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Special Lecture

The Chemotherapy of Lymphomas: Looking Back, Moving Forward—The Richard and Hinda Rosenthal Foundation Award Lecture[1]

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Lymphomas are a common cancer of humans. They occurred about 42,000 times in 1986 and the rubric lymphoma encompasses about a dozen variants of diseases of lymphocytes or related cells of the immune system (1). Two of the 12 most common types of lymphoma, Hodgkin's disease and the lymphoid malignancy which has been called reticulum cell sarcoma, diffuse histiocytic lymphoma, and most recently diffuse aggressive or large cell lymphomas, were the first two tumors of a major organ system of adults to succumb to chemotherapy (2, 3). They occurred in 20,000 patients in 1986: 8,000 cases of Hodgkin's disease and 12,000 cases of diffuse large cell lymphoma. Looking back, this has been a very satisfying experience, the major impact of which is the provision of proof of the hypothesis that advanced cancers could be cured by combinations of cancer drugs developed because of their antitumor effect in animals. As with most new approaches to treatment, however, looking back identifies previously unanticipated problems as well. One of the problems with combination chemotherapy is toxicity, real and sometimes exaggerated. With the benefit of hindsight, looking back reveals that concerns for toxicity, out of proportion to the fatal consequences of the diseases themselves, have frequently led to *ad hoc* modification of programs that, based on data from animal systems, predict a decrease in their capacity to cure.

Looking forward, the lessons learned from past attempts to modify treatment provide insight for the design of current and future treatment programs in all the lymphomas. The complexity of these programs grows as biologics enter the therapeutic arena and are integrated into treatment programs at an early stage in their development. The early enthusiasm for biologics followed by the feeling of disappointment over their incapacity to provide quick cures without side effects is reminiscent of the introduction of chemotherapy and should not deter the clinical investigators from defining their ultimate role in treatment in the most expeditious way. The lessons learned by looking back at the treatment of lymphomas are applicable to other common malignancies of adults.

Hodgkin's Disease: The NCI[2] MOPP Study Sequence

In 1964, Skipper and Schabel, at the Southern Research Institute, demonstrated the invariable inverse relationship between cell number and curability by chemotherapy in their studies that established that advanced leukemia 1210 could be cured by chemotherapy, especially if drug combinations were used in precisely drawn doses and schedules, based on cell kinetic data, to overcome the problem of excess tumor volume (4). This work in rodents provided continued impetus and insight for the design of new therapeutic programs in human malignancies. The details of similar experiments that led to the development of the so-called MOPP treatment program for advanced Hodgkin's disease have been described elsewhere (2). Fig. 1 shows the scheme for administration of the four-drug MOPP combination developed in 1964 for the treatment of advanced Hodgkin's disease. Single agents had not been able to cure advanced disease, even at the maximal tolerated doses. Each of the agents in the MOPP program was selected based on antitumor activity when used as a single agent and the drugs were given in full dose and in their optimal schedule. Drugs were also selected to minimize overlapping toxicity to any single organ. Therefore, vincristine was selected over its analogue vinblastine because it had less marrow toxicity, although it did produce more neurotoxicity. The four drugs were given over a 2-week period. Intervals between cycles were constructed around the known intervals for recovery of bone marrow from myelosuppression (5). Thus, a complete cycle of MOPP consisted of a 2-week treatment period and a 2-week recovery period. A minimum of six cycles were given every 29 days until the patient attained a complete remission or tumor grew despite treatment.

There were three features of MOPP that were unique at the time: (*a*) the goal of the program was to cure (as with leukemia 1210) rather than to palliate as was the practice at the time; (*b*) the cyclic use of combination chemotherapy for 6 months exceeded the duration for any prior treatment program in adult tumors; (*c*) it was the first regimen to make use of a sliding scale to adjust drug doses for marrow suppression and/or neurotoxicity. The sliding scale was designed to permit the administration of each cycle with maximal doses of each agent and to preserve both the dose rate and the integrity of the drug combination (2, 6). Provisions for delaying subsequent cycles were made only if toxicity of any individual drug were severe enough to otherwise require its omission from that cycle.

The sliding scale, a concept now used in most clinical protocols, had an interesting effect on dosing in the MOPP study. After two cycles at full doses, most people had significant myelosuppression and doses in the third cycle were frequently reduced according to the sliding scale. The impact of reducing dose in the third cycle allowed the use of full or near full doses in the fourth and later cycles. The net effect was preservation of dose rate. The average duration of administration for six cycles was 5.8 months, and the omission of any of the drugs from the program was rare. These two important points will be reemphasized later in the evaluation of results with other programs. MOPP was considered high dose, long duration che-

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[2] The abbreviations used are: NCI, National Cancer Institute; MOPP, nitrogen mustard-vincristine-procarbazine-prednisone; L-PAM, L-phenylalanine mustard; 6-MP, 6-mercaptopurine; RDI, relative dose intensity; BCVPP, 1,3-bis(2-chloroethyl)-1-nitrosourea-cyclophosphamide-velban-procarbazine-prednisone; SWOG, Southwestern Oncology Group; ABVD, Adriamycin-bleomycin-vinblastine-decarbazine; CABS, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)-Adriamycin-bleomycin-streptozotocin; C-MOPP, cyclophosphamide-vincristine-procarbazine-prednisone; ProMACE, prednisone-methotrexate-Adriamycin-cyclophosphamide-epipodophyllotoxin; CytaBOM, 1-β-D-arabinofuranosyl-cytosine-bleomycine-vincristine-methotrexate with leucovorin rescue; CHOP, cyclophosphamide-Adriamycin-vincristine-prednisone; BACOP, bleomycin-Adriamycin-cyclophosphamide-vincristine-prednisone; MACOP-B, methotrexate-Adriamycin-cyclophosphamide-vincristine-prednisone-bleomycin.

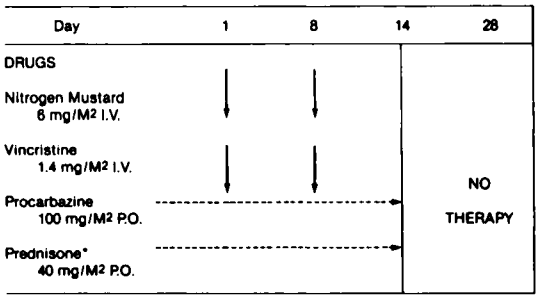

Fig. 1. Schema for the MOPP combination chemotherapy program. Nitrogen mustard and vincristine are given i.v. on days 1 and 8 of a 28-day cycle of therapy, procarbazine and prednisone are given once a day p.o. for 14 days, and no therapy is given on days 15 through 28. In the original program, prednisone was included only on cycles 1 and 4. The doses of drugs are adjusted down or up based on a sliding scale keyed to the nadir blood counts or symptoms from the previous cycle of therapy. The next cycle begins on time unless the peripheral blood counts on day 1 of the next cycle are too low to safely administer nitrogen mustard and procarbazine. In such an instance, it is permissible to wait a maximum of 1 week for the blood counts to recover. Maximum drug is then delivered based on the blood counts on the day of therapy. Delays of up to 1 week between cycles are rarely necessary. Note that the maximum vincristine dose is not limited to a total of 2 mg. Prednisone*, cycles 1 and 4 only.

