

## Historical Review

### A SELECTIVE HISTORY OF THE THERAPY OF HODGKIN'S DISEASE

This is, for the most part, the history of the development of curative combination chemotherapy for Hodgkin's disease, and its consequences, from 1963 up to the early 1990s [the MOPP (nitrogen mustard, oncovin, procarbazine, prednisone) programme]. Coupled with radiotherapy, it had a major impact on the management of the disease. It is also heavily weighted towards the description of the events that occurred at the Medicine Branch of the National Cancer Institute (NCI) in Bethesda, MD, USA, between 1963 and the early 1990s. To this is added a brief description of the follow-up development of the ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) treatment drug programme by the group in Milan, Italy. The latter added significantly to the therapeutic armamentarium available to physicians in the 1970s and beyond.

This selective history is perhaps justified because, although the focus of the studies discussed below was on Hodgkin's disease, there was a more important issue involved. A new breed of cancer investigators in the 1960s had been addressing the generic question of whether or not cytotoxic chemotherapy was ever capable of curing patients with any type of advanced malignancies. The answer would turn out to be 'yes', and this affirmative answer enabled chemotherapy to be used in many other tumours and, notably, in the adjuvant setting after treatment of apparently localized disease.

The question was addressed in two important human models, childhood acute leukaemia (Frei & Freireich, 1965) and Hodgkin's disease, and used combination chemotherapy, a concept that deviated from the practice of the time. The response in the academic community to this radical departure from dogma was initially quite negative. The protected environment of The Medicine Branch, at the Clinical Center of the NCI, facilitated studies in both diseases, under the inspired leadership of Dr Emil Frei, who was Chief until 1965 (Fig 1). In recounting these events, the novelty of the approaches and study results do not seem so radical in retrospect, but they were.

At the time the programmes began at the NCI, radiation therapy was already established for Hodgkin's disease patients presenting with apparently localized disease. We did not know the aetiology of Hodgkin's disease or the cellular origin of the Reed–Sternberg cell that characterizes the disease. Medical oncology, as a speciality, had not yet appeared on the scene. Physicians who would become the medical oncologists of the future worked with therapeutic radiologists and pathologists to integrate newer methods of diagnosis, staging and radiotherapy with the newly developed chemotherapy programmes and converted Hodgkin's disease from a largely fatal to a largely curable disease.

For the integration of chemotherapy and radiotherapy in Hodgkin's disease, we owe a debt of gratitude to the late Henry Kaplan (Fig 2), who was unique in his field in recognizing the value of the new chemotherapy. He set in motion a brilliant series of studies of the use of MOPP and radiotherapy at Stanford University in the late 1960s and 1970s that still serve as a model of clinical investigations (Kaplan, 1962, 1966; Kaplan & Rosenberg, 1966; Kaplan *et al.*, 1973). Curative chemotherapy had provided the missing link in the therapeutic equation.

The group of senior faculty members from the Medicine Branch, shown in Fig 3, went on to apply these same principles to other cancers (Bagley *et al.*, 1972; Canellos *et al.*, 1974). The development of the CMF programme (cyclophosphamide, methotrexate and 5-fluorouracil) for breast cancer (Canellos *et al.*, 1974) and the NCI's contract with the Istituto Tumori in Milan, Italy, to test it in the adjuvant situation helped to set in motion a similar series of events in breast cancer.

The author (Fig 4) chose to end this tale in the early 1990s because, at that point, we entered a new era of treatment for Hodgkin's disease. Investigators began to focus on the problems of curing a minority of patients not cured by the initial programmes and reducing the morbidity of treatment revealed in long-term follow-up studies. A daunting task, but another story entirely.

### EARLY RADIATION THERAPY FOR HODGKIN'S DISEASE

Pusey first used radiotherapy to treat Hodgkin's disease in 1902 (Pusey, 1902), only 8 years after Roentgen rays were discovered. The important observation that Hodgkin's disease spread by contiguity is owed to several investigators, most notably the Swiss radiotherapist Renee Gilbert in the 1920s (Gilbert, 1925) and the Canadian radiotherapist Vera Peters in the 1950s (Peters, 1950; Peters & Middlemiss, 1958). These observations had important implications for radiotherapy, as fields could now be shaped to encompass areas of presumed contiguous spread.

