Chemotherapy Strategies to Improve the Control of Hodgkin’s Disease: The Richard and Hinda Rosenthal Foundation Award Lecture

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Abstract

The paper reviews new chemotherapy strategies for intermediate and advanced stages of Hodgkin’s disease as well as the implications of recent biological concepts and mathematical models which appear useful in the interpretation and design of new treatments. The development and the application of the Adriamycin-bleomycin-vinblastine-dacarbazine (ABVD) combination was based on critical reevaluation of benefits and limits of the mechloretamine-vincristine-procarbazine-prednisone (MOPP) combination. The attempts to develop non-cross-resistant regimens, such as ABVD, arose intuitively at first from the desire to improve salvage treatment in MOPP-refractory patients; more recently, a theoretical framework for this approach has been proposed by Goldie and Coldman (Cancer Treat. Rep., 63: 1727–1733, 1979). The 5-year results achieved with different forms of salvage chemotherapy and with the cyclic delivery of non-cross-resistant combinations (MOPP and ABVD) can be explained largely by the assumption that drug-resistant mutants represent a major limiting factor in the cure of Hodgkin’s disease, as well as of other neoplasms, by chemotherapy. The initial results from a prospective randomized trial indicate that the administration as front-line therapy of non-cross-resistant regimens is a logical and powerful strategic approach and therefore that it may constitute an important avenue of clinical research. Recent observations also emphasized the problem of the quality of life, since the administration of multidrug combinations not including alkylating agents and/or procarbazine appears to be associated with a decreased incidence of carcinogenesis and sterility. The departure from the standard practice of utilizing a single multidrug regimen for chemotherapy of Hodgkin’s disease should be supported by sound research and controlled studies built on drug combinations of known efficacy and toxicity.

Ladies and gentlemen of the American Association for Cancer Research, and guests: I am deeply honored in being invited to give this prestigious lecture to a large audience of qualified colleagues, I wish to say that much of the therapeutic research carried out in Milan during the last 10 years with the intent of further improving the control of Hodgkin’s disease. By reviewing treatments conceived and developed in Italy, but which in reality originated from previous studies performed in the United States, I hope to pay in part my cultural debt to all of you. Among the numerous colleagues I had the privilege to work with, I would like to acknowledge the help of Armando Santoro and Pinuccia Valagussa, who have contributed their intelligence and professional dedication in the performance and analysis of our recent studies on Hodgkin’s disease.

MOPP and MOPP-derived Combinations

In 1974, the prognostic outlook for Hodgkin’s disease was definitely more favorable than that of the previous decade. Based on accurate clinical and surgical staging procedures, the strategy of megavoltage irradiation, as pioneered by the Stanford group (35), represented the treatment of choice for patients with Pathological Stages I, II, and III A disease. MOPP3 chemotherapy, as developed by the NCI group (26), dominated the field of chemotherapy, and its impressive CR rate was already confirmed by numerous research groups studying patients with Stage II A, III A, II B, and IV disease. Taken in toto, the favorable consequences of intensive megavoltage irradiation and of MOPP chemotherapy consisted of a progressive decline in the mortality rate for Hodgkin’s disease, gradual as a consequence of radiotherapy and then more abrupt when MOPP became widely used in the community (25).

The design and application of MOPP chemotherapy represented a masterly condensation of the biological concepts made available by Skipper et al. (62) in the mid-1960’s from

1 Presented at the 1982 Meeting of the American Association for Cancer Research in St. Louis, Mo.
2 To whom requests for reprints should be addressed.

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1 The abbreviations used are: MOPP, mechloretamine, vincristine, procarbazine, and prednisone; NCI, National Cancer Institute; CR, complete remission; RFS, relapse-free survival; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CCVPP, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; cyclophosphamide, vincristine, procarbazine, and prednisone; BCVPP, 1,3-bis(2-chloroethyl)-1-nitrosourea, cyclophosphamide, vincristine, procarbazine, and prednisone; B-MOPP, bleomycin, dacarbazine, vincristine, prednisone, and Adriamycin; B-DOPA, bleomycin, dacarbazine, vincristine, prednisone, and Adriamycin; B-GAV, bleomycin, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, Adriamycin, and vinblastine; B-VAC, vinblastine, Adriamycin, bleomycin, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, and dacarbazine; MABOP, mechloretamine, Adriamycin, bleomycin, vincristine, and prednisone; B-DOPA, bleomycin, dacarbazine, vincristine, prednisone, and Adriamycin; B-GAV, bleomycin, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, Adriamycin, and vinblastine; B-VAC, vinblastine, Adriamycin, bleomycin, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, and dacarbazine; CEP, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, etoposide (VP-16), and prednimustine; SCAB, streptozotocin, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, Adriamycin, and bleomycin; ABV, Adriamycin, bleomycin, and vinblastine; MVPP, mechloretamine, vincristine, vinblastine, procarbazine, and prednisone, CMF, cyclophosphamide, methotrexate, and fluorouracil.
the rodent leukemia L1210 model. The concepts were related to fractional tumor-killing effect of drugs, dose-response effect, and inverse relationship between cure by drugs and number of tumor cells present at the time of treatment. The strategy utilized in the design of the MOPP protocol was for the first time aimed at the cure of Hodgkin's disease by use of effective, available drugs (24). The strategic concepts concerning full drug doses of the clinically active drugs, cyclic drug administration, and prolonged duration of therapy became subsequently the principal guidelines in designing combination regimens for practically all other forms of cancer.

The confirmed evidence that MOPP could render a large fraction of patients completely free of all evidence of disease (CR, 80%; 10-year RFS, 63.4%) (25, 27) at the expense of considerable, although transient, acute toxicity led some investigators to modify the original drug combination by deletion, substitution, or addition of various MOPP components (11, 39). The aim was either to develop a more effective drug regimen or to reduce some of the immediate side effects. However, the newly derived MOPP regimens failed to improve significantly the incidence of durable CR. Even recent studies (2, 42), in which nitrosourea derivatives such as carmustine or BCNU and lomustine or CCNU were utilized, failed to show definitive evidence of the superiority of the new drug regimens over MOPP. In fact, CCVPP and BCVPP yielded a 5-year RFS which was very close to that reported by De Vita et al. (25, 27), although in a randomized study the results achieved with BCVPP (2) were significantly superior to those achieved with MOPP. Some of the derived MOPP regimens such as BCVPP and ChVPP produced less gastrointestinal toxicity and neurotoxicity than did MOPP (37).

Within a few years of their introduction into the medical community, important long-term adverse consequences of MOPP and MOPP-derived treatments began to appear. These are the possibilities of carcinogenesis and of sterility because of intensive prolonged chemotherapy (8, 43). Today, these concerns are well documented.

