Intensive Combination Chemotherapy and X-Irradiation in Hodgkin’s Disease

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See related article by Moxley et al., Cancer Res 1967;27:1258–63.

This article was a pilot study of the first attempt to cure an advanced solid tumor, in this case Hodgkin disease, with combination chemotherapy (1). It was very controversial. Virtually no one at the time believed it was possible to cure cancer with drugs. Furthermore, it was a general tenet of medicine then that drugs, for any disease, should not be used in combination. The administration of combinations of cytotoxic anticancer drugs was therefore considered a radical departure from the norm. The conflict and hostility that surrounded these early attempts to cure cancer with chemotherapy are described in detail in a recent book by V.T. DeVita, Jr. and E. DeVita-Raeburn, The Death of Cancer (Farrar Straus Giroux, 2015).

There were three circumstances that led coauthors J.H. Moxley and V.T. DeVita, Jr. to design the study. The first was the publication of an article by Easson and Russell entitled “The Cure of Hodgkin’s Disease” (2). The article addressed the use of radiotherapy for early disease. But it was the title, more than the content, which helped trigger the thought of doing a similar study using combination chemotherapy. The second was ongoing research at the National Cancer Institute at the time with childhood leukemia. Frei and Freireich were experimenting with a four drug combination called VAMP (vincristine, amethopterin, 6-mercaptopurine, and prednisone), designed with the specific intent to eradicate all leukemia cells in children with leukemia (3). The third was the work of Howard Skipper at the Southern Research Institute. Skipper reported that, with special attention to leukemia cell kinetics, dosing, and scheduling, mice bearing leukemia 1210 could be cured of their disease using combinations of four active drugs (4).

The Hodgkin study, called MOMP, after the first initials of the drugs used, needed to take into account that Hodgkin disease was a disease of the lymph nodes and major organ systems, whereas leukemia was a disease of the bone marrow and blood. In leukemia, the bone marrow was the point of attack. In treating Hodgkin disease, the bone marrow needed to be preserved. Another major challenge was the need (based on the work of Frei, Freireich, and Skipper) for a minimum of four drugs active against Hodgkin disease that could be given in full doses. Nitrogen mustard was the standard at the time and was the first drug selected. The new vinca alkaloids, vinblastine and vincristine, were being actively tested against lymphomas and leukemias. Vinblastine was thought to be the preferred agent in Hodgkin disease, but the bone marrow toxicity of vinblastine and nitrogen mustard overlapped. A more detailed analysis of the data by the authors suggested that vincristine, with little or no marrow toxicity, was equally active, so vincristine was selected as the second drug (“O” for Oncovin, the brand name for vincristine; ref. 5). Prednisone was the third drug, but there was no known active fourth drug. Procarbazine, then called ibenzmethazin, was in early trials in Hodgkin disease at NCI, but the data was thought to be insufficient to include at the time. Without a better option, methotrexate, an active antileukemia agent, was selected on the basis of meager data of activity against lymphomas and was used in a schedule that had been derived from mouse models and was used to treat acute childhood leukemia.

The number of patients in the study (14) was, at the time, the standard design of a phase II study, the rule of thumb being that if no one responded, the drug or treatment program would be discarded. If two or more responded, then further study was indicated.

Because of the influence of the article by Easson and Russell (2), all patients were seen by a radiotherapist in consultation. If they had disease deemed treatable by radiotherapy, they were treated after the first cycle of chemotherapy was completed to allow the assessment of the effects of chemotherapy on measurable disease. The second cycle of chemotherapy began after radiotherapy was completed. Nine of the 14 patients received some form of radiotherapy to involved nodes only.

Three cycles of MOMP were given. Vincristine and nitrogen mustard were given in full doses on days 1 and 8. Prednisone was given continuously daily orally for 3 months at a dose of 60 mgs/sq. meter. Methotrexate was given intramuscularly at a dose of 30 mgs/sq. meter on days 1, 4, 8, and 11 of each of three cycles. After the last dose of methotrexate, no therapy except for prednisone was given for a minimum of 10 days or until complete recovery of blood counts. As a precaution, all patients were treated in reverse isolation.

