [13, 14]. Until 1946, the publication of these case reports was precluded due to the secrecy associated with the war gas program [13]. Continuous parallel advances during WWII resulted in synthesizing antifolate compounds (methotrexate); proved to achieve noticeable remissions in childhood leukemia in 1948. However, these remissions were temporary [15]. In addition to the US OSRD program studying the possible therapeutic effects of Nitrogen mustard, there was another program concerned with searching for antibiotics, and it found that Actinomycin D had antitumor activity. It was extensively used in pediatric tumors during the 1950s and 1960s [16]. In 1951, 6-thioquanine and 6-mercaptopurine were developed, and were widely used in acute leukemias [17]. In addition, they were used as immunosuppressive agents in the organ transplantation, and in the treatment of other diseases as gout, and viral infections as herpes [7]. Among the drug development programs that took place in the immediate postwar years, the largest was managed by Dr. Cornelius Rhoads at the Sloan-Kettering Institute (SKI). The murine S180 was the main model used by the SKI investigators, as it showed moderate sensitivity to identified compounds, and was smoothly transplanted with almost 100 % success [18]. At that time, many tumor systems became available, and the main concern of drug screeners was finding out which transplantable tumor was the best to predict human activity. Leukemia L1210 (L1210) model system, defined by Lloyd Law at the NCI was a murine leukemia induced by a carcinogen [19]. Skipper and colleagues at Southern Research Institute [20], and then DeVita and colleagues [21]

carefully studied the kinetics of this model. The L 1210 was recognized as the best multipurpose animal tumor screening system, and the NCI used it as its prime screen. Selecting the best screening system was reviewed by Goldin et al. [11] in an article published in 1979.

#### **The 1950s**

The failure of nitrogen mustard to produce long-lasting remissions led to pessimism during the 1950s, which was then counterbalanced through the discovery of corticosteroids. However, corticosteroids were also rapidly proved to produce just transitory results when used solely [22]. In 1955, the confusion following the results of using methotrexate in acute leukemia in children, along with the availability of new screening systems paved the way for the establishment of Cancer Chemotherapy National Service Center (CCNSC). This program, regardless of having a political side, contributed to changing the face of cancer drug development all over the world. Among the articles that extensively studied this interesting history were those of Zubrod et al. [18], and Goldin et al. [11]. After a lot of debates about the program, and the appropriate way to fund it, the 1950s ended with the same pessimism of their beginning [23, 24]. However, establishing the CCNSC led to the multibillion-dollar cancer pharmaceutical industry [7].

#### **The 1960s**

Rapid development of chemotherapeutic agents took place in the 1960s [25]. In the middle of this decade, investigators at the NCI first applied the four drug combination chemotherapy regimen using mechlorethamine, vincristine, methotrexate, and prednisone (MOMP) [26]. A lot of chemotherapeutic agents that are in use today had been synthesized by the end of this period of time, for example, vinca alkaloids, nitrosoureas, and anthracyclines. Among the main achievements during the 1960s was the new understanding of the cancer cells kinetics and the chemotherapeutic agents' pharmacokinetics [27].

#### **The 1970s**

Methotrexate treatment led to some metabolic perturbations which were studied for the first time in the early 1970s [28]. By the mid-1970s, polychemotherapy programs were developed following the identification of activity of numerous single agents in severe diseases [29]. Most importantly, curative chemotherapy programs were developed for different cancers as testicular cancer and some embryonal rhabdomyosarcomas [27].

#### **The 1980s**

Combination therapy became the standard treatment for the majority of patients by the early 1980s. Cisplatin and Carboplatin which increased the response rates and the median survival periods in most studies were introduced in the 1980s. [30]. In this decade, the publicized guidance documents indicated further that the necessity for efficacy should be verified by elongation of life, a higher quality of life (e.g. symptomatic relief), or a recognized substitute for at minimum one of these [31]. Numerous trials that compared chemotherapy to best supportive care in 1980s showed the benefit of systemic chemotherapy in treatment of lung cancer [32].