By observing the natural history of the disease in large patient populations, Vera Peters (Peters, 1966) and Henry Kaplan (Kaplan *et al.*, 1973) were able to map the patterns of spread and apply appropriate radiotherapy fields (Rosenberg & Kaplan, 1966). Although Vera Peters implied that the disease was curable (Peters & Middlemiss, 1958), it was Easson and Russell from the Christie Hospital, Manchester, UK, using her data, who first broached the subject of 'The Cure of Hodgkin's disease' (Easson & Russell, 1963). It was a sign of the pessimism of the times that the title was



Fig 1. Dr Emil (Tom) Frei in Bethesda in the 1960s. Chief of Medicine at the NCI until 1965. Photograph from the author's collection.

considered provocative and controversial. It was Kaplan who made the point that localized Hodgkin's disease could be cured by radiotherapy with finality and conducted the trials to show the doses and extent of radiotherapy necessary to cure early stages of the disease.

At Kaplan's insistence, a conference of leading investigators was convened in Rye, New York, in 1966 that not only married the new histological classification developed by Lukes & Butler (1966) to treatment, but laid out the principles of staging necessary for an orderly approach to treatment. Combination chemotherapy was just in its seminal phase at this time but already the cure of localized stages with good radiotherapy was noted to be about 30%.

#### THE EVOLUTION OF THE CHEMOTHERAPY OF HODGKIN'S DISEASE

In the early 1960s, the debate that dominated chemotherapy was not could it cure, but whether or not the palliation achievable was worth the toxicity associated with anticancer drugs. The first chemotherapy study to have an impact on the management of patients with Hodgkin's disease was published in 1963 (Scott, 1963). Eighty-nine patients with advanced Hodgkin's disease received a conventional induction course of nitrogen mustard (0.4 mg/kg), of whom 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 the 16 patients who received chlorambucil, the time to relapse averaged 35 weeks compared with 11.7 weeks without further treatment. This highly significant difference

in the duration of a 'satisfactory remission' provided the first useful information on alternatives in the day-to-day management of patients with Hodgkin's disease. No mention was made in this study, however, as to whether any survival benefit accrued to the patients maintained on chlorambucil. A report by Jacobs *et al* (1968) presented one of the first survival curves published in the modern chemotherapy era. Drug treatment in patients with advanced Hodgkin's disease was associated with a median survival of less than 2 years, with only 5% living beyond 4 years, all with evidence of disease, only slightly superior to patients left untreated for the entire course of their disease (Craft, 1940) (Fig 5).

The next major advance came with the identification of the antitumour activity of the plant-derived natural products, the vinca alkaloids. The availability of two non-cross-resistant classes of antitumour agents and the conceptual separation of induction and maintenance therapy gave impetus to a large study initiated through the combined effort of two clinical co-operative groups supported by the NCI (Acute Leukaemia Group B and the Eastern Solid Tumor Group). The principal investigator was the late Paul Carbone of the NCI's Medicine Branch (Carbone *et al*, 1968).

Patients were randomized by disease and prior therapy to remission induction with cyclophosphamide or one of the vinca alkaloids. The objectives of this study were to compare the effectiveness of the vinca alkaloids with an alkylating agent in remission induction in lymphomas. Patients received either cyclophosphamide or placebo to maintain the remission, which enabled the effectiveness of continuous