Table 1 *Results of the original NCI MOPP study after 20 years of follow-up*

A significant fraction of patients with advanced Hodgkin's disease remain alive and well and apparently cured of their disease.

	Last analyses	Current analyses
No. of evaluable patients	198	188
Complete responders	159 (80)[a]	157 (84)
Induction failures	39 (20)	31 (16)
Relapsed	52 (33)	56 (34)
Complete responders free of disease	(67)	(64)
Total population free of disease	107 (54)	101 (54)

[a] Numbers in parentheses, percentage of patients.

motherapy in 1964. However, subsequent calculations of its dose intensity, using the method of Hryniuk and Bush (7, 8), calculating doses on the basis of mg/m^2/week, which takes into account the impact of the treatment-free intervals on total dose delivered over time, revealed that the MOPP program we used has a relative dose intensity of 70% of a hypothetical version of MOPP that would use the drugs continuously, without rest intervals, over 6 months. This turns out to be true of all cyclically administered drug treatment programs. The net effect is that all cytotoxic drug combinations in the clinic today are given at reduced doses *vis-à-vis* the optimal single drug schedules.

The first results of the MOPP study presented in 1967 (9) and published in 1970 (2) demonstrated a quadrupling in the complete remission rate compared to single agents and a continuation of most complete responses after cessation of treatment. This led us to conclude that advanced Hodgkin's disease was curable using this approach (2, 10). These results have been confirmed by others and the effect has been maintained in our own study over the past 20 years (11). Table 1 shows the results of treatment at 20 years (11), during which 198 patients were treated with MOPP; all are at risk for a minimum of 10 years and 140 are at risk for 15 years. This population, as described below, has more patients with poor prognostic features than more recent studies. For example, 88% of the patients were classified as having B symptoms, a variable that carries a poor prognosis independent of all prognostic factors; only 12% were asymptomatic (category A). Since the follow-up report published in 1980 the pathologists at NCI have re-reviewed the histological material of these patients and found that 10 patients in the original study, diagnosed as having lymphocyte-depleted Hodgkin's disease, would now be called diffuse large cell lymphoma (12). This subset with these 10 patients excluded is evaluated separately in the current analysis shown in Table 1.

The two most important points in Table 1 are the relapse-free survival rate (64%) and the fraction of all treated patients who remain free of disease (54%) after 20-year follow-up. The relapse-free survival curve is shown in Fig. 2 and illustrates that most negative events take place over the first 4 years of follow-up after which the curve tends to flatten out and relapses are uncommon. The latest relapse in the MOPP study has occurred 11 years after treatment was discontinued. The toxicity of MOPP was not excessive; only five patients died of treatment-related toxicity (2.5%). Despite the neurotoxicity associated with full doses of vincristine (1.4 mg/m^2), no patients were permanently paralyzed using the sliding scale adjustment based on symptoms.

The first series of studies that followed our reports in 1967 and 1970 confirmed the results in an uncontrolled trial (13) and showed MOPP to be superior to nitrogen mustard used continuously for 6 months in a controlled trial (14) and superior to a new five-drug combination and the same five drugs used in a fixed sequence (15, 16). The uncontrolled Stanford trial, however, reported severe toxicity from vincristine at the doses used at NCI and began the now widely adopted practice of limiting the dose of vincristine to no more than 2 mg/dose regardless of body weight or surface area. A decade of additional studies designed to reduce the side effects of MOPP by substituting or adding additional drugs has addressed the effects of modifying the MOPP program. Three combinations emerged with effects equivalent to MOPP in Hodgkin's disease, but with a different array of side effects that makes them useful under certain clinical circumstances (17–20). Omitting a drug from MOPP, however, reduced the effectiveness as was shown in one controlled trial comparing MOPP to the three cytotoxic drugs without prednisone (21).

In the 1960s it was fashionable to give additional chemotherapy after a maximum response was attained to maintain this response (maintenance chemotherapy) because there was no expectation of cure. In these studies, doses of drugs were invariably reduced and given at widely spaced intervals. A study at NCI showed maintenance treatment to be ineffective. A total

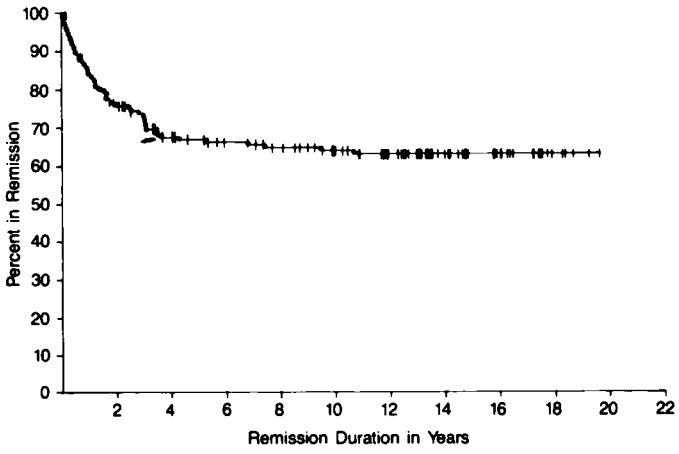

Fig. 2. Duration of complete response to MOPP combination chemotherapy. The percentage of patients remaining in their initial MOPP-induced complete remission is plotted against time in years from the end of therapy. Only 34% of the complete responders have relapsed with a median follow-up of over 14 years. Fewer than 10% of the relapses occur after 4 years.

of nine studies of maintenance treatment after remission with MOPP have now shown that it adds nothing to overall relapse-free survival achieved at the NCI (11).

All of the asymptomatic patients (stages IIIA and IVA) attained a complete remission in the NCI study and only two have relapsed with over 15 years of follow-up. The results of the treatment of these patients bear on the issue of the invariable relationship between cell number and curability by chemotherapy since these patients are regarded as having a lower tumor burden than symptomatic patients. Before MOPP, asymptomatic patients with stage IIIA disease had traditionally been treated with radiotherapy. Long-term survival, free of disease, was consistently less than 50%. After a series of trials showed that the addition of MOPP combination chemotherapy to radiotherapy significantly improved the results over radiotherapy alone, two trials compared combination chemotherapy alone to radiotherapy alone or to chemotherapy plus radiotherapy and they have clearly shown that drugs alone can achieve results equal to or better than the use of combined radiation therapy and combination chemotherapy, with less toxicity. In these studies, the relapse-free survivals are equivalent to the original NCI report and 96 and 91% of asymptomatic patients remain relapse free, respectively (22, 23). About a decade ago, we took this experiment to its logical conclusion and initiated a study of MOPP chemotherapy alone compared to radiotherapy in patients with stage IIA and IIB Hodgkin's disease to try to improve on the cure rate attained with radiotherapy alone without the burden of toxicity of combining radiotherapy with combination chemotherapy. The preliminary results have recently been presented (24) and show, thus far, that the inverse relationship between tumor cell volume and outcome holds and chemotherapy may be superior to radiotherapy, in patients with localized disease, in terms of relapse-free and overall survival.