Thus, at the end of 1974, the effectiveness as well as the limits of intensive irradiation and of single multidrug regimens were clearly evident, and the initiation of combined modality studies represented an attempt to overcome the plateau of cure rate inherent in the administration of single modalities. The failure of optimal radiation therapy to obtain a long-term RFS for 25 to 60% of patients with Hodgkin's disease either spread extensively above and below the diaphragm and/or with systemic symptoms is usually ascribed to the presence of occult foci beyond the fields of irradiation. The limits of MOPP and MOPP-like combinations can be ascribed to 2 main factors (Table 1). The first factor concerns selective drug resistance, which is responsible for the lack of attaining initial CR or durable CR in a fraction of patients. The second factor involves chronic toxicity, namely, sterility and carcinogenesis, and appears to be primarily related to the intensity of treatment, i.e., the cumulative doses of procarbazine and alkylating agents as well the association of intensive irradiation with intensive polychemotherapy.

For the above-mentioned reasons, the real alternatives to MOPP chemotherapy should involve the design of entirely new regimens consisting of effective drugs not included in the original MOPP combination. The main purpose for designing these new combinations is the management of the considerable fraction of patients with Hodgkin's disease who are resistant to MOPP, even when chemotherapy is administered at full or nearly full doses and for an adequate period of time. An additional important facet of new drug combinations should be the attempt to decrease the incidence of treatment-related sterility and carcinogenesis. To improve the results being achieved with either radiotherapy or chemotherapy alone, the appropriate sequential combination of the 2 modalities also appears to be worthy of study, at least in given subsets.

### Development of ABVD

By the end of 1972, our research group in Milan had completed the Phase II study of 2 new anticancer antibiotics, Adriamycin and bleomycin (3, 4, 6). Since objective tumor response in Hodgkin's disease refractory to alkylating agents, Vinca alkaloids, and procarbazine was documented at 70 and 50%, respectively, we thought that it was appropriate to include these agents in a multidrug combination. This was the reason for designing MABOP chemotherapy, wherein we substituted Adriamycin and bleomycin for procarbazine in a combination regimen otherwise very similar to MOPP. Like other MOPP-derived regimens, MABOP failed to improve incidence and duration of CR, both in patients previously untreated and in those relapsing after primary irradiation (3, 23). However, the experience with MABOP taught us 2 important lessons. The first lesson concerned strategy. By utilizing a single multidrug regimen and regardless of the type of drugs included in the combination, we realized that there was a plateau in the incidence of durable CR. The second lesson concerned toxicity. We noticed that a single 25-mg/sq m dose of Adriamycin failed to produce a high incidence of severe myelosuppression when this drug was injected with mechlorethamine (6 mg/sq m). Furthermore, if the cumulative dose of Adriamycin was kept below 300 mg/sq m, none of our patients developed cardiomyopathy, not even those who had received prior irradiation to the mediastinum or who were subsequently given radiation therapy to the mediastinal region. In contrast, the single i.v. dose of bleomycin (30 mg/sq m) produced nonfatal pulmonary toxicity in 20% of the first series of patients who received 6 cycles of MABOP chemotherapy (23).

The rationale for designing ABVD chemotherapy in 1973 (5, 15) was essentially based on the following considerations: (a) the need to treat effectively MOPP-resistant patients utilizing a combination of regimen drugs which were individually non-cross-resistant with MOPP components; (b) the therapeutic and toxicological information achieved with Adriamycin and...
bleomycin given either alone or through MABOP combination; (c) the effectiveness of dacarbazine in about 50% of previously treated patients with Hodgkin's disease, as reported by Frei et al. (29) and later confirmed by our group (11); (d) the little cross-resistance between vinblastine and vincristine in humans. Other considerations included the synergistic effect, with no additive toxicity, of dacarbazine and Adriamycin in experimental animal systems, as reported by Skibba et al. (57). We elected not to utilize one of the nitrosourea derivatives such as BCNU or CCNU because of their characteristic delayed myelosuppression which could prevent treatment recycling at rather short intervals. To avoid or limit toxicity from new antibiotics, the single dose of Adriamycin remained 25 mg/sq m, and that of bleomycin was lowered to 10 mg/sq m. Their cumulative doses were planned not to exceed 300 and 150 mg/sq m, respectively. To limit as much as possible the need for a dose reduction schedule, all drugs were injected i.v. on Days 1 and 15 of each treatment cycle. Thus, the initial dose schedule of dacarbazine (150 mg/sq m from Days 1 to 5) as tested by Frei et al. (29) was soon modified to 375 mg/sq m on Days 1 and 15 to limit vomiting which initially occurred for 5 consecutive days.

The strategy utilized in the development of ABVD protocols consisted of 3 phases (7, 9). First, we planned to compare the efficacy of ABVD versus MOPP in advanced Hodgkin's disease previously untreated with chemotherapy and, through a cross-over design, to test either regimen in resistant patients. In a second phase, we elected to alternate one cycle of MOPP with one cycle of ABVD as first-line treatment in Pathological Stage IV Hodgkin's disease in the attempt to increase the percentage of durable CR. The third phase included a combined modality study with chemotherapy and radiotherapy and was primarily aimed at decreasing the incidence of treatment-induced leukemias.

MOPP versus ABVD

Utilizing a fixed number of 6 cycles, the first prospective randomized study indicated that the CR induction rate between MOPP (63%) and ABVD (71%) was comparable. The study design was actually more complex and consisted of subsequent low-dose irradiation to complete and almost complete responders, including patients with Stage IV disease who received radiotherapy to all previously involved extranodal sites except the bone marrow (10, 14, 15). Since patients were previously stratified for histological subtypes as well as whether or not they had received prior irradiation, this study also provided initial information concerning the comparability between MOPP and ABVD of relapse-free and total survival rates at 5 years (Table 2). Similar 5-year results, utilizing polychemotherapy followed by low-dose radiotherapy in advanced Hodgkin's disease, were independently reported by Prosnitz et al. (45) at Yale University. An additional comparison between the 2 regimens is now available from the analysis of a larger series than that studied previously (7, 9, 52). Patients were randomly allocated to receive 3 cycles of either MOPP or ABVD, administered according to the classical dose schedules. In the absence of tumor progression, treatment was continued with high-energy radiotherapy (subtotal nodal irradiation in patients with Pathological Stage III A or II B and retroperitoneal adenopathy). The radiotherapy doses were 3500 rads to involved lymphoid areas and 3000 rads to adjacent uninvolved areas. About 1 month after the end of radiotherapy, treatment was completed with 3 additional cycles of either chemotherapy. The updated comparative treatment results in 196 consecutive patients (MOPP group, 100; ABVD group, 96) have indicated that ABVD combined with radiotherapy is significantly superior to MOPP plus radiotherapy in terms of CR, particularly in patients with systemic symptoms, and freedom from progression. The best comparative results were observed in Pathological Stage III A where the 5-year RFS was 100% in the ABVD group and 78.4% in the MOPP group (p = 0.03). The analysis of total survival failed to show a significant difference between the 2 treatment groups, also because of salvage therapy with ABVD in MOPP-resistant patients (Table 3). In both groups, the first 3 cycles of combination chemotherapy induced a prompt tumor shrinkage, thus allowing the delivery of subsequent irradiation with lower doses than usual and smaller ports at the level of mediastinal and paraaortic regions. On the basis of these findings and considering that radiotherapy can effectively kill drug-resistant cells, we believe that, when indicated, combined treatment strategy should begin with chemotherapy.