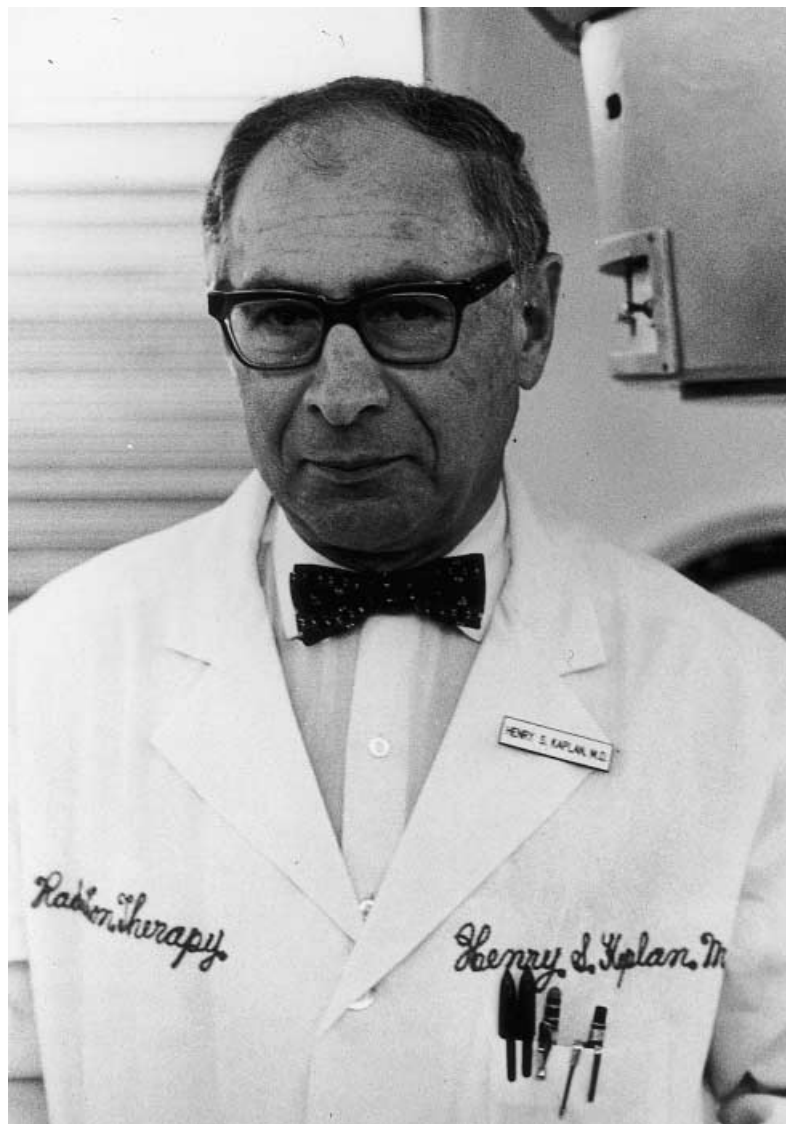


Fig 2. The late Harry Kaplan at Stanford in the early 1970s. Photograph from the author's collection.

therapy to be compared with intermittent treatment with cyclophosphamide at the time of disease progression. The results of this study established the superiority of vinblastine over cyclophosphamide in patients with Hodgkin's disease. In all disease categories, the average duration of placebo-maintained remission was a remarkably short 4–6 weeks, irrespective of the drug used to induce remission. Daily oral cyclophosphamide significantly prolonged remission duration when compared with placebo, confirming the observation of Scott (1963). Remission duration with drug maintenance treatment was, however, only 32 weeks for Hodgkin's disease.

Two features of this study influenced the studies designed later by NCI investigators. First, patients were separated by whether they had partial or complete remissions, a practice used to evaluate treatments in leukaemias but not generally used at that time in 'solid tumours'. Secondly, regardless of the approach to treatment, overall survival in the various

subgroups in each disease category was almost identical. Those data enabled investigators at the NCI, using the first combination chemotherapy programmes, to set achieving a high complete remission rate as their major initial goal in the first combination chemotherapy programme, and to leave patients who attained a complete remission off therapy to evaluate the capacity of their new treatment programme to eradicate the tumour permanently.

The appearance of vinca alkaloids was followed shortly by the discovery of the antitumour activity of the methylhydrazine derivative, procarbazine, then called ibenzmen-thylin, in Hodgkin's disease (Bollag & Grunberg, 1963; Mathe *et al*, 1963; DeVita *et al*, 1965a).

#### THE BIRTH OF COMBINATION CHEMOTHERAPY

The first intensive drug combination programme designed to exploit the new principles of chemotherapy in Hodgkin's