Importance of Dose Intensity Highlighted by Animal Data

The importance of dose density can also be gleaned using animal data. The results of many experiments, performed by Skipper (25) and colleagues, using mice with similarly staged 2–3-g Ridgway osteogenic sarcomas, are shown in Tables 2, 3, and 4. It should be noted that these experiments can be carried out in 90 days while their human counterparts in lymphomas take 5 to 10 years. Dose intensity in these experiments is calculated using as a reference point a set of doses and schedules that would be used if each drug were used in its optimal dose and schedule alone. The use of a hypothetical standard is useful in emphasizing the degree of reduction of doses required when drugs are used in combination. Average dose intensity of the two-drug combination, cyclophosphamide and L-PAM, in the Ridgway osteogenic sarcoma experiments is shown in Table 2 and is related to two important and clinically relevant end points, the ability to achieve a complete response and the ability to cure tumor-bearing animals. These two drugs are equally effective in this system and a good dose-response effect is noted. An important point is, however, illustrated in Table 2. A reduction of average dose intensity from 0.6 to 0.44, a 27% decrease in relative dose intensity, maintains the ability to cause complete disappearance of palpable tumor but reducees the cure rate from 60% to 10%, an 80% decrease in the capacity to cure. Tables 4 and 5 examine dose intensity relationships for the two-drug combination of L-PAM and 6-MP in the same tumor system. Here L-PAM is a superior drug. When ranked by average dose intensity of both drugs (Table 3) there is no consistent dose response. However, when ranked by the dose intensity of the better drug, L-PAM, the same relationship is seen as noted in Table 2. A 34% reduction in the dose intensity of L-PAM (0.82 to 0.55) results in only a 20% reduction in the response rate but a 67% decrease in the cure rate. Regardless of the dose intensity of 6-MP, a decrease of the dose intensity of L-PAM below 0.55 leads to significant reduction in the capacity to cure mice bearing these tumors.

The clinical implications of these data are extraordinary. A clinical study achieving 100% complete response rate with a reduction in average dose intensity of this magnitude, without apparently reducing its early effectiveness, would be hailed as a significant step forward in decreasing treatment morbidity

Table 2 *Results of treatment of 2–3-g Ridgway osteogenic sarcomas with cyclophosphamide and L-PAM in differing doses*

Dose intensities are decimal fractions of standard dose of drugs when used alone. Reduction in average RDI results in a significant loss in cure rate before a decrease in response rate is noted [from Skipper (25); reprinted with permission].

RDI			% of complete remissions	% of cures
Cyclophosphamide	L-PAM	Av.		
0.38	0.82	0.60	100	60
0.75	0.18	0.47	100	44
0.25	0.55	0.44	100	10
0.50	0.12	0.31	10	0
0.17	0.36	0.27	0	0

Table 3 *Results of treatment of 2–3-g Ridgway osteogenic sarcomas with L-PAM and 6-MP*

Doses are decimal fraction of standard dose of each drug used alone [from Skipper (25); reprinted with permission]. L-PAM is the superior drug and cure rate is not directly related to the average of the dose intensity of 6-MP and L-PAM combined, but to the dose intensity of L-PAM.

Relative dose intensity				Observed	
L-PAM	6-MP	Ratio (L-PAM/6-MP)	Av.	% of complete remissions	% of cures
0.73	1.3	0.56	1.0	90	50
0.27	1.5	0.18	0.89	70	0
0.55	1.0	0.55	0.78	90	20
0.82	0.49	1.7	0.66	100	60
0.18	1.0	0.18	0.59	0	0
0.36	0.67	0.54	0.52	56	0
0.55	0.33	1.7	0.44	80	20
0.12	0.67	0.18	0.40	0	0
0.24	0.44	0.57	0.35	0	0
0.36	0.21	1.7	0.29	30	0
0.08	0.44	0.18	0.26	0	0
0.24	0.15	1.6	0.20	0	0

Table 4 *Results of treatment of 2–3-g Ridgway osteogenic sarcomas with L-PAM and 6-MP*

Doses are decimal fraction of standard dose of each drug used alone [from Skipper (25); reprinted with permission]. A linear relationship between the dose intensity of L-PAM is noted. Below a dose intensity of 0.55, the capacity to cure is lost although a substantial response rate is maintained.

Relative dose intensity				Observed	
L-PAM	6-MP	Ratio (L-PAM/6-MP)	Av.	% of complete remissions	% of cures
0.82	0.49	1.7	0.66	100	60
0.73	1.3	0.56	1.0	90	50
0.55	1.0	0.55	0.78	90	20
0.55	0.33	1.7	0.44	80	20
0.36	0.67	0.54	0.52	56	0
0.36	0.21	1.7	0.29	30	0
0.27	1.5	0.18	0.89	70	0
0.24	0.44	0.57	0.35	0	0
0.24	0.15	1.6	0.20	0	0
0.18	1.0	0.18	0.59	0	0
0.12	0.67	0.18	0.50	0	0
0.08	0.44	0.18	0.26	0	0

many years before it might or might not be recognized that the ability to cure was sacrificed to dose reduction.

Impact of Dose Intensity on Outcome in Hodgkin's Disease

While drugs and schedules in the various combinations were manipulated frequently, dose rate itself was never examined as an independent variable in any controlled trial. Recently several groups, including our own, have begun to analyze, retrospectively, the dose effect on outcome. Table 5 shows the percentage of projected dose and dose rate over three and six cycles of MOPP chemotherapy as used at the NCI. In general, we maintained the intended dose rate at a high level as evidenced by the average dose of nitrogen mustard, vincristine, and procarbazine given over six cycles. Particularly noteworthy is the fact that dose and dose rate for vincristine were maintained at a high level without undue toxicity and without artificially capping the dose. In a regression analysis, the single most important treatment variable in the NCI study was the rate of delivery of vincristine over six cycles (11) which correlates significantly with the likelihood of both attaining a complete remission and surviving free of recurrent disease. In the NCI study time to reach a complete remission also had a significant effect on the likelihood of maintaining a complete remission. Those who attained a complete remission in less than 5 months did significantly better than those whose remission was achieved after 5 months of treatment.

A report by Carde *et al.* (26) from Stanford University has also found that lower doses were related to poorer outcome. The dose and dose rate of nitrogen mustard, vincristine, and procarbazine (Stanford omits prednisone out of fear of radiation pneumonitis) were important variables in the ability to achieve a complete remission. A regression analysis showed the mean of the total dose and dose rate of the three drugs as having an impact on remission rate, particularly in patients with B symptoms, suggesting that preserving the integrity of the combination was important. The regression analysis also revealed that patients who received less than 65% of the projected dose of nitrogen mustard had a significantly poorer survival than those who received more than 65% of the projected dose. An interesting comparison on relative dosing between Stanford and NCI comes from these two studies. As shown in Table 5, the NCI group received 88% of the projected dose of nitrogen mustard over three cycles and 80% over six cycles. Too few patients were treated with less than 65% of the projected dose of nitrogen mustard at NCI to examine the impact of low dose nitrogen mustard on survival. Another report from Stanford indicated that MOPP failures often achieved good palliation with the use of single alkylating agent chemotherapy which also suggests that significant reduction in alkylating agent administration is occurring during the initial treatment in their patient population (27).