A third comparative test between MOPP and ABVD is provided by our recent analysis of patients with nodular sclerosing histology (13). The scope of the study was to retrospectively evaluate the comparative CR and the 5-year survival rates in the subgroup of patients with nodular sclerosing Hodgkin's disease. Since patients belonged to prospective randomized studies, they were comparable in terms of age subgroups, bulky disease, extranodal involvement, systemic symptoms, and that studied previously (7, 9, 52). Patients were randomly

<table>
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<tr>
<th>Table 2</th>
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<tr>
<td>Comparative results with MOPP versus ABVD</td>
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<tr>
<td>MOPP → radiotherapy (41)</td>
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<tr>
<td>CR</td>
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<tr>
<td>Chemotherapy alone</td>
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<tr>
<td>Chemotherapy plus radiotherapy</td>
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<tr>
<td>At 5 yr</td>
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<td>Freedom from progression</td>
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<td>RFS</td>
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<td>Survival of complete responders</td>
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<tr>
<td>Overall survival</td>
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<tr>
<td>Survival with NED*</td>
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* NED, no evidence of disease after first- and second-line chemotherapy.

<table>
<thead>
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<th>Table 3</th>
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<tr>
<td>Comparative results with MOPP versus ABVD combined with radiotherapy in Stage II B-IIIA-IIIB</td>
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<tr>
<td>MOPP group (100 cases) (%)</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>No symptoms</td>
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<tr>
<td>Systemic symptoms</td>
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<tr>
<td>Nodular sclerosis</td>
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<tr>
<td>At 5 yr</td>
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<tr>
<td>Freedom from progression</td>
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<tr>
<td>RFS</td>
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<tr>
<td>Survival of complete responders</td>
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<tr>
<td>Total survival</td>
</tr>
<tr>
<td>Survival with NED*</td>
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</table>

* NED, no evidence of disease after first- and second-line chemotherapy.
and median follow-up time. There was a comparatively higher CR rate favoring ABVD in all classical prognostic variables, but the differences between the 2 treatment groups were not significant. In patients with nodular sclerosis histology and bulky disease, the difference between the ABVD group (86.8%) and the MOPP group (71.4%) was of borderline significance ($p = 0.05$). In contrast, the comparative probability of freedom from progression at 5 years from the start of chemotherapy was significantly in favor of ABVD in the entire series (MOPP 55.6% versus ABVD 80.8%, $p = 0.0001$) as well as in the subgroup with bulky lymphoma (MOPP 57.5% versus ABVD 75.8%, $p = 0.02$). The comparative 5-year RFS and survival results in all complete responders with nodular sclerosis histology are summarized in Table 4. RFS was significantly superior in the ABVD group compared to the MOPP group, regardless of absence ("A") or presence ("B") of systemic symptoms. The lack of comparative difference in the total survival rates was most probably due to salvage ABVD chemotherapy in MOPP-resistant patients. Our findings suggest that ABVD chemotherapy should now be considered in the treatment plan for nodular sclerosing Hodgkin’s disease.

The efficacy of Adriamycin-containing regimens (MABOP, ABVD) versus MOPP also emerged from a comparative analysis of salvage chemotherapy regimens in patients failing to respond to primary irradiation. In a recent retrospective study of 96 cases (53), CR occurred in 36 of 48 relapsing patients given MOPP (75%) and in 44 of 48 patients treated with an Adriamycin combination (91.7%, $p = 0.05$). Also, the 5-year freedom from progression (51.6 versus 76.8%, $p = 0.006$), RFS (64.1 versus 84.1%, $p = 0.02$), survival of complete responders (62.8 versus 85.8%, $p = 0.02$), and total survival (53.9 versus 77.2%, $p = 0.009$) were significantly in favor of a regimen containing Adriamycin. Table 5 shows that our findings with salvage MOPP are comparable to those obtained by the NCI (16), Stanford (44), and Harvard (41) research groups. In contrast, our results with Adriamycin-containing combinations appear comparatively superior and reaffirm the usefulness of Adriamycin in the treatment of advanced Hodgkin’s disease.

### Table 4

| Nodular sclerosing histology: comparative 5-yr results in complete responders |
|---------------------------------|-----------------|-------|-----------------|
| Total                           | MOPP group (%)  | ABVD group (%) | $p$   |
| RFS                             | 71.5            | 88.5            | 0.004 |
| Survival                        | 80.4            | 91.2            | 0.10  |
| "A"                             |                 |                 |       |
| RFS                             | 67.0            | 95.6            | 0.03  |
| Survival                        | 71.0            | 94.1            | 0.07  |
| "B"                             |                 |                 |       |
| RFS                             | 73.3            | 85.5            | 0.03  |
| Survival                        | 84.1            | 90.0            | 0.48  |

### Table 5

<table>
<thead>
<tr>
<th>Salvage chemotherapy in patients with Hodgkin’s disease relapsing after radiotherapy</th>
</tr>
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<tbody>
<tr>
<td>Regimen</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>NCI (16)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Stanford (44)</td>
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<tr>
<td>Harvard (41)</td>
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<td>Milan (53)</td>
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**Lack of Cross-Resistance**

We have recently published our updated results on ABVD as second-line chemotherapy in 54 adult patients resistant to MOPP (49). Resistant patients were considered those showing progressive disease during primary chemotherapy administered at full or nearly full doses as well as those relapsing within the first 12 months after achievement of pathological CR (48, 49). Although the CR rate was influenced by certain prognostic parameters, such as disease extent (nodal, 74%; extranodal, 44%) and systemic symptoms ("A", 82%; "B", 49%), available data indicate that ABVD is a useful salvage regimen to be used as first treatment in MOPP-resistant patients. Besides inducing a prompt high frequency of CR (total, 59%) followed by improved 5-year survival, at the expenses of moderate and reversible toxicity, ABVD can probably cure one-third of complete responders and therefore about 20% of all MOPP-resistant patients. In our experience, the delivery of MOPP in ABVD-resistant patients yielded less brilliant results (total CR, 25%), but the difference should be partly ascribed to the comparatively lower number of evaluable patients in the MOPP group. However, the observed findings were sufficient to demonstrate absence of cross-resistance between the 2 combinations (Table 6). At least in the United States, ABVD as salvage regimen has not yet been properly tested in patients refractory to MOPP only for a number of reasons (e.g., additional chemotherapy after failing ABVD, significant modification of the treatment regimen, prior resistance to either vinblastine or bleomycin).