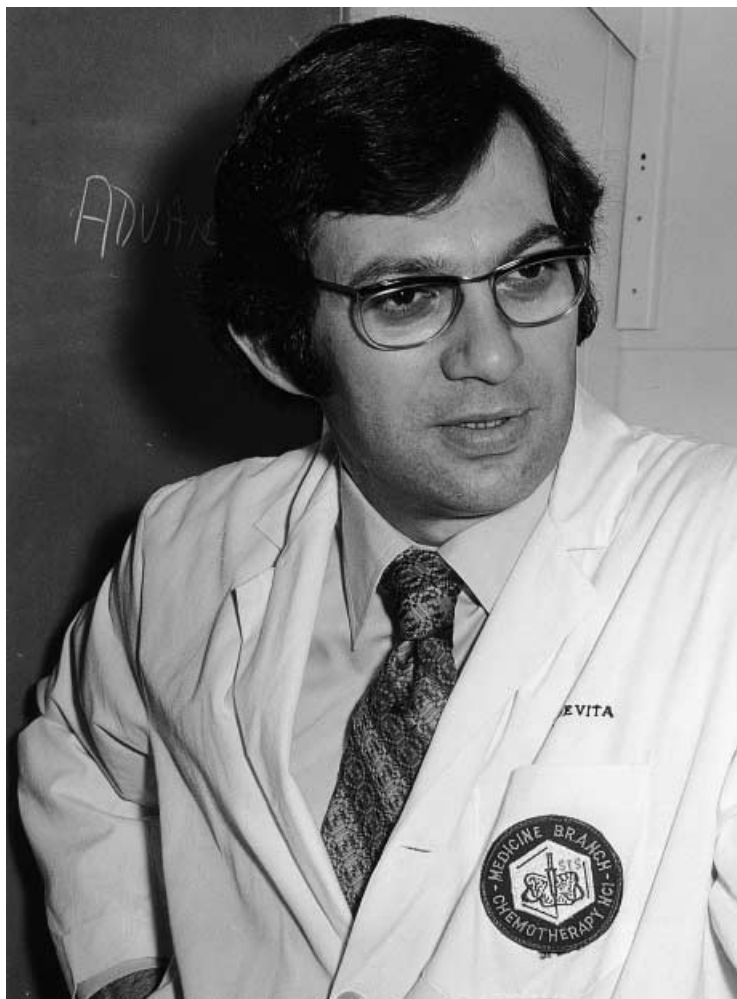
**Fig 3.** The author, then Chief of Medicine at the NCI (second from right), with the senior faculty of the Branch who played a role in advancing the studies on all the lymphomas. Left to right: Drs George Canellos, Bruce Chabner, Phillip Schein, the author and Robert Young (about 1970). Photograph from the author's collection.

disease began at the NCI in 1963 and used the combination of vincristine, methotrexate, cyclophosphamide and prednisone (MOMP) given for only 2.5 months (DeVita *et al.*, 1965b; Moxley *et al.*, 1967). The goal of this pilot protocol was to test the safety of combination chemotherapy in advanced Hodgkin's disease. The vinca alkaloid, vincristine, was selected over vinblastine because it has little associated marrow toxicity, and preclinical studies suggested therapeutic effects equal to vinblastine. In an era devoid of reliable methods to support patients during periods of bone marrow suppression, this was an important issue. Only 14 patients were treated with MOMP, and all were hospitalized and kept in reverse isolation. This small study showed that the approach was safe. In 1964, the MOMP programme was modified in several ways.

At that time, most data on the doses and schedules of anticancer drugs in humans were derived and translated directly to the clinic from tumour-bearing mouse models. But, comparative cell kinetic data in mouse and human tumours had shown much-prolonged human tumour cell

cycle times, compared with the mouse (Yankee *et al.*, 1967; Young & DeVita, 1970; DeVita, 1971; DeVita & Schein, 1973). So, the duration of MOPP treatment was increased from 2.5 months, the standard of the time, to 6 months. And, procarbazine, by now an agent known to be active in Hodgkin's disease, was substituted for the antifol methotrexate. Each drug was used in its optimal dose and schedule. This new programme was named MOPP ('M' for nitrogen mustard, 'O' for oncovin, the brand name for vincristine, and 'PP' for procarbazine and prednisone).

Cyclical administration every 28 d was introduced, and the interval selected between cycles was the narrowest possible to allow for recovery of the most sensitive normal target tissue, the bone marrow. Again, cell kinetic studies on the mouse bone marrow, compared with humans, showed that, like mouse and human tumours, the kinetics of human marrow were also quite prolonged compared with the mouse (Yankee *et al.*, 1967; DeVita *et al.*, 1969a; Young & DeVita, 1970; DeVita, 1971). Thus, for patients whose



**Fig 4.** The author in the Medicine Branch of the NCI in 1968. Photograph from the author's collection.

tumour, unlike leukaemia, infrequently involved bone marrow, adjustments in schedules were made to introduce wider intervals between treatments than previously allowed.

In 1967, the results of the use of MOPP in the first 43 chemotherapy-naïve patients were reported in abstract form, and formal results were published in 1970 (DeVita *et al*, 1970). 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 survival of treated patients was impressively different from those treated with single agents (Fig 6). British investigators, under the leadership of the late G. Hamilton Fairley, confirmed the effectiveness of combination chemotherapy with a modified version of MOPP (Nicholson *et al*, 1970). Others followed suit in either controlled (Huguley *et al*, 1975) or uncontrolled (Frey *et al*, 1972a; Moore *et al*, 1973) studies. While the Stanford group confirmed the NCI results, their concern with the neurotoxicity of vincristine led them to recommend capping the dose at 2 mg total dose. This widely practised dose adjustment negatively affected the

dose intensity of vincristine in all future studies of MOPP (Moore *et al*, 1973).

