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REVIEW

The contribution of Gianni Bonadonna to the history of chemotherapy

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Abstract The history of cancer chemotherapy and of the discipline of medical oncology has been that of drug discovery. The pioneering discoveries of the early days of chemotherapy have allowed the development of a paradigm for drug discovery that persists, with modifications to the present day. This review article summarizes the seminal work of the Italian scientist Gianni Bonadonna on the treatment of breast cancer and Hodgkin's disease.

Keywords Breast cancer · Chemotherapy · History of medicine · Hodgkin's disease · Tumor

Historical background

The German scientist, Paul Ehrlich (1845–1915), coined the word "chemotherapy" in reference to the systemic treatment of both infectious diseases and neoplasms. Ehrlich's use of in vivo rodent model systems to develop antibiotics for the treatment of infectious diseases led Georges Lowes, at Roswell Park Memorial Institute in Buffalo, New York, in the early 1900s, to develop inbred rodents lines bearing transplanted tumor that could be used to screen potential anticancer drugs. This in vivo system provided the foundation for mass screening of novel compounds [1]. Alkylating agents represent the first class of chemotherapeutic drugs to be used in clinical settings.

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The introduction of chemotherapy in the fifth and sixth decades of the 20th century has resulted in the development of curative therapeutic interventions for patients with several types of advanced solid tumors and hematologic neoplasms.

In the past four decades, the clinical oncologist Gianni Bonadonna, working in the Department of Medical Oncology of the "Istituto Nazionale Tumori" in Milan, Italy, introduced two extremely innovative protocols for the treatment of breast cancer and Hodgkin's disease. Here, an overview of these two milestones in the history of chemotherapy is traced.

The cyclophosphamide, methotrexate and fluorouracil (CMF) regimen in the treatment of breast cancer

Up to the mid-1970s, the treatment strategy for primary breast cancer based on radical (and even superradical) resection of the primary tumor, en bloc with full dissection of axillary content, represented the unchallenged curative method [2].

Over the past three decades, revolutionary changes have occurred in the locoregional management of primary breast cancer. As a result, radical and extended radical mastectomy have been relegated in the archives of surgical history and today there are few, if any, indications for radical mastectomy.

The first trials of adjuvant chemotherapy in the treatment of breast cancer were launched in the 1950s, but it was not until the late 1960s that the first modern trials of combination chemotherapy were initiated. Since the 1970s, randomized trials have addressed many fundamental questions related to adjuvant chemotherapy.

In May 1972, Paul P. Carbone of the National Cancer Institute (NCI) showed Bonadonna the Medicine Branch Annual Report, including the initial NCI data on a quadruple drug regimen, cyclophosphamide, metotrexate, fluorouracil and prednisone (CMFP). The results of the study conducted in clinical disseminated breast cancer and published later by Canellos et al. [3, 4] showed a remarkable response rate (complete remission, 20%; partial remission, 40%) with a median duration of response of 8 months. Combination chemotherapy was developed based on the rationale that combining agents with different mechanisms of action and non-overlapping toxicities would increase treatment benefit, prevent or delay the emergence of drug resistance without significantly worsening morbidity or quality of life.

Using the large case series of breast cancer patients available at the Milan Cancer Institute, Bonadonna drafted two CMF protocols, one for clinically advanced breast cancer and the other for surgically resectable tumors with histologically positive axillary nodes. Carbone, together with Pietro Becalossi and Umberto Veronesi in Milan, approved and supported Bonadonna's proposal.

Bonadonna and co-workers first started the trial on advanced breast cancer, and their findings with CMF [5, 6] were similar to those obtained by the Eastern Cooperative Oncology Group (ECOG) [7].

In 1976, Bonadonna et al. [8] presented the first report on the efficacy of CMF as adjuvant treatment for node-positive breast cancer. These results, along with those reported in a similar population of patients by the National Surgical Adjuvant Breast Project [9], raised hopes that chemotherapy could have a more central role in the primary management of breast cancer.

The ease of administration and the virtual absence of severe acute toxicity made CMF the most frequently used combination of drugs in clinical practice in oncology, as well as the regimen against which all new systemic adjuvant treatments were tested.

In 1995, Bonadonna et al. [10] reported the results of 20 years of follow-up of their original series of women, who had a radical mastectomy and who were randomly assigned to receive no further treatment of CFM chemotherapy for 12 monthly cycles. The long-term results continued to show a significant overall benefit for adjuvant chemotherapy.

In 2005, Bonadonna et al. [11] reported the results of 30 years of follow-up and confirmed that the effects of such a regimen are long lasting and may benefit patients with favorable and unfavorable prognostic indicators, at the cost of minimal long-term sequelae. Moreover, the poor prognosis associated with unfavorable indicators in patients treated locoregionally alone was improved by the administration of adjuvant CMF.

The adriamycin, bleomycin, vinblastine and dacarbazide (ABVD) regimen in the treatment of Hodgkin's disease

Among the unexpected results of the both World Wars was the development of the highly toxic, but therapeutically useful mustard gas derivative, nitrogen mustard [methyl bis(beta-chloroethyl) amine]. The observation made during the First World War that mustard gas poisoning caused leukopenia and the exposure of military seamen to mustard gas in the Second World War, as a consequence of the explosion of a ship containing material manufactured for use in chemical warfare, led to the observation that alkylating agents caused marrow and lymphoid hypoplasia [12, 13].