Over the past few years, other MOPP-salvage combinations were designed in the United States and Europe (39, 49), and all regimens but B-DOPA have included a nitrosourea derivative, either CCNU or streptozotocin, in the combination (Table 7). All salvage regimens appeared promising, particularly when B-DOPA and B-CAVes were utilized. In fact, the CR rate ranged from 50 to 60%, a result similar to that achieved with ABVD (Table 8). At present, the 5-year results in terms of survival and toxicity were not reported in detail. More recently, Einhorn et al. (28) have reported the results of a salvage regimen utilizing the drugs in ABVD and adding CCNU. The VABCD regimen was tested in 18 evaluable patients resistant to MOPP. CR was
Chemotherapy Strategies to Control Hodgkin’s Disease

Table 7
Examples of MOPP-salvage drug combinations other than ABVD

<table>
<thead>
<tr>
<th>Drug combinations</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Median duration of CR (mos.)</th>
<th>Median survival after CR (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-DOPA Bleomycin Dacarbazine</td>
<td>84.5</td>
<td>4.5+</td>
<td>4.5+</td>
<td></td>
</tr>
<tr>
<td>Vincristine Prednisone Adriamycin</td>
<td>50</td>
<td>26</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>B-CAVe Bleomycin CCNU Adriamycin</td>
<td>8</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Vinblastine Doxorubicin Streptozotocin</td>
<td>26+</td>
<td>20+</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>BVDS Bleomycin Vinblastine</td>
<td>82.5</td>
<td>28+</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin Streptozotocin</td>
<td>59</td>
<td>17</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>B-CAVe 50</td>
<td>77</td>
<td>35+</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>ABDIC Adriamycin Bleomycin CCNU</td>
<td>59</td>
<td>17</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>85</td>
<td>24+</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>SCAB Streptozotocin CCNU Adriamycin</td>
<td>82.5</td>
<td>28+</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>72</td>
<td>17</td>
<td>60</td>
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<tr>
<td>CVB CCNU</td>
<td>88</td>
<td>24+</td>
<td>28</td>
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Table 8
Drug combinations effective in MOPP-refractory patients

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of patients</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Median duration of CR (mos.)</th>
<th>Median survival after CR (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVB</td>
<td>39</td>
<td>26</td>
<td>84.5</td>
<td>4.5+</td>
<td>4.5+</td>
</tr>
<tr>
<td>SCAB</td>
<td>17</td>
<td>35</td>
<td>59</td>
<td>8+</td>
<td>16+</td>
</tr>
<tr>
<td>BVDS</td>
<td>10</td>
<td>50</td>
<td>50</td>
<td>7</td>
<td>26+</td>
</tr>
<tr>
<td>B-DOPA</td>
<td>15</td>
<td>60</td>
<td>60</td>
<td>14+</td>
<td>7</td>
</tr>
<tr>
<td>B-CAVe</td>
<td>22</td>
<td>50</td>
<td>77</td>
<td>35+</td>
<td>24</td>
</tr>
<tr>
<td>ABDIC</td>
<td>29</td>
<td>34.5</td>
<td>82.5</td>
<td>28+</td>
<td>28</td>
</tr>
<tr>
<td>ABVD</td>
<td>54</td>
<td>59</td>
<td>72</td>
<td>17</td>
<td>60+</td>
</tr>
<tr>
<td>VABCD</td>
<td>18</td>
<td>44</td>
<td>88</td>
<td>24+</td>
<td>28</td>
</tr>
</tbody>
</table>

PR: partial remission.

For description of regimens, see Table 7.

achieved in 8 patients, and partial response was noted in 8 patients. Five of 8 complete responders remain continuously relapse free from 5 to 36 months. In spite of considerable toxicity (severe myelosuppression, stomatitis, reversible pulmonary toxicity in 6 patients, vomiting and alopecia in virtually all patients), the therapeutic results of VABCD confirm that durable CR and potential cure are possible with non-cross-resistant combination chemotherapy in a fraction of MOPP-resistant patients.

This year, we have also reported the usefulness of a third-line combination consisting of p.o. administration of CEP in 24 patients resistant to both MOPP and ABVD chemotherapy (50). The preliminary results of CEP appeared promising in terms of clinical relevance (CR in 33% of patients for a median duration of 10 months, partial response in 21% of patients for a median duration of 8 months). Toxicity was moderate and reversible.

The important clinical message to be derived from all salvage programs currently in use is that, in spite of an appreciably high complete response rate, the incidence of durable remissions in MOPP-resistant patients remains, in most instances, rather low. Present findings appear therefore more interesting from the conceptual viewpoint for they may allow interpretation of the results of chemotherapy trials along new lines of thought. We are now considering new, attractive experimental hypotheses that we can develop into more ambitious treatment strategies. Chart 1 illustrates the influx of new drugs effective against Hodgkin’s disease into clinical use over time, as well as the drug combinations developed for first-, second-, and third-line chemotherapy. Vindesine has been recently added to the list of drugs moderately active in advanced refractory Hodgkin’s disease. By properly utilizing available agents, we can indeed design more than one non-cross-resistant combination which may also be tested in tandem as primary treatment to overcome the limits inherent in a single drug combination.

The Mutation Theory

Today, as stressed by Skipper (58, 60), the results of chemotherapy trials in humans are consistent with inferences of the

![Chart 1](image_url)

Chart 1. Influx over time of clinically effective drugs in Hodgkin’s disease and drug combinations developed for first-, second-, and third-line chemotherapy. Methyl GAG + Me GAG, methyl-glyoxal-bis-guanylhydrazone; MOMP, mechlorethamine, vincristine, methotrexate, prednisone; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; MVPP, mechlorethamine, vinblastine, procarbazine, prednisone; BOPP, 1, 3-bis(2 chloroethyl)1-nitrosourea, vincristine, procarbazine, prednisone.

Drugs available to develop third-line combinations

- DCF-PLATINUM CDDP
- Methyl GAG. Me GAG
- PREONIMUSTINE
- TENOPOSIDE. VM-26
- ETOPOSIDE. VP-16
- CEP

Drugs utilized to develop second-line combinations

- ABVD
- B-DOPA
- B-CAVe
- SCAB
- BVDS
- ABDIC
- CVB

Drugs utilized to develop initial combinations

- MOMP
- MOPP
- COPP
- MVPP
- BOPP
- BVCPP

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The mutation theory of Luria and Delbruck (40), which was originally based on studies of the fluctuation in numbers of phage-resistant *Escherichia coli* in independent cell populations of the same size. Since survival and overgrowth of drug-resistant neoplastic cells are major causes of chemotherapeutic failure in human cancers, as in animal cancers, the clinical findings which are consistent with inferences of the mutation theory are: (a) the wide fluctuation in the degree and duration of response of similarly staged and treated patients bearing a given neoplastic disease; (b) many observations of partial and complete response followed by tumor regrowth in the presence of continuing undiminished treatment with the same drug or combination of drugs; (c) the variance in survival time of treatment failures.