When the NCI investigators later reported on the long-term follow-up of the MOPP treatment of the first 198 patients, the initial results were maintained (DeVita *et al*, 1980; Longo *et al*, 1986) (Fig 7). Of 198 patients, 159 (80%), achieved a complete remission with a median of three treatment cycles. All 23 patients without symptoms attained complete remission, compared with 78% of the symptomatic patients. This difference was highly significant, and only one asymptomatic patient had relapsed in subsequent years.

Sixty-three per cent of patients achieving complete remission, who were at risk for longer than 10 years, remained disease free. Because 80% of the entire treated population achieved a complete remission, the proportion of all treated patients who remained free of relapse at 10 years and beyond was 54.6%. The vast majority of relapses occurred within 42 months after cessation of therapy. Two features had a powerful effect on outcome, the absence of symptoms and the dose delivery rate of the drug vincristine.

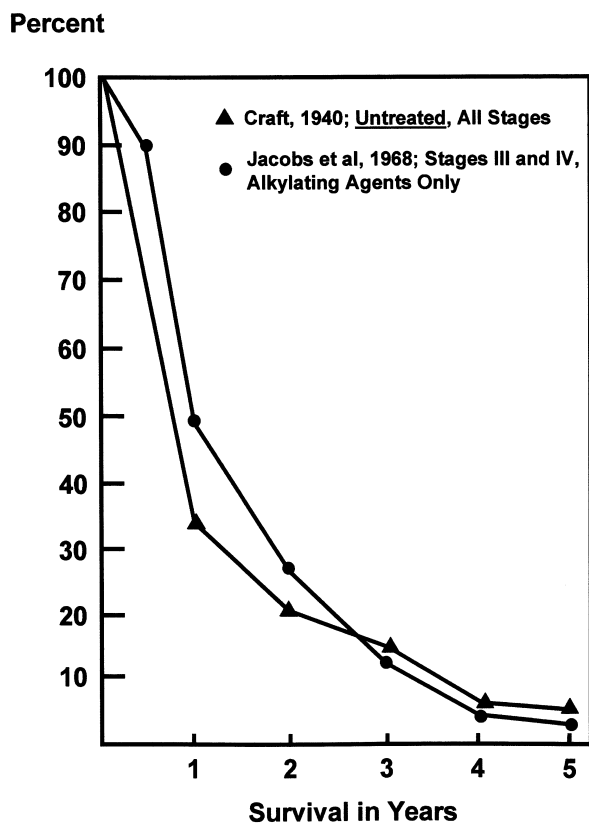


Fig 5. Survival curves of patients with Hodgkin's disease either untreated (Craft, 1940) or treated only with alkylating agents (Jacobs *et al*, 1968) before the advent of combination chemotherapy.

The next question posed was whether maintenance drug therapy would be beneficial after achieving a complete remission, as 35–50% of patients relapsed by the fifth year

of follow-up. The first such study was also conducted at the NCI (Young *et al*, 1973). After achieving complete remission, patients were randomly allocated to intermittent cycles of carmustine (the then new nitrosourea, BCNU) or no therapy or intermittent cycles of MOPP. Maintenance treatment was given for 15 months. When the results of this study were reported in 1973, and reanalysed in 1980, there were no significant advantages for either continued intermittent MOPP or intermittent carmustine therapy. Seven other studies designed to test the usefulness of maintenance therapy have been conducted, also with no long-term positive effects noted (Coltman *et al*, 1976; DeVita, 1981).

An important biological principle, related to the issue of *de novo* resistance to chemotherapy, was first observed from the retreatment of relapsed patients. Only five out of 17 patients whose initial complete remission was less than 1 year in duration achieved a second complete remission (29%), compared with 14 out of 15 patients whose initial complete remission was 1 year or longer (93%), a statistically significant difference ( $P = 0.001$ ) and, once again, remissions in this latter group were durable (Fisher *et al*, 1970). Overall, survival was significantly improved in those patients who achieved second remission over those who did not achieve a second remission ( $P = 0.005$ ).

