

This Week's Citation Classic

DeVita V T, Serpick A A & Carbone P P. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann. Intern. Med.* 73: 881-95, 1970.

The paper reported two new and excitingly different results; a quadrupling of the number of patients with Hodgkin's disease who achieved complete remission (disappearance of all evidence of tumor) after treatment with a four drug combination (MOPP) (80% vs. 20% for single drug treatment). The second and most important observation reported was that over half of patients who had achieved complete remission had not developed recurrences with five years of followup after all treatment had been discontinued. It was one of the few papers in the cancer treatment field reported with sufficient follow time to give data on survival and relapse free survival, both of which were strikingly different from past experience. [The *SCⁱ*® indicates that this paper has been cited over 390 times since 1970]

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"This paper reported the results of our second attempt to develop a curative drug treatment for advanced Hodgkin's disease. This was a pilot trial to test the safety of the general approach. The second, now commonly referred to as the "MOPP" study, after the first initials of the drugs used (Nitrogen Mustard, Vincristin [Oncovin®], Prednisone and Procarbazine), was developed to incorporate new information suggesting an advantage of the then new drug, procarbazine, that led us to use it instead of an older drug methotrexate, used in the first program. In retrospect, all of us recall the trepidation with which we approached both trials. Although MOPP is now the standard drug treatment for advanced Hodgkin's disease, and used routinely as outpatient therapy, all of the groups of patients were hospitalized because of our fear of toxicity. We discussed cure as our goal, but we did so softly, since the use of the word cure in conjunction with treatment of patients with metastatic cancer was not academically acceptable in 1963 when this program was first started.

"It is worth noting how something representing as radical a departure from medical practice as MOPP got started. First, the investigators involved were relatively

new in the field and not jaded by what more experienced hematologists taught was not possible. Second, the environment of the

Clinical Center at the NIH, where the study was conducted, provided a buffer from the normal restraints of standard medical practice. These two facts allowed us to take advantage of principles developed in rodent tumor models and bring them rapidly to the clinic. The principles used to design MOPP were fourfold: (1) The use of individually effective non-cross-resistant drugs, in combination, in full doses, with a reasonable expectation of additive or even synergistic anti-tumor effects, (2) intermittent cycled administration of drugs at intervals calculated to match recovery of human bone marrow (laboratory data indicated marrow recovery 21-28 days after a toxic insult and MOPP was cycled at 28 days). Recovery of bone marrow turned out to be the rate limiting step for repeated cycles of drugs and the 28 day cycle still appears ideal. (3) The selection of agents with differing mechanisms of action and differing toxicities. For example, vincristine (minimally toxic to bone marrow) instead of vinblastine (marrow toxic) to minimize the side effects to the most sensitive organ, the bone marrow. (4) A long duration of treatment (6 months) as opposed to the practice at the time of treating for six week periods.

"Although it doesn't seem so now, these were all radical ideas. The intensity and duration of treatment and the use of drugs in combination were not medically sanctioned approaches to the treatment of any disease at the time. The example of the misuse of antibiotics in combination to treat infectious diseases was often cited to us as reason for not taking this approach. The results, reported in 1970, were dramatically different from those previously possible with older approaches. The article is often cited, I suppose, because the MOPP program results have since been amply confirmed and proven durable. A ten year followup report has shown that 66% of all patients who achieved remission have not developed tumor recurrences. We think these patients are rightfully considered cured of their disease. The MOPP program remains the best drug combination for treating advanced Hodgkin's disease attesting to the validity of the principles that led to its design."