Based on the early work of Luria and Delbruck (40) on mutation to resistance in bacterial populations, in 1979 Goldie and Goldman (33) developed a mathematical model "relating the drug sensitivity of a tumor to its own spontaneous mutation rate toward phenotypic drug resistance." Briefly, the assumptions underlying the model are the following. (a) Genetic instability is an intrinsic property of growing mammalian cancer cells. Genetically unstable cells develop somatic mutations that lead to phenotypic resistance to drugs to which they have never been exposed. (b) No 2 neoplasms of the same histological subtype and stage need have the same mutation rate. Therefore, a large fluctuation in the proportion and absolute number of drug-resistant tumor cells, a necessary consequence of the mutation theory, probably exists in comparably staged individuals with a given tumor, depending on whether the first mutation occurred early or late in the history of the tumor. This basic tenet of the mutation theory applied to cancer chemotherapy may provide a reasonable explanation for some of the problems that have puzzled oncologists for years, namely, wide variations in the incidences of remissions as well as their degree and duration in individuals bearing tumors of the same stage and type, as well as variations in the cure rate of patients who have achieved complete response (58, 60). (c) As tumor size increases, the probability of resistant clones increases, and thus for reasons quite independent of growth kinetics we would expect increasing resistance to treatment with increasing tumor size. These assumptions from the Goldie and Goldman model fit very well with the known concepts that tumor heterogeneity increases with the size of cancer cell populations and that there is an invariable relationship between the neoplastic cell burden at the initiation of chemotherapy and curability.

The origin of doubly resistant phenotypes usually is thought to be a 2-step process (61). The drug-resistant cells are totally resistant to a given drug or drug combination, and thus it is not at all necessary for the total tumor cell burden to approach $10^{12}$ before we must expect the presence of doubly or multi-drug-resistant tumor cells of different types. Therefore, the more rapidly the singly resistant cells are eradicated, the lower is the probability of the emergence of doubly or multidrug-resistant cells. Clinical resistance will be observed when 10 to 50% of the surviving neoplastic cells are resistant to the drug or drugs being used (60). Since doubly drug-resistant neoplastic cells will negate the usefulness of 2-drug combinations and markedly reduce the effectiveness of 3- or 4-drug combinations, the most effective means for preventing the emergence of doubly resistant phenotypes during chemotherapy is the simultaneous delivery of a combination of non-cross-resistant drugs or, probably better, the alternating delivery of 2 or more than 2 non-cross-resistant combinations of drugs.

The MOPP-ABVD Program

The rationale for alternating one cycle of MOPP with one cycle of ABVD in Hodgkin's disease was first based on the clinical observation that patients resistant to MOPP showed either progressive disease after the first 2 to 4 cycles or disease recurrence within a few months from an initial complete response. A second reason for the alternating program was also derived from clinical experience. In fact, MOPP and ABVD appeared to be equally effective non-cross-resistant combinations, and the median time to CR with either regimen was the third cycle. Today, the mathematical model of Goldie and Goldman (33) as well as the experimental studies of Skipper, Schabel, and coworkers (54, 58–61) provide a strong support for changing treatment at each cycle of therapy, at least for exponentially growing tumors in which chemotherapy produces log kill.

Our first cyclic MOPP-ABVD program versus MOPP alone was started in 1974 in adults with Pathological Stage IV Hodgkin's disease (7, 9, 51). In the absence of disease progression, a total of 12 cycles of either regimen was planned because we were aware that in a fraction of patients, particularly those with nodular sclerosis histology, as many as 12 cycles could be required to achieve CR. The 5-year results of the trial were recently published (51). More patients are presently evaluable for the comparative complete remission rate and the 5-year actuarial results (Table 9). No patient was excluded from analysis because of toxicity or refusal to take drugs before completing 12 cycles. From the strategic point of view, the first interesting finding is the lack of disease progression during the administration of alternating chemotherapy, compared to the 22.5% which occurred during the administration of MOPP alone. CR after MOPP was 72.5%, a result very close to that reported in Stage IV by NCI investigators (25, 27), compared to 92.3% after MOPP alternated with ABVD. The findings confirm that the systematic switching of effective non-cross-resistant combinations after each cycle of therapy can significantly affect the mix of sensitive and resistant neoplastic cells. The alternating regimen was superior to a single multidrug regimen in all prognostic subgroups, particularly in patients more than 40 years old, with single extranodal site and no prior irradiation. The lack of statistical significance in various subgroups was due to the limited number of evaluable patients in each category. The comparative 5-year results also confirmed the superiority of the MOPP-ABVD program versus MOPP alone. Our comparative 5-year RFS related to disease extent was as follows. Single extranodal site: MOPP, 42%; MOPP-ABVD, 77%. Multiple extranodal sites: MOPP, 66%; MOPP-ABVD, 100%. The difference in the RFS of Stage IV with MOPP chemotherapy between NCI (65%) and Milan (45.2%) is actually difficult to explain and may be related to the biological factors outlined before, namely, the large fluctuation in the proportion and absolute number of drug-resistant cells, affecting incidence of remissions as well as their degree and duration. However, it is worth mentioning that, also from another randomized study (2), the 5-year RFS following MOPP chemotherapy was 50%. Our comparative analysis of total survival,
primary chemotherapy with non-cross-resistant regimens in Stages III and IV. At present, the results of the NCI MOPP-SCAB program versus MOPP alone are premature (24, 39).

In light of the present results, should the delivery of cyclic MOPP-ABVD become the standard form of chemotherapy for advanced Hodgkin’s disease? Although I have little doubt about the superiority of alternating chemotherapy over a single drug combination, I believe we are still in the data-collecting period. Therefore, other research groups are invited to mount prospective randomized studies to independently confirm our results before this alternating program becomes the established treatment plan in the medical community. To meet the most stringent requirements for the initial assumption to work, we are now testing, through a prospective randomized study, the efficacy of an alternating regimen which includes monthly administration of a half-cycle of MOPP (mechlorethamine and vincristine on Day 1, procarbazine and prednisone from Day 1 to 7) followed by one dose of ABVD on Day 15 (Chart 2). Theoretically, this alternating regimen should test more appropriately the validity of the hypothesis of Goldie and Coldman in a larger number of cases since the study is being performed in patients with Stages II (bulky mediastinum), III (A and B), and IV (A and B). In complete responders, low-dose radiotherapy will be delivered only to the mediastinal area if bulky adenopathy (mass/thoracic ratio, >0.33) is present at the start of chemotherapy, since this is a subgroup which can benefit from combined modality treatment, particularly in the presence of nodular sclerosis histology. Otherwise, no further treatment will be administered once CR is achieved by drug therapy. Patients not achieving CR after 6 cycles of either alternating regimen will receive CEP chemotherapy, with or without irradiation depending on individual clinical situations. Through incorporation of more stringent requirements in alternating-sequence therapies, the present study essentially attempts to increase the 5-year RFS obtained in Stage IV (85%) by alternating one full cycle of MOPP with one full cycle of ABVD. In other words, our goal is to improve the survival rate with no evidence of disease by the first treatment program, since practically all salvage regimens have limited efficacy in terms of durable remission.