Retained sensitivity to MOPP in patients who stayed in remission in excess of 1 year was a novel observation at the time and indicated that these patients were 'almost cured' by the induction programme, and might benefit from future intensification of treatment. This has proven to be the case in the modern era. The relative insensitivity of the tumour of patients who experience short remissions (< 12 months) suggested that the primary cause of treatment failure in this group was the presence and overgrowth of cells resistant to the drugs in the MOPP programme at the time of diagnosis. More importantly, the observation on retained sensitivity

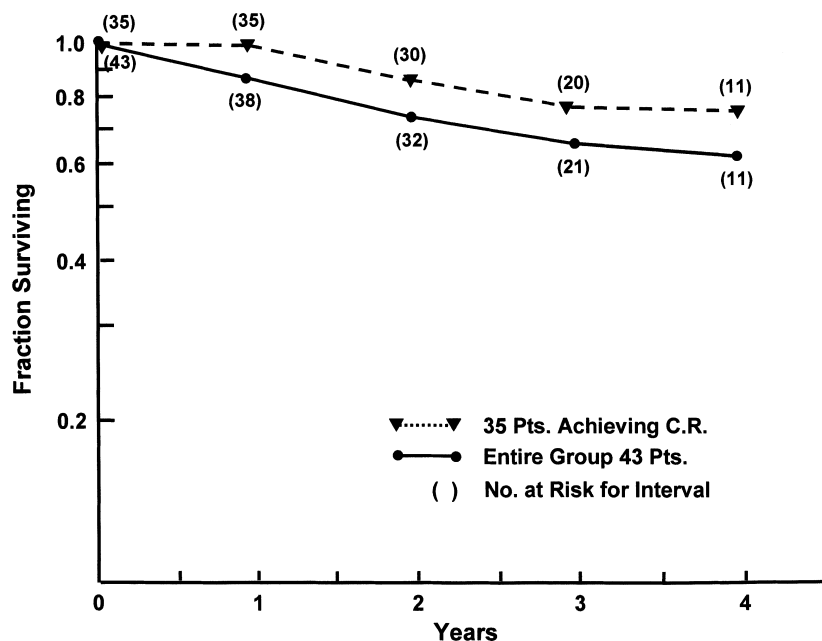


Fig 6. Life table analysis of survival for the entire group of 43 patients (solid line) and the 35 patients achieving a complete remission (CR; dotted line). Figures in parentheses next to each point indicate the number of patients at risk for that interval. From the original MOPP trial (DeVita *et al*, 1970). Published with permission.

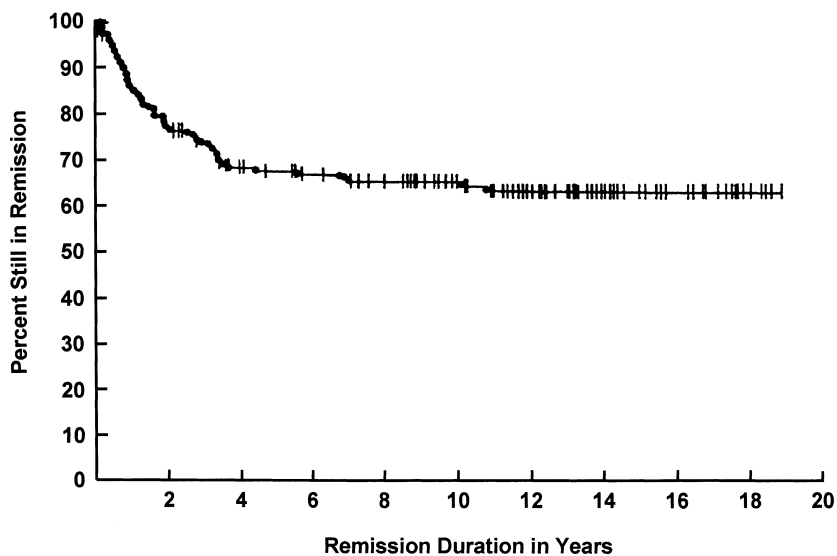


Fig 7. Plot of remission duration in 198 patients with advanced Hodgkin's disease treated with MOPP at 20 years follow-up from Longo *et al.* (1986). Reprinted with permission from the American Society of Clinical Oncology.

after a long drug-induced remission has carried over to virtually all advanced cancers where complete remissions in response to drug combinations are attainable, and illustrates an important and generally unexplained biological principle that is still under investigation (Fisher *et al.*, 1970; Viviani *et al.*, 1990; DeVita, 1991; Longo *et al.*, 1992).