Table 5 *Percentage of projected dose and dose rate of nitrogen mustard, vincristine, and procarbazine in the MOPP program*

	3 cycles (%)	6 cycles (%)
Dose		
HN2[a]	92	83
VCR	99	97
PCZ	83	76
Dose rate		
HN2	88	80
VCR	98	92
PCZ	81	72
Av. % for 3 drugs	91	85
Av. dose rate for 3 drugs	89	81

[a] HN2, nitrogen mustard; VCR, vincristine; PCZ, procarbazine.

In order to compare results across studies in Hodgkin's disease we have followed the practice of Hryniuk and Bush (7, 8, 28) of converting drug doses to mg/m^2/week for each drug and averaging the doses of cytotoxic drugs to obtain an average dose intensity over the 6-month MOPP treatment program duration. Depending on data available, one can calculate either the intended dose intensity, the protocol doses projected to be delivered, or the actual dose intensity, if specific data on actual doses delivered are available, which is rarely the case. The program with the highest dose rate (which in Hodgkin's disease is NCI's MOPP program) is used as the standard and dose intensities of other studies are compared to the standard. RDI is reported as the decimal fraction of the dose for individual drugs or the average dose for all the drugs in the combination. Calculating RDI has several advantages over comparing percentages of projected dose delivered. While the percentages of projected dose for different studies may appear similar, it is often not, since the projected dose, as is true for vincristine in most studies, may already be arbitrarily limited. This method also allows comparisons of the impact of the average dose intensity of all the cytotoxic drugs or the relative dose intensity of individual drugs in the combination.

However useful the method is in ranking dosing practices, it is imprecise as applied to clinical studies for several important reasons: (*a*) actual dose intensity varies significantly from intended dose intensity because of the different dosing practices and the nature of dose adjustment using the sliding scale, and actual dosing data are rarely given in sufficient detail to make the necessary calculations; (*b*) the end points used in the clinic are also often imprecise. Studies are reported at different time intervals and often give data only on relapse-free survival and overall survival of those patients who attain a complete remission. The most sought after data on outcome, *vis-à-vis* dose intensity, is the fraction of all treated patients who survive beyond 5 years from the end of treatment free of recurrence. These data often must be extrapolated using the complete remission rate and the published relapse-free survival curves of patients who attain a complete response. In the estimates made in this review, data on actual dose intensity were obtained from published papers. In comparing survival outcome either the total population was used or matching subsets of similar stages were selected to make comparisons between studies. These subsets are indicated in the tables where appropriate. However imprecise the method is at present, Hryniuk *et al.* (7, 8, 28) have been able to draw some useful conclusions on the impact of dose intensity on outcome in both breast and ovarian cancer.

Table 6 shows intended dose intensity calculations of three versions of the MOPP program based on body surface area of 1.7 m^2 when given over a 6-month period. Table 6 also shows the impact of prolonging the administration of each cycle by 1,

Table 6 *Dose intensity of three versions of the MOPP program used under differing circumstances*

While the average dose intensity relative to the NCI version is significantly reduced with the dose modifications shown, the greatest impact is noted with prolonging the intervals between cycles, a common clinical practice.

	Cycle intervals (wk)			
Versions	4	5	6	8
I. MOPP, standard	1	0.80	0.67	0.50
II. VCR[a] total, 2 mg; PCZ scaled up; 14 days	0.92	0.74	0.61	0.46
III. VCR total, 2 mg; PCZ scaled up; 10 days	0.82	0.66	0.55	0.41

[a] VCR, vincristine; PCZ, procarbazine.

2, and 4 weeks, respectively. Schedule 1 uses a 4-week cycle interval and is the intended dose intensity of the MOPP program as used at NCI. As already indicated, it is only 70% of the dose intensity of all three drugs given at full doses over 6 months without rest intervals. Giving the NCI standard with an extra week between cycles results in a 20% reduction in average dose intensity per cycle. Version 2 is used in many clinical studies (29–32) and limits the dose of vincristine to a 2-mg total dose, in effect a full dose for a person with a 1.43 m^2 area, and procarbazine is scaled up in dose slowly, a practice used in the clinic to avoid nausea and vomiting. If given on schedule, version 2 has an 8% decrease in average dose intensity. Version 3 is used in some clinical trials and by many practicing oncologists (14–16, 33, 34). The schedule of administration of procarbazine is shortened to 10 days along with the other dose modifications already mentioned. This results in an average decrease in RDI of 18%, a reduction in the range that causes significant loss of cure rate in the Ridgway osteogenic sarcoma, even if given on schedule. It is, however, rarely given on schedule. This version of MOPP is more often given at 5-week intervals with a resulting dose intensity decrease of 34%. It will be noted that in some studies of Hodgkin's disease additional significant changes are made such as the omission of a single drug, usually vincristine or procarbazine, entirely from the combination.

Table 7 shows estimates of both intended and actual dose intensity in eight studies with MOPP (11, 14–16, 26, 29–32, 35, 36). It was possible to estimate actual dose intensities in only five of these studies. No consistent effect of intended or actual dose intensity is noted on complete response rates. However, the relationship between dose intensity and the fraction of patients treated who are free of disease for a reasonable interval is more revealing. If we examine the data on actual dose intensity, a 29 to 38% decrease in dose intensity in the Eastern Cooperative Oncology Group and Milan studies, respectively, results in a 33 and 35% decrease in overall disease-free survival. A regression analysis shows a correlation coefficient of 0.88 ($P < 0.02$). The difference in outcome between MOPP and the next three programs in Fig. 3 is significant at $P < 0.001$. Translated to a national basis, a decrease in dose from 85% of the intended dose to 60% could result in the overall loss of the lives of 1000 patients per year, a side effect that far exceeds any serious toxicity and/or mortality from full doses of MOPP treatment.

Table 7 *Intended and actual dose intensity of MOPP from eight clinical trials related to complete response rate and survival free of disease*

Data on actual dose intensity are estimated from published papers, and the fraction of patients free of disease was determined using both the complete remission rates and relapse-free survival curves for specific matched subsets of patients to make the data comparable across studies.

Study/author	RDI *vs.* NCI MOPP	Actual RDI	Complete remission rate (%)	% of patients free of disease at yr
NCI/DeVita (11)	1	0.85	84	55 (15)
Stanford/Carde (26)	0.95	0.64[a]	72	30[b] (5)
BNLI[c]/Goldman (35)	0.82		52	30 (5)
SEG/Huguley (14)	0.82	0.64	46	16 (2)
CALGB/Nissen (30)	0.81		74	37 (5)
ECOG/Bakemeier (29)	0.77	0.60	73	37 (5)
Milan/Bonadonna (32)	0.76	0.53–0.66	74	36[d] (8)
SWOG/Frei (15)	0.70		78	31 (5)

[a] Actual RDI from a prior paper.
[b] Estimate made from patients with marrow stage IV.
[c] BNLI, British National Lymphoma Investigation; SEG, Southeastern Cancer Study Group; ECOG, Eastern Cooperative Oncology Group; CALGB, Cancer and Acute Leukemia Group B.
[d] Estimate made from prior publication of same study.