A research program utilizing 2 (MOPP-ABVD) versus 3-drug combinations (CCNU-Alkeran-vindesine, or CAD-MOPP-ABV) is presently in progress at Memorial Hospital (63). In the study arm, decarbazine was dropped from ABVD to reduce vomiting although showing a marked trend in favor of alternating chemotherapy (85.1 versus 65.6%), failed, at present, to reach statistical significance (p = 0.09) because the survival difference became evident only after the first 30 months. The results can also be ascribed partly to the transient effect of salvage therapy with ABVD in MOPP-resistant patients.

Aside from marked vomiting, particularly after each ABVD exposure, toxicity from alternating chemotherapy was moderate. From the viewpoint of bone marrow tolerance, cyclic MOPP-ABVD was better tolerated than MOPP alone, as indicated by the percentage of optimal dose administered in patients who have completed 12 cycles of either regimen (7, 51). Since it has been shown by the Stanford group (17) that the attainment of CR is best for patients who had a higher mean rate of drug delivery in the first 3 consecutive MOPP cycles, our mean dose levels (mechlorethamine, 83%, vincristine, 88%; and procarbazine, 80%) are very close to those administered by the NCI group during the first 3 cycles (26). Complete or almost complete alopecia was documented in only about 10% of patients. No patient showed symptoms and signs of Adriamycin cardiomyopathy or of bleomycin pulmonary fibrosis. One patient given MOPP alone following prior extensive irradiation developed fatal acute nonlymphoblastic leukemia 37 months from starting chemotherapy.

Altogether, our findings indicate that alternating chemotherapy emerges as a logical and powerful strategic approach for advanced Hodgkin’s disease, assuming that one postulates drug-resistant mutants as being a major limiting factor in cure. Similar results with MOPP-ABVD in Stage III and IV Hodgkin’s disease were achieved at Memorial Hospital in a prospective nonrandomized study which also included consolidation radiotherapy to the sites of initial bulky disease (64). The NCI group, the Cancer Leukemia Group B, and the Eastern Cooperative Group are currently engaged in the therapeutic evaluation of

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**Chemotherapy Strategies to Control Hodgkin’s Disease**

**Table 9**

<table>
<thead>
<tr>
<th>Results of MOPP versus MOPP/ABVD in Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>MOPP (40 cases)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Progression</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>Age &lt;40 yr</td>
</tr>
<tr>
<td>&gt;40 yr</td>
</tr>
<tr>
<td>Symptoms A</td>
</tr>
<tr>
<td>&gt;B</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
</tr>
<tr>
<td>Disease extent</td>
</tr>
<tr>
<td>&lt;3 sites</td>
</tr>
<tr>
<td>Single extranodal</td>
</tr>
<tr>
<td>Multiple extranodal</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>At 5 yr</td>
</tr>
<tr>
<td>Freedom from progression</td>
</tr>
<tr>
<td>RFS</td>
</tr>
<tr>
<td>Survival of complete responders</td>
</tr>
<tr>
<td>Overall survival</td>
</tr>
<tr>
<td>Survival with NED</td>
</tr>
</tbody>
</table>

* NED, no evidence of disease after first- and second-line chemotherapy.

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**Chart 2.** Prospective randomized trial ongoing at the Milan Tumor Institute for intermediate and advanced Hodgkin’s disease. M, half MOPP cycle; A, half ABVD cycle; DTIC, 5(4)-dimethyltriazinoimidazole-4-carboximide; RT, radiotherapy. For details, see text.
while in both arms low-dose (2000 rads) radiotherapy is deliv-
ered to initially involved regions. Also, the Yale group is treating
with MOPP-ABVD and low-dose irradiation in a nonrandomized
fashion a high-risk subgroup with Hodgkin’s disease charac-
terized by patients more than 40 years old and/or with Stage
IV disease with multiple sites of involvement. In the above-
mentioned subgroup, the treatment program resulted in a 3-
year survival of 87% compared to 58% for those treated with
MVPP and radiation in previous years. However, the reported
results of both research groups (36, 63) as well as those of our
previous multimodal study (10) do not appear to be superior
compared to the results achieved with MOPP-ABVD alone.
Therefore, the real usefulness of involved-field irradiation in-
terspersed with alternating cycles of combination chemotherapy
remains highly questionable unless patients have initial bulky
disease in the mediastinum.

Should alternating chemotherapy alone be tested in early
Hodgkin’s disease in the attempt to replace radiotherapy? Admittedly, the temptation is great but should be tempered by
a few important considerations dealing with treatment-related
morbidity. Assuming that the delivery of optimal alternating
chemotherapy will be as effective as and even more effective
than current megavoltage irradiation programs for Stage IA and
IIA Hodgkin’s disease, i.e., that effective polychemotherapy
will cure 20 to 30% of patients who are not cured by primary
radiation therapy alone, the precise risk of long-term compli-
cations over the life span following combinations with 6 to 9
drugs remains unknown. Although by rotating drug combina-
tions at each cycle of therapy we may expect a decrease of the
acute and delayed toxic manifestations as a consequence
of less intensive and prolonged drug exposure to the target
tissues, we should also remember that the administration of an
adequate chemotherapy program remains today a distressful
experience for every patient. In fact, “loss of employment,
disruption of schooling, dislocation from home, change in phy-

cical appearance, fear of treatment programs, loss of libido,
separation, and divorce are all very important aspects of treat-

ing Hodgkin’s disease. These problems are difficult to express
as actuarial curves, cure rates, and P values, but are important
considerations in selecting treatment programs.” These words
come from a recent article written by Rosenberg (46), and I am
unable to add anything important to his wise conclusions. Thus,
in my opinion, the evaluation of primary chemotherapy for
Stage I and II Hodgkin’s disease should remain restricted to a
very few qualified research centers, which will be able to
manage the entire spectrum of problems; it should not become
the new treatment approach in a private office or local hospital.

Attempts to Decrease Treatment Complications

The days of minimizing the potential long-term toxicity of
treatment programs for Hodgkin’s disease are past, and in
devising therapy for all stage subgroups the increased risk for
relapse must be weighed against the increased risk of iatro-
genic morbidity involving single or multiple organs (43).
Regarding the risk of iatrogenic morbidity, the results of a recent
Stanford study (20) reviewing the clinical and pathological
features of 80 patients who came to autopsy from 1972 through
1977 are very interesting in that they revealed that nearly one-
third of the patients died without evidence of Hodgkin’s dis-
ease. In particular, a significant number of patients died of
treatment complications, both benign and malignant, including
5 patients with hematological or de novo lymphoid cancers,
while nonfatal histopathological effects of therapy were com-
mon and specifically assessed in thyroid, gonads, and pericar-
dium.