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 (DeVita *et al.*, 1970). As the capacity to cure early-stage disease with radiotherapy was limited, the cure of advanced disease made it ethically possible to ask the question whether the use of chemotherapy alone, in lieu of radiotherapy, would improve the cure rate when the tumour volume was low. A trial testing this hypothesis was initiated at the NCI in 1978, comparing MOPP therapy alone, in laparotomy-staged patients, with subtotal nodal irradiation therapy (Longo *et al.*, 1991a). MOPP, indeed, proved superior to radiotherapy. Only one other similar trial has been done (Biti *et al.*, 1992). Although the results are only partially concordant, they have made it possible to explore chemotherapy as an alternative to radiotherapy in early-stage patients, an approach that is now under intense investigation in the modern era.

With a population of chemotherapy-cured patients available for study, other important observations related to the use of chemotherapy were first made in these initial MOPP studies (DeVita, 1981). They included: the first evidence of the long-term carcinogenic effects of cancer chemotherapeutic agents in cured humans (Arseneau *et al.*, 1972; DeVita *et al.*, 1973); the first evidence of male sterility from cytotoxic drugs (Sherins & DeVita, 1973) and the age-related impact of chemotherapy on ovarian function (Schilsky *et al.*, 1982); the first evidence of the recovery of the immune defect unique to Hodgkin's disease, with therapy that was in itself immunosuppressive (Fisher *et al.*, 1980); and the identification of infectious complications unique to cancer patients at that time, including the first

successful diagnosis and treatment of *Pneumocystis carinii* pneumonia in an adult (DeVita *et al.*, 1969b).

These studies, conducted by a single group at one institution, took over 20 years to complete, as measured by the time it took to publish the results of all the studies designed in the 1960s and 1970s. It is a testimony to the difficulties of a career in clinical investigation. It also led to the first cure of the most common subset of non-Hodgkin's lymphomas known as the diffuse large cell lymphomas, with a variant of the MOPP programme, another story in itself (DeVita *et al.*, 1975).

#### ABVD AND THE SAGA OF ALTERNATING CYCLICAL COMBINATION CHEMOTHERAPY

Although the MOPP studies established that an advanced cancer of a major organ system in adults could be cured by combination chemotherapy, 15–30% of patients did not achieve complete remission after MOPP, and approximately 20–30% of complete responders eventually relapsed. With the availability of new compounds in the late 1960s and 1970s, investigators began to design and test new chemotherapeutic regimens. The four-drug regimen known as ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) was developed at the Istituto Nazionale Tumori in Milan, Italy (Bonadonna *et al.*, 1975a), based on evidence of the antilymphoma properties of all four drugs and their non-overlapping sensitivity profiles with MOPP (Frei *et al.*, 1972b; Bonadonna *et al.*, 1970, 1975a,b; Santoro *et al.*, 1982).

A randomized trial was mounted in 1973 to test whether ABVD chemotherapy could induce a complete remission rate comparable with that of MOPP chemotherapy (Bonadonna *et al.*, 1975b). Overall, six cycles of either regimen yielded a comparable incidence of complete remissions, and this trend had an influence on the 5-year freedom from progression and relapse-free survival rates. This study showed that ABVD chemotherapy was as effective as MOPP in inducing durable remissions in advanced Hodgkin's

disease. Acute toxic effects were similar in both drug regimens, but the later sequelae were ultimately different. Radiation therapy contributed to the development of acute leukaemias in the alkylating agent-containing MOPP regimen, whereas the concomitant effect of adriamycin, bleomycin and irradiation to the heart and lungs proved to be the major problem with ABVD.

Data from both the NCI and the Milan group showed that patients who did not achieve a complete remission after either MOPP or ABVD showed progression of tumour after the first few cycles of chemotherapy, or within a few months after an initial complete remission, and that a fraction of these patients could be salvaged by the alternative chemotherapy. To maximize the benefits of the availability of two non-cross-resistant drug combinations, investigators at the Milan Cancer Institute designed what was called the alternating MOPP and ABVD regimen that featured alternating monthly cycles of MOPP and ABVD to be given initially, not for 6 months, the usual schedule, but over 12 months. By May 1982, 88 consecutive, previously untreated, stage IV patients were randomized to receive either 12-monthly cycles of MOPP or 12 months of MOPP/ABVD (Bonadonna *et al.*, 1986). Although there were no differences in survival, alternating two effective, non-cross-resistant drug combinations appeared to yield a superior initial response rate. Attempting to give MOPP for 12 months, however, led to a marked reduction in dose intensity, particularly for vincristine, which had never been given for that duration of time, and this may have affected the response rate to MOPP.