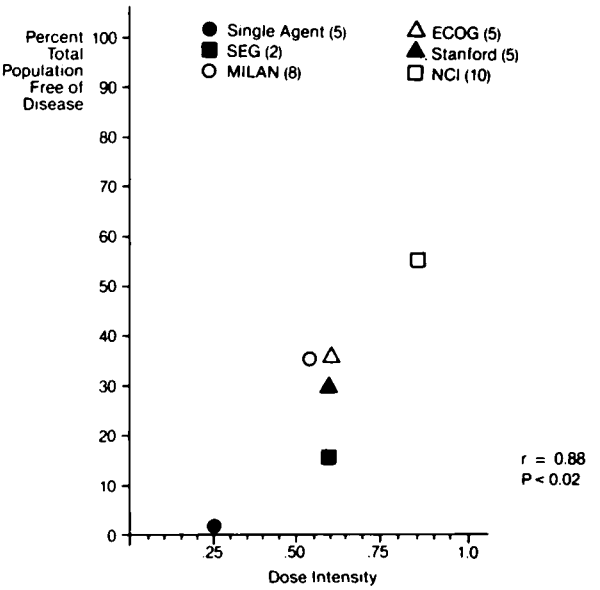

Fig. 3. Relationship between actual dose intensity of MOPP and disease-free survival in Hodgkin's disease. In only a small number of studies of MOPP chemotherapy is it possible to calculate an actual dose intensity based upon delivery of 100% of projected doses of drugs in the original MOPP schema (Fig. 1). In this figure, the idealized MOPP program is designated as 1.0 and the actual dose intensity is calculated as a fraction of the ideal dose actually used to treat the patient population. Actual dose intensity is plotted against disease-free survival at variable times of follow-up indicated by the *number* in *parentheses*. The data demonstrate a statistically significant direct relationship between dose intensity and disease-free survival. *ECOG*, Eastern Cooperative Oncology Group; *SEG*, Southeastern Cancer Study Group.

Table 8 *Actual and intended dose intensities of treatment programs that represent modifications of MOPP by substitutions of vinblastine for vincristine or by substitution of chlorambucil, cyclophosphamide, or a nitrosourea for nitrogen mustard*

Dose intensity was estimated by converting doses of the other drugs to nitrogen mustard and vincristine equivalent doses using the standard dose of each drug as the reference point.

	RDI *vs.* standard MOPP	Actual RDI	Complete remission rate (%)	% free of disease at 5 yr
ChlVPP[a]/McElwain (18)	0.93	0.92	73	46
COPP/Cooper (37)	0.84		67	39[b]
BCVPP/Durant (20)	0.75	0.68	68	47[b]
BCVPP/Bakemeir (29)	0.75	0.62	76	43[b]
MVPP/Sutcliffe (40)	0.67–0.78		82	49[b]
MVPP/Cooper (37)	0.87		72	30[b]

[a] ChlVPP, chlorambucil-vinblastine-procarbazine-prednisone; COPP, cyclophosphamide-vincristine-prednisone-procarbazine; MVPP, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea-vinblastine-prednisone-procarbazine.
[b] Patients received maintenance chemotherapy.

Table 8 shows similar data for combinations that represent modifications of MOPP by additions and substitutions of drugs (18–20, 29, 37–40). Here, we have also followed the practice of Hryniuk and Bush in converting doses of nitrosourea and vinblastine to alkylating agent and vincristine equivalent doses, respectively, (see legend to Table 8). It is not possible to draw any firm conclusions about the impact of the relative dose intensity of these combinations compared to MOPP since the patients in all but one of the studies received continuous maintenance treatment for the duration of the trial.

Several clinical trials have compared MOPP, usually in a reduced version, to one or more of these modifications of MOPP. The Eastern Cooperative Oncology Group compared BCVPP to MOPP (29). The results are significantly different only in their toxicity; MOPP causes more troublesome acute toxicity and BCVPP causes more life-threatening toxicity and leukemia. The version of MOPP used in this study is close to

version 2 in Table 6 given at 5-week intervals. Dose intensity was not considered in the design of this study.

SWOG conducted a study comparing MOPP to MOPP plus the new drug bleomycin (41, 42). The complete response rate with MOPP in the first SWOG study was 70% compared to MOPP-bleomycin of 87%. The latter program was selected for the next study as the control and it was compared to a new version of MOPP referred to as MOP-BAP (43), a treatment program that replaces a full dose of nitrogen mustard with a half-dose of adriamycin. The complete response rate with MOPP-bleomycin in the second study decreased to 67%, which was inferior to the complete response rate for MOP-BAP of 77%. Although MOP-BAP is said to be superior, the superiority comes at the expense of a declining complete response rate for the control arm in each study with the complete response rate of MOP-BAP not being significantly better than that of MOPP alone in the original SWOG study. While these trends could be accounted for by a shift of prognostic factors in the patients in later studies to a poorer prognostic group, which is often cited as the reason for the failure to improve results with each subsequent study, there is no evidence that such a shift in the patient population has occurred. The only consistent change in variables is the manipulation of dose intensity and untested drug substitutions.

In the Milan trial already referred to (31, 32), an effect of dose intensity seems even clearer. After a series of clinical trials showed the new four-drug combination, ABVD, to be effective in patients who had failed MOPP (44) and equivalent to MOPP in previously untreated patients (31, 45), the Milan group conducted a comparison between MOPP alone and MOPP and ABVD given as alternating monthly cycles (46). The rationale for this approach is reviewed elsewhere (31, 32, 46). The results are summarized in Table 9. While the complete remission rates and overall survival are not significantly different between the two programs, the relapse-free survival and overall survival was superior for MOPP-ABVD (32).

The results with MOPP, however, are the worst ever reported. Fifty percent of all patients in the MOPP arm of the Milan study relapsed in the first 24 months compared to only 36% of patients relapsing over a 14-year median follow-up in the NCI study. The poor results are best illustrated by focusing the analysis on the response and survival of the good prognosis asymptomatic patients who make up a substantially larger portion of this study population than at NCI. Rather than the 96% relapse-free survival rates seen in the studies reviewed above, only 35% of asymptomatic patients in stage IIIA in the Milan trial remain free of disease. Close scrutiny of Table 9 reveals that doses of some drugs in MOPP alone were severely curtailed. For example, 35% of patients received a 50% reduction in the dose of vincristine and, in 9% of patients, the integrity of the combination was entirely disrupted as vincristine was permanently discontinued. The problem with dose rate in this study is reemphasized by the median time to complete remission, 5 months in the Milan trial, compared to 2 months in the NCI study, a significant variable related to remission duration in our study. Considering the importance of dose and dose rate of vincristine in the NCI study, these are serious disruptions of the MOPP program and probably account for the difference in overall outcome. The reason seems related to dose rate. The newer program, MOPP-ABVD, was designed as a 12-month treatment program; MOPP is normally given for 6 months. When the duration of MOPP is prolonged to match the duration of the new program, the capacity of most patients to tolerate vincristine and the other MOPP drugs is exceeded and sharp dose reductions are required.