Remarkably, 12 of 14 patients achieved a complete remission. All 9 patients treated with radiotherapy went into remission before radiotherapy was given. Nine of 12 patients stayed in complete remission. Two patients were still responding to chemotherapy at the end of three cycles, but therapy was stopped according to protocol nonetheless.

Toxicity was severe. There were no drugs available then to treat nausea and vomiting, and all patients suffered from both. All of the patients also developed neurologic toxicity from vincristine, although this was manageable. All 14 patients developed severe mouth ulcers from methotrexate and Cushingoide features from the continuous dosing of prednisone. Some degree of leukopenia was universal, although only one patient developed febrile leukopenia. This patient recovered with antibiotics.

The pilot trial was a success. The therapy easily passed the phase II test for responses and the toxicity was manageable.

The MOMP study that had begun in the fall of 1963 was presented at the 1965 meeting of the American Association for Cancer Research. Despite its novelty and its relative success, however, it attracted no particular notice, except for the concern...
about toxicity and the use of the term "complete remission," heretofore reserved only for use in leukemia. This was due, in part, to the small study size and the complicated addition of radiotherapy to the treatment protocol. But general disbelief in the effectiveness of chemotherapy for cancer also played a role.

Despite its lukewarm reception, MOMP was an important landmark in the history of chemotherapy, and it had a profound influence on the design of the next trial, which would be named MOPP (nitrogen mustard, Oncovin, procarbazine, and prednisone). MOPP would prove the definitive therapy of advanced Hodgkin disease.

MOPP was an improvement on MOMP. While the MOMP trial was proceeding, experimentation with procarbazine proceeded to the point where it was evident that it had clear and unique activity against Hodgkin disease. In MOPP, therefore, procarbazine replaced the toxic methotrexate in MOMP (6). The dosing and duration of treatment of MOPP was also an improvement upon its predecessor. Studies using the new isotope, tritiated thymidine, led to cell kinetic data in mice and humans that clarified the different growth characteristics of leukemia and solid tumors and bone marrow in mouse and man (7–9). Because of a much lower growth fraction in solid tumors compared with leukemia, it was thought that an ideal duration of treatment would be at a minimum 6 months, and the marrow regeneration time of human marrow would require a minimum of two weeks between cycles of therapy. To avoid the development of resistance and to prevent tumor growth between cycles, a strict schedule was developed for MOPP that required repeat cycles every 28 days regardless of blood counts. To accomplish this, a sliding scale was used to reduce doses proportional to the blood counts, assuring the administration of some fraction of all four drugs for each cycle.

A unique rule was also created with regard to the duration of therapy. Two patients in the MOMP trial were still responding when treatment was stopped because the protocol dictated an end at three cycles. In hindsight, this had clearly been a missed opportunity for these patients. To avoid this, MOPP was given for a minimum of six cycles or until two cycles beyond achievement of complete remission. These changes were an even more radical departure from standard therapy than with MOMP. They introduced a unique degree of flexibility in a treatment protocol based on the response of both the patient’s bone marrow and their tumor.

MOPP was presented at the American Association for Cancer Research meeting in 1967 and was published in 1970. Eighty percent of patients with very advanced disease went into complete remission and 40 years later, over half of those patients are alive, continuously free of disease. It revolutionized the treatment of advanced Hodgkin disease (10) and became the standard treatment for advanced Hodgkin disease for over 25 years. MOPP provided proof of principle that advanced cancers of a major organ system in adults could be cured by combination chemotherapy. All subsequent treatment programs for Hodgkin disease and other malignancies were based on the principles developed in the MOMP and MOPP programs and are still in use in protocols today.

Within a decade of the development of the MOMP protocol, the mortality rates for Hodgkin disease in the United States had declined by almost 70%. Today, 85% of all cases of Hodgkin disease are curable, almost all by using combination chemotherapy alone or in combination with radiotherapy.

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References
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