Another study of alternating cyclical non-cross-resistant chemotherapy, started at about the same time at the NCI, had a different outcome. It compared MOPP, this time in its usual 6-month schedule, with 6 months of MOPP alternating with CABS (cyclohexyl-nitrosourea, adriamycin, bleomycin and streptozotocin), a combination of drugs that had also been shown to be an effective alternative to MOPP (Longo *et al.*, 1991b). The results showed no advantage for alternating cyclical chemotherapy when MOPP was given at full doses.

Goldie & Coldman (1979) published a theoretical model to explain the failure of chemotherapy to cure more patients with advanced cancers. Their model predicted that tumour cells spontaneously mutate towards drug resistance before exposure to chemotherapy, and at cell numbers that would be below the diagnostic capability of tests of the day. Drug resistance was therefore, according to their hypothesis, likely to be present in all tumours to a greater or lesser degree at the time of diagnosis. This was, perhaps, why combination chemotherapy was working in some cases by overcoming some resistant lines with multiple drugs. Their predicted solution was to apply all available effective drugs simultaneously. As, clinically, this was not feasible, alternating cyclical approaches were the next best approach. Despite the conflicting information in the two trials from the NCI and Milan, they took the results of the Italian study as clinical validation of their experimental model. This set in motion a decade of clinical trials of alternating cyclical delivery of the two non-cross-resistant regimens around the

world that dominated clinical trials in Hodgkin's disease (Klimo & Connors, 1986; DeVita, 1991).

The definitive test of the Goldie–Coldman hypothesis in Hodgkin's disease came from the Cancer and Acute Leukaemia Group-B (CALGB). This co-operative group tested MOPP alone versus ABVD alone versus MOPP alternating with ABVD in stage III and IV patients (Canellos *et al.*, 1992). As was the case in the NCI MOPP/CABS study, the CALGB study confirmed that a well-delivered four-drug combination programme (ABVD in this case), given in adequate doses, can be as effective as alternating therapy. To date, neither the early reports nor long-term follow-up data have shown any survival differences among the three treatment arms, and the common practice today is the use of a standard four-drug regimen (DeVita, 1991; Canellos & Niedzwiecki, 2002).

## CONCLUSIONS

Today, 40 years after the development of combination chemotherapy, Hodgkin's disease patients are cured in approximately 80% of cases, and national mortality rates from the disease have fallen dramatically in the United States. At 15 years from the end of treatment, a patient has a greater risk today of dying of a complication of treatment than of Hodgkin's disease itself. Most patients receive combination chemotherapy and radiotherapy (Longo *et al.*, 1992), and those that fail, especially those with long first remissions, are often salvaged with intensive treatment programmes, coupled with autologous stem cell transplantation as support for marrow suppression. The search for newer combinations of more effective and/or less toxic drug combinations goes on with only one programme from Germany showing real promise, despite retaining the toxicity of both MOPP and ABVD (Diehl *et al.*, 1998).

We think we know that the Reed–Sternberg cell is a crippled B cell, although this has not helped us therapeutically, and the aetiology of the disease still eludes us. Markers expressed by the Reed–Sternberg cell are now, however, targets for either monoclonal antibodies or recombinant immunotoxins derived from them, but neither of the latter methods has advanced rapidly in a clinical situation crowded by a bewildering array of treatment options. Interestingly, stem cell allografts used in the form of 'mini-transplants', that is with reduced toxicity preparative regimens, with far less mortality, have reawakened an interest in allografting as a therapeutic approach of considerable promise.

The revolution set in motion by the cure of acute childhood leukaemia and Hodgkin's disease has maintained its momentum. A variety of advanced cancers can be cured by combination chemotherapy, and the application of chemotherapy as an adjunct to surgery has revolutionized the management of common cancers, such as those of the breast and colon.

As molecular targets continue to emerge and drugs specific for them reach the clinic, there is considerable promise for a newer, more targeted form of systemic treatment that will exact a reduced toll on the patient with

cancer and, perhaps, convert most cancers from a lethal to a readily manageable chronic disease, like Hodgkin's disease (Deisseroth & DeVita, 1995).

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