#### **The 1990s**

The 1990s witnessed the launch of the targeted therapy. The first tyrosine kinase inhibitor imatinib mesylate became available for general use in 1996 [33], which led to a dramatic change in the treatment and outcome of human myelogenous leukemia. Data generated from genome sequencing created a focal point for further drug development research suggesting that the abnormal function of protein kinases led to a lot of the abnormalities of

cancer cells [14]. Treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors was revolutionized by the introduction of protein kinase inhibitors as imatinib [33]. Chemotherapy has significantly decreased the rate of breast cancer recurrence, and by the 1990s, it was recommended for women presenting with stages I through III breast cancer [34]. Most importantly, monoclonal antibodies (MAbs) were introduced in the 1990s. The combination of MAbs with chemotherapy improved the efficacy of treatment through allowing for targeting of specific cancer cell receptors; Rituximab was the first released Mab [7].

#### **The 2000s**

##### **Topotecan**

Topotecan is a drug originating from a family of chemotherapeutic agents that inhibit the DNA topoisomerase I enzyme. The DNA topoisomerase I enzyme is responsible for relaxing a supercoiled DNA helix during DNA synthesis. Topoisomerase I inhibitors stabilize the DNA enzyme complex to inhibit the religation step of the enzymatic reaction. It then causes accumulation of persistent single strand DNA breaks. After the inhibition of the enzyme, it is not clear how the camptothecins cause cell death. Camptothecin, the parent drug, is a plant alkaloid extract derived from the oriental tree *Camptotheca acuminata*. Topotecan is a water-soluble analog. Topotecan is excreted in urine and is concentrated in bile. O'Reilly et al. [35] found that dose adjustments should be made in patients with reduced renal function. Patients who had been heavily pretreated with other chemotherapy agents and lower creatinine clearances had worse toxicities at 1.5 mg/m<sup>2</sup>/d given i.v. over 30 min for five days. Cycles were repeated every 21 days. In patients with creatinine clearances of 20-39 ml/min, and 40-59 ml/min, the dose of topotecan should be reduced to 0.5 mg/m<sup>2</sup>/d and 1.0 mg/m<sup>2</sup>/d, respectively. The dose of topotecan does not have to be adjusted for abnormal liver function if the bilirubin is less than 10 mg/dl. Topotecan is a relatively well-tolerated drug. Hematologic toxicity, mainly neutropenia, is the dose-limiting toxicity, in addition to anemia and thrombocytopenia [35, 36].

##### **Pegylated liposomal doxorubicin**

Pegylated liposomal doxorubicin is one of drug formulations that is delivered in vesicles called liposomes. Bilayer sphere of lipids encapsulates doxorubicin molecules in pegylated liposomal doxorubicin. This vesicle is then surrounded by a dense layer of polyethylene glycol (PEG), hence the name pegylated liposomal doxorubicin. The size of the liposomes, approximately 100 nm, prevents them from entering tissues with tight capillary junctions, such as the heart and gastrointestinal tract, as well as selectively depositing the liposome into the tumor [37].

In contrast to normal vessels, the vessels of the tumor are tortuous, dilated, have morphologically abnormal endothelial cells, and are leaky due to large spaces between pericytes [38]. These physical characteristics allow more extravasation of the vesicles into the tumor, thus encouraging more deposition of the chemotherapy agent into the tumor. The PEG coating on the liposome creates a hydrophilic layer around the liposome that buffers the liposome wall from the surrounding milieu. This decreases proteins from binding to the lipid bilayer. These proteins act as opsonins, attracting foreign particles that in and returned to the circulation. In tumor tissue, however, there are no lymphatics. Therefore, when the liposome is deposited it remains for a longer time. This allows a higher dose of doxorubicin to be released in the tumor, and a lower dose in normal tissue [39]. Collectively, there is preferential uptake and decreased clearance of the drug delivery system, increasing the exposure of the tumor to the drug. This was termed by Cattel et al. [40] as the enhanced permeation retention effect.

## Bendamustine

Bendamustine was approved for the treatment of chronic lymphocytic leukemia (CLL) based on a randomized, international, multicenter, open-label phase 3 study that compared the drug with chlorambucil [41]. Bendamustine has demonstrated clinical activity against various cancers, including non-Hodgkin's lymphoma (NHL), multiple myelomas, breast cancers, small-cell lung cancer, and other solid tumors [42-50].

In preclinical studies, Bendamustine displayed a unique profile compared with other alkylating agents; it exhibits several mechanisms of action, including induction of cell necrosis and apoptosis, activation of DNA repair by base excision, and inhibition of mitotic checkpoints [51].

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