As mentioned before, late complications which are relevant
to the treatment strategy of Hodgkin’s disease are treatment-
induced secondary neoplasms, sterility, cardiotoxicity, and
lung fibrosis (43). As far as secondary neoplasms are con-
cerned, there is general agreement that acute nonlympho-
blastic leukemia represents the most frequently observed iatro-
genic cancer followed by diffuse non-Hodgkin’s lymphomas
and by a variety of solid tumors. With the objective of comparing
the incidence of treatment-related morbidity, we initiated in
1974 a prospective randomized study between MOPP and
ABVD within a combined modality setting in previously un-
treated patients with pathological Stages IIB, IIIA, and IIIIB.

In Table 10, I have selected 4 representative series of pa-
tients to show that the highest incidence of acute leukemia has
occurred after intensive irradiation and intensive multidrug
chemotherapy including procarbazine and alkylating agents,
particularly when given as salvage treatment. Similar results
have been observed by other investigators utilizing MOPP or
MOPP-derived regimens (38). In the experience of Cancer and
Leukemia Group B (31), induction chemotherapy with mech-
lorethamine-containing regimen, followed by chlorambucil
maintenance therapy, had the highest relative risk ratio and life
table estimate (26%). Our present findings do not confirm that
age >40 years at the start of treatment has an important
adverse effect on the incidence (about 20%) of treatment-
induced leukemia, as observed by the Southwest Oncology
Group (22). Our research group has recently confirmed that
no secondary cancers were observed in 104 patients given
ABVD either alone or combined with radiotherapy at a projected
risk 10 years from the diagnosis of Hodgkin’s disease (68, 69).
A variety of other secondary tumors was also documented in
patients given radiotherapy, with or without MOPP or MOPP-
like chemotherapy (31, 68). Present comparative results are
not definitive since the full extent of the expression of the risk
of a secondary cancer may not be appreciated for another
decade (31). However, it is worth emphasizing that, in 191
patients randomized to receive MOPP plus radiotherapy versus
ABVD plus radiotherapy, acute leukemia (2 cases), non-Hodg-
kin’s lymphoma (1 case), and solid tumors (2 cases) developed
within 5 years, and all patients belonged to the MOPP group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NCI (25)</th>
<th>Stanford (21)</th>
<th>SWOG (22)</th>
<th>Milan (68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT a alone</td>
<td>0/149</td>
<td>0/417</td>
<td>0/95</td>
<td>0/272</td>
</tr>
<tr>
<td>No intensive chemotherapy or RT</td>
<td>0/131</td>
<td>3/65</td>
<td>3/102</td>
<td>1/50</td>
</tr>
<tr>
<td>RT + 198Au</td>
<td>0/110</td>
<td>2/37</td>
<td>1/283</td>
<td>3/191</td>
</tr>
<tr>
<td>MOPP or MOPP-like regimens</td>
<td>4/65</td>
<td>3/357</td>
<td>4/58</td>
<td>0/104</td>
</tr>
</tbody>
</table>

a RT, radiotherapy.

b Extended field or total nodal irradiation.
Although drug-induced azoospermia and amenorrhea were known side effects for a number of years, until recently the impact of gonadal toxicity on the quality of life has received little attention (18). Infertility in males is of particular concern because many patients with Hodgkin's disease are young and the potential for cure is high. When spermatogenesis is impaired follicle-stimulating hormone blood levels rise, while in complete Leydig cell failure levels of luteinizing hormone rise and testosterone levels fall. Combination chemotherapy regimens including procarbazine and/or alkylating agents have a profound effect on spermatogenesis, as first reported in Hodgkin's disease by the NCI group (56). At least 80% of the men treated with MOPP or MOPP-like regimens become azoospermic or severely oligospermic. Recovery of spermatogenesis is unpredictable and, through retrospective studies, it has been reported to vary from 20 to 40%. This appears to be directly related to the length of time off therapy and indirectly related to the total dose of chemotherapy (8, 18). The sterility problem appears to be less common in adult females than in males, probably because the low germ cell proliferative rate of the ovary is less sensitive to drugs compared to the testicular epithelium and Leydig cells. When ovarian failure occurs, there are greatly increased levels of follicle-stimulating hormone and luteinizing hormone with abnormally low estradiol and progesterone levels. Available data would indicate that 40 to 50% of women treated with drug regimens containing procarbazine and alkylating agents will become amenorrheic. The premature ovarian failure appears related to age (>25 years, about 20%; <25 years, about 20%), is most probably related to the total dose of drugs, and is progressive rather than an all-or-none phenomenon (8, 18). The relationship of age to ovarian dysfunction has been reported in numerous studies of adjuvant chemotherapy for breast cancer involving various alkylating and alkylating agents (12, 47). Reestablishment of menses and the possibility of pregnancy in a treated woman is also correlated with age and cumulative drug exposure. However, pregnancy does not prove lack of ovarian damage (18). The ovaries of prepubertal and pubertal girls are relatively insensitive to anticancer drugs unless high and prolonged doses are administered.

Our own preliminary findings derived from the randomized study with MOPP plus radiotherapy versus ABVD plus radiotherapy limited to patients less than 45 years of age and having no pelvic irradiation indicated that ABVD combination affected spermatogenesis in a considerably lesser percentage than did MOPP. Furthermore, the recovery of spermatogenesis in patients in whom the sperm count was repeated was observed in all instances in the ABVD-treated group (4 of 4), compared to 1 of 3 cases treated with MOPP. The comparative difference for drug-induced amenorrhea appears, at present, less evident although the trend favors ABVD (Table 1). Since gonadal function is also related to the intensity of drug treatment, it will be useful to document in future evaluations whether the incidence of azoospermia and of permanent amenorrhea will be decreased by alternating MOPP with ABVD, particularly when a half-cycle of either regimen will be delivered within a 1-month period. Thus, our findings with ABVD are in keeping with the results of other investigators who have observed limited and transient germ cell toxicity following the administration of anticancer drugs other than alkylating agents or procarbazine (55). Future studies should also be able to determine more precisely the percentage of patients with Hodgkin's disease in whom gonadal dysfunction is impaired before starting treatment, particularly when systemic fever is present (18).

To minimize the psychological and the physical impact of chemical castration, semen cryopreservation prior to therapy in males, oral contraceptives in premenopausal women (19), and appropriate trials with an analog of gonadotropin-releasing hormone (32) are highly recommended.