A study testing the utility of alternating cycles of two non-cross-resistant drug combinations (Fig. 4) has also been conducted by our group in a randomized trial comparing MOPP with MOPP-CABS (47). In this trial, cycles of CABS are alternated with MOPP, but in both arms of the study the projected number of cycles for remission induction is 6 instead of 12 as in the Milan trial. One hundred twenty-seven patients have been randomized: 64 to MOPP and 63 to MOPP-CABS of which 59 and 56, respectively, are currently evaluable. The complete response rate for MOPP is 92% and for MOPP-CABS it is 88%, an insignificant difference, and at 5 years of follow-up the results in both arms are equivalent to or slightly better than the original MOPP study (Fig. 5). Dose intensity of MOPP in this study exceeds that of the original MOPP study because of a dose escalation allowed in this later study. Untested attenuation of doses and dose rate in the Milan trial may have compromised the ability to determine if alternating cycles of non-cross-resistant treatments are significantly better than a single four-drug program alone.

Looking back, all these studies in Hodgkin's disease indicate that advanced disease is indeed curable. Combination chemotherapy is required for cure with a minimum of three cytotoxic non-cross-resistant drugs per program, and the invariable inverse relationship between tumor volume and curability appears to hold in the clinic. Dose and dose rate also seem to have an important impact on outcome.

Table 9 *Result of the 8-year clinical trial comparing 12 months of MOPP to alternating cycles of MOPP and ABVD reported from Milan, Italy*

The long duration of MOPP treatment resulted in marked decreases in doses of vincristine.

	MOPP (%)	MOPP/ABVD (%)	*P*
Complete remissions	74 (32/43)	89 (40/45)	0.14
Median cycles to remission	5	5	
<80% dose	71 (24/43)	86 (22/45)	
Relapse-free survival	45	73	0.01
A	34	64	
B	47	76	
<80% dose	39	71	
Survival	62	76	0.11
Toxicity			
Leukopenia (↓1500)	9	22	
Thrombocytopenia (↓50,000)	16	7	
Alopecia	7	18	
Vincristine			
↓50%	35	7	
Discontinued	9	4	

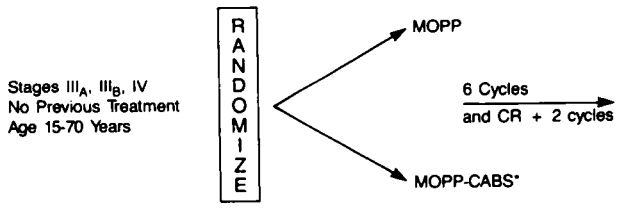

Fig. 4. Current National Cancer Institute study in advanced stage Hodgkin's disease. Patients with advanced stage Hodgkin's disease (without a mediastinal mass greater than one-third the greatest anteroposterior chest diameter) are randomized to receive MOPP combination chemotherapy or MOPP alternating with CABS, a four-drug regimen that has been shown to obtain complete remissions (*CR*) in about 35% of MOPP-resistant patients. The duration of treatment is 6 months except in the presence of responding disease in the last two cycles. *, MOPP days 1–28 alternating with 1-(2-chloroethyl)3-cyclohexyl-1-nitrosourea (100 mg/m² p.o., day 29); Adriamycin (45 mg/m² i.v. day 29); bleomycin (15 mg/m² i.m. days 29 and 36); streptozotocin (500 mg/m² i.v. days 29–33).

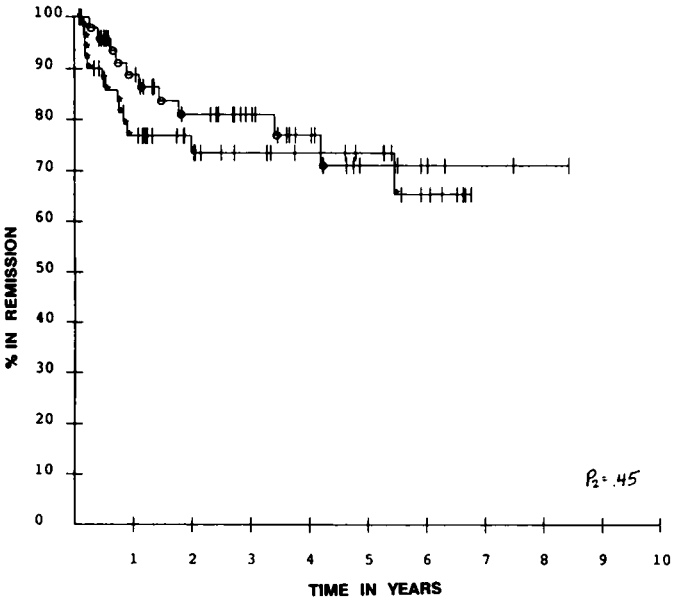

Fig. 5. Duration of complete response in the MOPP *versus* MOPP-CABS study. The percentage of patients remaining in their first chemotherapy-induced remission is plotted against time from the end of therapy for each treatment regimen. There are no significant differences between these treatment programs in duration of complete remission. •, MOPP (13 of 54 failed); O, MOPP-CABS (10 of 49 failed).

Table 10 *Three generations of treatment programs for diffuse aggressive lymphomas*

See references for details of drugs, schedules, and side effects.

Regimen (Institution)	No. of patients	Complete remissions (%)	Long-term survivors (%)
First generation			
MOPP/C-MOPP (NCI) (3)	24	45	35
BACOP (NCI) (49)	32	46	35
CHOP (SWOG) (53)	112	58	<30
COMLA[a] (Chicago) (55)	42	55	<33
Second generation			
COP/BLAM (Cornell) (57)	33	73	55
M-BACOD (Sidney Farber) (60)	101	72	48
CHOP/HOAP/IM VP-16 (61)	56	82	
ProMACE/MOPP (NCI) (62)	80	80	48
HDACC (University of Michigan) (63)	30	80	63
Third generation			
ProMACE/MOPP (75) hybrid cycles	86	77	58
ProMACE/CytaBOM (75) hybrid cycles	82	83	70
MACOP-B (74) (Vancouver, British Columbia, Canada)	125	84	69

[a] COMLA, cyclophosphamide-oncovin-methotrexate-leukovorin-1-β-D-arabino-furanosylcytosine; VP-16, etoposide; M-BACOD, methotrexate-bleomycin-adriamycin-cyclophosphamide-vincristine-dexamethasone; COP-BLAM, cyclophosphamide-vincristine-prednisone-bleomycin-Adriamycin-methotrexate; IM, indomethacin; HOAP, Adriamycin, vincristine, 1-β-D-arabinofuranosylcytosine prednisone; IM VP-16, ifosphamide, methotrexate, VP-16; HDACC, high-dose Adriamycin, vincristine, prednisone, cyclophosphamide, 1-β-D-arabinofuranosyl-cytosine.