Gilman and Philips [14] conducted the first clinical trial with nitrogen mustard in patients with malignant lymphomas at Yale University in 1942. This material was the first modern antitumor drug to regularly produce significant response in Hodgkin's disease [15].

Before 1960, chemotherapeutic agents to treat Hodgkin's disease were used only for palliation. The first chemotherapy study to have an impact on the management of patients with Hodgkin's disease was published in 1963 [16]. Of the 89 patients with advanced Hodgkin's disease who received a conventional induction course of nitrogen mustard, 40 patients with satisfactory response were randomized to receive either no further treatment or continuous treatment with the newly developed oral alkylating agent, chlorambucil. In 16 patients who received chlorambucil, the time for relapse averaged 35 weeks compared with 11.7 weeks without further treatment.

The treatment of Hodgkin's disease with multiple chemotherapeutic agents was developed from sequential studies defining curative treatment for acute lymphoblastic leukemia in children [17]. In 1963, a pilot study was initiated to test the feasibility of using a combination of chemotherapeutic agents, cyclophosphamide, vincristine, methotrexate and prednisone, followed by radiation therapy for the treatment of Hodgkin's disease [18].

In 1964, the nitrogen mustard, vincristine, prednisone, procarbazine (MOPP, "M" for nitrogen mustard, "O" for oncovin, the brand name for vincristine, and "PP" for prednisone and procarbazine) scheme was conceived, following the initial report by Lacher and Durant [19], employing chlorambucil and vinblastine

in combination, and was the first regimen to achieve cure in a proportion of patients with advanced lymphoma [20]. An 80% complete remission rate was noted. This was a fourfold increase over results achieved with the best use of single agents of the day, and those remissions proved durable and appeared to influence survival. The impressive survival curves in MOPP-treated patients published in 1970 indicated that it was possible to cure advanced Hodgkin's disease with combination chemotherapy.

In 1975, investigators at the NCI [21] reported the cure of a small number of patients with advanced stage diffuse large cell lymphoma with the C-MOPP (cyclophosphamide, vincristine, prednisone, procarbazine) drug combination. The next year, the first of many reports appeared attesting the efficacy of the doxorubicin-containing CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen in intermediate- and high-grade lymphomas.

The observation that approximately 20% of the treated patients failed to achieve complete remission of their lymphoma, coupled with the relative insensitivity of the tumor patients who experienced short remissions, suggested that the primary cause of treatment failure was the presence and overgrowth of cells resistant to the drugs in the MOPP regimen.

Following the introduction of MOPP for the treatment of Hodgkin's disease, other effective drug combinations were reported of which the ABVD program was developed by Bonadonna et al. [22]. This four-drug regimen included adriamycin, a new anticancer antibiotic, available for clinical use in the summer of 1968, bleomycin, vinblastine and dacarbazide. The selection of the four agents was based on the evidence of the anti-lymphoma properties of each individual drug and on their non-overlapping sensitivity profiles with MOPP.

A randomized trial was mounted in 1973 to test whether ABVD chemotherapy could induce a complete remission comparable with that of MOPP chemotherapy [23]. Overall, six cycles of either regimen yielded a comparable incidence of complete remission, and this trend had an influence on the 5-year freedom from progression and relapse-free survival rates. This study showed that ABVD was as effective as MOPP in inducing durable remission in advanced Hodgkin's disease.

Later, a larger randomized study, which also included radiation therapy, proved that ABVD was able to improve long-term treatment outcome compared to MOPP [24]. The higher therapeutic activity of ABVD, which is easy to administer, devoid of severe side effects and well tolerated by the patients, was confirmed in many other studies. Salvage treatment with ABVD in patients failing during or soon after MOPP yielded higher complete remission rates (46%) compared with the opposite sequence, i.e., salvage MOPP in ABVD-resistant patients. In the first study, Bonadonna and Santoro [25] compared the efficacy of ABVD vs. MOPP in advanced Hodgkin's disease previously untreated with chemotherapy and, thorough a cross-over design, they tested each regimen in resistant patients [26]. The following study aimed at assessing the relative efficacy and long-term complications of a combined modality approach, with three cycles of either MOPP or ABVD delivered before and after extensive irradiation in patients with stage II B and III disease [27].

In the third study, Bonadonna et al. [28] designed an effective light-drug program, alternating cycles of MOPP and ABVD. The findings demonstrated a superiority of the alternating regimen over MOPP alone in the achievement of complete remission. This regimen was particularly effective for those with advanced and symptomatic Hodgkin's disease (stages III B and IV B). A further study reported the results of a new trial aimed at assessing whether a more rapid alternation of the eight drugs could improve the treatment outcome [29].

These treatment findings, along with those reported in randomized studies conducted by the cancer and leukaemia group (CALBG) [30] and by the North American Intergroup Study, in which the MOPP/ABVD hybrid regimen was tested against ABVD [31], confirm that ABVD should be considered the standard regimen for the treatment of Hodgkin's disease.

Over the past 25 years, the ABVD regimen has gradually replaced the MOPP regimen as the most commonly used chemotherapeutic regimen for all stages in Hodgkin's disease. In head-to-head trials, it has been found to be superior to MOPP in both early-stage and advanced-stage disease [30]. Although the regimen carries some risk of cardiac and pulmonary toxicity, it is not associated with leukemogenesis or sterility, the two major complications associated with MOPP.

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