Recent observations (1) have indicated that we can expect long-term cardiac effects from radiotherapy as a consequence of direct damage to cardiac vessels and muscles. Since the factors which may increase a patient's risk for Adriamycin-induced cardiomyopathy include total dose, schedule, age, preexisting cardiac disease, prior mediastinal radiotherapy, and administration of other cytotoxic drugs (e.g., cyclophosphamide, dacarbazine) (70), of particular concern are the possible long-term complications of the use of Adriamycin-containing combinations and radiation to the mediastinum. Probably because the cumulative dose of Adriamycin was always less than 300 mg/m² and the single dose was only 25 mg/m², thus far no patient in our trials has developed symptoms and signs consistent with drug-induced cardiomyopathy. Clearly, a longer follow-up analysis and more sophisticated studies (e.g., ejection fraction) to determine occult myocardial damage are required before firm conclusions can be drawn on this important point. Prior or concomitant thoracic radiotherapy increases the incidence of severe pulmonary toxicity (30). Preliminary findings from our prospective trial with combined modality therapy would indicate that the incidence of paramediastinal fibrosis was higher in the ABVD group (41%) compared to the MOPP group (19%) regardless of the size of mediastinal adenopathy and the total dose of radiotherapy delivered. However, thus far, we have not documented episodes of classical pul-

### Table 1

Comparative incidence of gonadal failure in patients given MOPP versus ABVD

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total evaluable</strong></td>
<td><strong>Median age (yr)</strong></td>
</tr>
<tr>
<td><strong>MOPP + RT</strong>&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>16</td>
</tr>
<tr>
<td><strong>ABVD + RT</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12</td>
</tr>
</tbody>
</table>

<sup>a</sup> RT, radiotherapy.
<sup>b</sup> Pelvic lymph nodes excluded.
<sup>c</sup> Numbers in parentheses, range.
monary fibrosis involving the entire lung. Also the problem of pulmonary toxicity will require a long-term analysis.

In summary, the positive aspects of ABVD chemotherapy appear numerous (Table 12). In my opinion, they should be properly utilized in the treatment strategy to improve the control and minimize the toxicity in given subsets with Hodgkin's disease. It is likely that more extensive trials utilizing alternating chemotherapy, with or without irradiation, for patients with Stage II and bulky disease or nodular sclerosis histology, Stage IIIA, IIIB, and IV, could further increase the chances for a total conquest of Hodgkin's disease at the expense of less overt and relatively occult morbidity.

Conclusions

The overview of our study protocols in which MOPP was tested versus ABVD and alternated with ABVD should provide the opportunity for broad conclusions. In particular, it should invite research physicians to reconsider current approaches to the design of chemotherapy trials not only in Hodgkin's disease but also in many other forms of cancer. This line of rethinking may involve a few important steps. First, many medical oncologists should focus more on strategic approaches than on minor changes in drug regimens. Drug combinations should now be regarded as medical tools rather than symbols to identify the skill or the imagination of individual investigators or research groups. Since we have to recognize that a plateau has been reached in the control of various neoplastic diseases with current drug regimens and new effective compounds are not readily available, only different strategies which utilize established combinations, such as MOPP and ABVD in Hodgkin's disease, might open important avenues of research and improve treatment results.

Second, the strategic approaches should be considerate of some of the implications of new biological concepts and models. In reviewing his numerous experimental chemotherapeutic trials, Skipper (59, 60) has come to the conclusion that "we are now at the point that the mutation theory of Luria and Delbruck should be considered as a basic theory or law that underlies and explains much of what is observed on chemotherapy treatment of experimental leukemia and solid tumors. The model of Goldie and Coldman has helped to simplify application of inferences of the mutation theory in the area of cancer treatment." I believe that our results achieved with MOPP, ABVD, and CEP greatly support the concept that the presence of drug-resistant neoplastic cells prior to the initiation of treatment, or their emergence and overgrowth during therapy, is a major cause (not the only cause) of chemotherapeutic failure in Hodgkin's disease. This type of lymphoma also may well represent in this context a useful human model for other human neoplasms (24). The limits of single drug combinations in terms of incidence and duration of remission are already clearly evident in all solid tumors. For instance, in advanced breast cancer the same response rate was recently reported by the Southwest Oncology Group regardless of the number of drugs administered (67) and our group has shown that in an adjuvant situation 6 cycles of CMF cyclophosphamide, methotrexate, and fluorouracil provided the same therapeutic benefit as did 12 cycles (66). When platinum-vinblastine-bleomycin chemotherapy is given in advanced testicular cancer, complete remission is not likely to occur by prolonging the same therapy if not achieved by the third cycle (65), while in acute leukemia, Hodgkin's disease, and high-grade malignancy non-Hodgkin's lymphomas all forms of maintenance treatment have proved to be useless in increasing the duration of CR (24). All these examples can be related to inferences of the mutation theory. Thus, the cyclic or sequential delivery of combinations of non-cross-resistant drugs, which are frequently less than additive in toxicity when administered in an optimal manner, appears worthy of appropriate controlled studies in a broad variety of neoplasms, and particularly in an adjuvant situation.

Goldie and Coldman (34) correctly caution that "not every alternating program can be expected to show benefit." They have listed the situation in which alternating at every cycle might not prove to be the optimal strategy, namely, a situation in which, by chance, one resistant fraction in a given tumor is considerably larger than the other, even if the values for their mutation rates are identical. To commence by alternating treatment courses would permit the larger of the 2 resistant populations to have intervals when it would grow unimpeded by therapy; therefore, its further increase in size would greatly increase the probability of mutation to double resistance. Furthermore, when the 2 resistant cell compartments will not exhibit the same kinetic behavior, alternating chemotherapy will not be superior to a single drug combination. Finally, it should be recognized that, today, 2 generally equivalent and non-cross-resistant combinations, such as MOPP and ABVD for Hodgkin's disease, do not appear to be readily available in clinical practice. Thus, "alternating sequence therapies that do not incorporate stringent requirements, that are similar mutation rate to single, double, or multidrug resistance, same log-kill on the sensitive compartment, same log-kill to the single resistant compartment and the same growth curves of the single resistant subpopulations, may well fail to show therapeutic advantage" (34). Theoretically, in solid tumors, less substantial deviations from this symmetry are most likely to occur in the treatment of micrometastases. Therefore, alternating chemotherapy may constitute the optimal therapeutic approach in an adjuvant situation. Here, new studies and research efforts should be concentrated with a reasonable expectation that optimal alternating chemotherapy will emerge as superior strategy.

Regarding the design of new chemotherapy trials with more than one drug combination, research physicians should gain experience with the new methodology of computer simulations of actual trials in which combinations of drugs are delivered in different ways. Such simulations should try to improve visualizations of the influence of diverse combination regimens on...
the surviving neoplastic cells at the nadir and at the end of treatment. "If used with prudence, the retrospective simulations of past chemotherapeutic trial results obtained in human cancers (along with prospective simulation of the possible influence of changing combinations and their methods of delivery), should probably play an important role in new protocol design. The main reason for changing our current semi-empiric methodology should be that such efforts already have proven useful in the design of better therapeutic regimens for treating experimental cancers. Furthermore, simulation exercises almost always point to possibilities and limitations that would not be conceived intuitively" (59).

References


Chemotherapy Strategies to Improve the Control of Hodgkin’s Disease: The Richard and Hinda Rosenthal Foundation Award Lecture

Gianni Bonadonna


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