Diffuse Large Cell Lymphomas

In 1974, we reported that patients with advanced stages of the tumor then known as reticulum cell sarcoma or diffuse histiocytic lymphoma were curable using a variant of the MOPP program referred to as C-MOPP which substitutes cyclophosphamide for nitrogen mustard (3, 48). Cures had, as in Hodgkin's disease, not been possible with single agents. These results were quickly confirmed by others (49, 50). In these first generation studies (Table 10) about one-third of all treated patients achieve long-term disease-free survival (48–55).

The generation of studies that followed, shown in Table 10, added drugs to the treatment programs which generally improved results (56–63). When the aggregate results of the two generations of studies are compared it appears that the addition of two drugs to each combination has, on the average, increased the remission rate by about 30% and increased the overall survival by 40–50%. The outline of the ProMACE part of our own second generation study, ProMACE-MOPP flexitherapy, is shown in Fig. 6. ProMACE is given in alternate cycles with MOPP starting with ProMACE, and using each to maximum rate of clinical response (62). When we compared tumor mortality of our first generation programs (C-MOPP and BACOP) to the second generation program, (ProMACE-MOPP flexitherapy) we found a significant advantage for the six-drug combination (Fig. 7). You should note the shape of the relapse-free survival curve. It differs from Hodgkin's disease in that most adverse events tend to take place in the first 2 rather than the first 4 years, so it is possible to estimate the effectiveness of a new program in diffuse aggressive lymphomas from the complete remission rate and relapse-free survival somewhat sooner. The ability to achieve a complete remission is affected

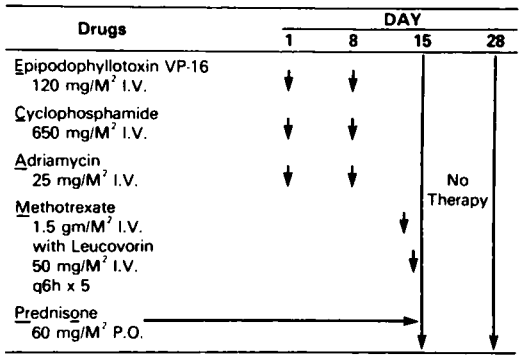

Fig. 6. Schema for the ProMACE combination chemotherapy regimen. Etoposide (*VP-16*), cyclophosphamide, and doxorubicin are administered i.v. on days 1 and 8, high dose methotrexate is administered on day 14 with leucovorin rescue on day 15, and prednisone is given p.o. each day on days 1–14. No therapy is given on days 16–28. The flexitherapy program was designed to adjust the therapy to the rate of response in individual patients. ProMACE was given until the rate of response decreased. Then patients received MOPP chemotherapy for the same number of cycles for which ProMACE had been given. Finally, patients received consolidation therapy with ProMACE. In general, patients received 2 or 3 cycles of each phase of treatment.

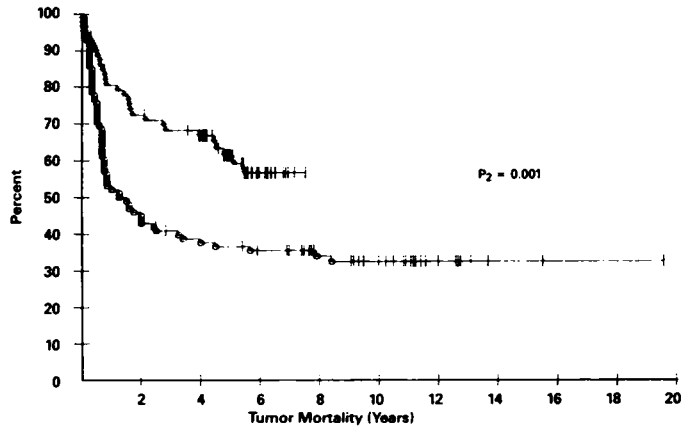

Fig. 7. Tumor mortality of diffuse lymphoma patients treated with ProMACE/MOPP flexitherapy *versus* C-MOPP or BACOP. The percentage of patients not dead of lymphoma is plotted against time of diagnosis for patients treated with either ProMACE-MOPP flexitherapy or either C-MOPP or BACOP. Patients treated with C-MOPP or BACOP are pooled because of their similar complete response rates and disease-free survival. Although comparisons of nonconcurrent series of patients may fail to consider some important differences in the two populations, it appears that the second generation treatment program results in a significantly larger fraction of patients surviving their lymphoma. •, ProMACE-MOPP (30 of 80 failed); O, C-MOPP-BACOP (65 of 99 failed).

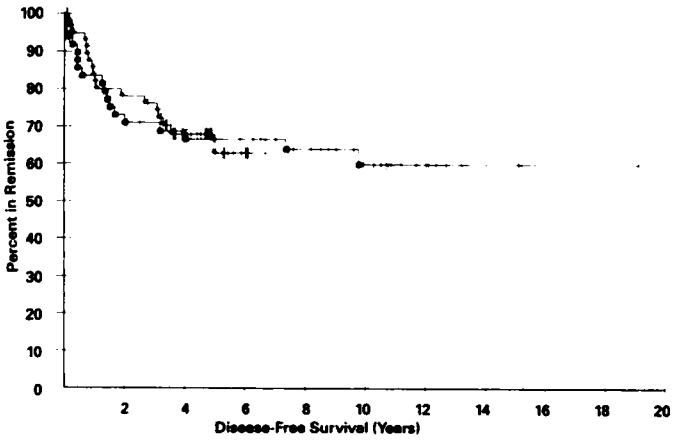

Fig. 8. Disease-free survival of diffuse lymphoma patients achieving complete remission with ProMACE-MOPP flexitherapy *versus* C-MOPP or BACOP. The percentage of patients remaining in their initial chemotherapy-induced complete remission is plotted against time in years from the end of therapy for patients treated with ProMACE-MOPP flexitherapy *versus* C-MOPP or BACOP. The data suggest that the major difference in outcome between the first and second generation treatment programs is in the fraction of patients achieving complete remission. Once complete remission is achieved, the probability of remaining free of disease is comparable between the regimens. •, ProMACE-MOPP (18 of 60 failed); ●, C-MOPP-BACOP (18 of 49 failed).

by prognostic factors that reflect tumor volume such as levels of lactate dehydrogenase, which reflects tumor mass, large measurable tumor masses, and specific sites of involvement such as bone marrow or gastrointestinal tract (64). The importance of attaining a complete remission is illustrated in Fig. 8 in which the relapse-free survival curves of the two generations of programs at NCI are compared. Once remission is achieved there appears to be no difference in the likelihood of relapse and cure. The improvement in the overall survival between the two programs appears to be solely related to the ability of patients who previously fell in a poor prognostic category to attain complete remissions with the newer programs. This appears to be due to the greater dose intensity or to greater exposure to a variety of non-cross-resistant antitumor agents in the second generation programs or both.

A Hypothesis on the Development of Drug Resistance to Alter Protocol Design for the Lymphomas

In 1979, Goldie and Coldman proposed that tumor cells undergo spontaneous mutation, resulting in resistance to chemotherapeutic drugs they have never been exposed to, and suggested that this provided the only reasonable explanation for the invariable inverse relationship between cell number and curability by chemotherapy and the effectiveness of combination chemotherapy when compared to single drugs (65). Their model predicted that resistance was occurring at very low tumor burdens, 10^3 to 10^8 cells, levels that are not detectable with usual clinical tests, suggesting that by the time a tumor could be detected, and certainly in patients with advanced stages of cancer, one or more singly or doubly resistant cell lines would be expected to be present (66, 67). The implications for protocol design were that the introduction of as many non-cross-resistant chemotherapeutic agents into treatment programs as early as possible might overcome or circumvent drug resistance. In the clinic, lymphomas served as a convenient model to test this hypothesis since they are partially but not totally curable by chemotherapy and more drugs are available to construct new combination programs. Some of the studies already mentioned used alternating cyclical chemotherapy and have been used as examples of the testing of this hypothesis in clinical practice. Most of these studies, however, were designed intuitively, before the hypothesis was developed. Others did not consistently incorporate three of the important features required for the testing of the Goldie-Coldman hypothesis, such as the requirement for equivalent efficacy, the use of equieffective doses, and the clear demonstration that newer programs were not cross-resistant to the older programs. From the data reviewed above in Hodgkin's disease, a test of the hypothesis was possible in the two studies comparing MOPP-ABVD and MOPP-CABS to MOPP alone. The results are conflicting. Because of dose variables that were not adequately controlled, the apparent success of alternating non-cross-resistant combinations in the Milan trial appears spurious. The MOPP-CABS data suggest that the hypothesis does not apply in Hodgkin's disease or that agents fulfilling the criteria for non-cross-resistance are not yet available.

The several studies generated after the publication of the Goldie-Coldman hypothesis are, however, of considerable interest although it is too early to be certain of their impact on the outcome in advanced lymphomas. In Hodgkin's disease there are two such studies in progress. The Milan group introduced more agents sooner by giving a hybrid cycle consisting of a half-cycle of MOPP on day 1 and a half-cycle of ABVD on day 15 (MA-MA program). This allowed exposure to eight drugs in 2 weeks at full protocol doses rather than over 2 months. This program is now being compared to MOPP-ABVD (68, 69).

A group from Vancouver, British Columbia, Canada, used a different hybrid program (70). MOPP is given with a truncated dose of procarbazine (7 days) and on day 8, three of the ABVD drugs are given (Adriamycin, bleomycin, and vinblastine). Dacarbazine, normally used in ABVD, is deleted due to its potent emetogenic effects but the dose of Adriamycin is increased to compensate for the deletion. The relative dose intensity of the MOPP portion of the hybrid compared to NCI MOPP is 0.45 but the effect is compensated by the addition of the three drugs from ABVD and the fact that the patient now is exposed to seven different antitumor drugs in 8 days rather than in 2 weeks for the MA-MA program and 5 weeks for the programs used as originally designed. This therapy also has the advantage of requiring only 7 months to administer. A pilot trial showed a complete response rate of 88% for the Vancouver hybrid. With a median follow-up of 35 months, the actuarial relapse-free survival is 90% at 5 years (71). This hybrid program is being compared to MOPP-ABVD, used as reported by Bonadonna, in a Canadian national clinical trial (71).

In diffuse aggressive lymphomas a similar approach has been used. These third generation programs are shown in Table 10 (72–75). The two from NCI alternate half-cycles of ProMACE and MOPP or ProMACE and a new combination, CytaBOM, on days 1 and 8. Exposure to eight drugs occurs in the first 2 weeks of treatment without any significant sacrifice of dose. The treatment programs are illustrated in Figs. 9 and 10. The results have been reported recently (75). The newest program from the Vancouver group [MACOP-B (Table 11)] omits intervals between cycles entirely by alternating, on a weekly basis, myelotoxic and nonmyelotoxic drugs (72–74). The advantage is a higher dose intensity since drugs are administered every week and the duration of treatment is shorter. ProMACE-CytaBOM and MACOP-B require only 18 and 12 weeks of treatment, respectively. The results are encouraging and suggestively better than second generation programs. Interestingly, these programs are less marrow toxic than the same programs

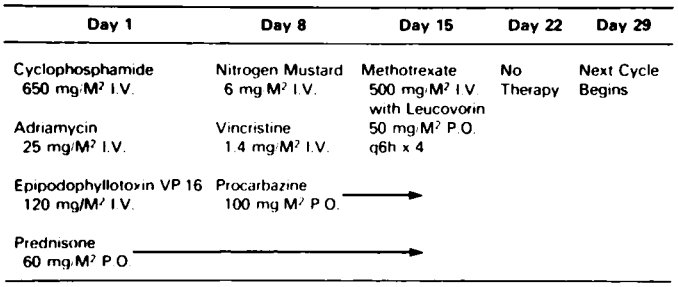

Fig. 9. Schema for the ProMACE-MOPP combination chemotherapy program. Etoposide (*VP-16*), cyclophosphamide, and doxorubicin are given i.v. on day 1 as in the ProMACE program, nitrogen mustard and vincristine are given i.v. on day 8, procarbazine is given p.o. each day on days 8–14, prednisone is given p.o. on days 1–14, and high dose methotrexate with leucovorin rescue is started on day 15. In this program, the ProMACE drugs and MOPP drugs are incorporated into one monthly cycle at full doses with the exception of the methotrexate, which was reduced to one-third of the dose in ProMACE so that it could be safely administered in the outpatient clinic. One cycle is 28 days long.

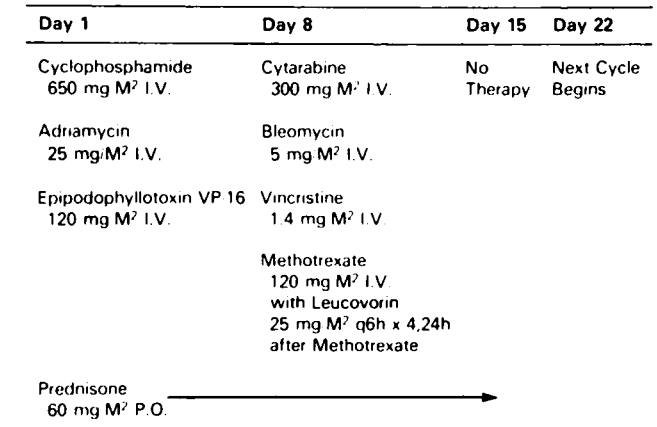

Fig. 10. Schema for the ProMACE-CytaBOM combination chemotherapy program. Day 1 drugs are given as in ProMACE-MOPP and prednisone is administered p.o. each day on days 1–14. However, in contrast to ProMACE-MOPP, on day 8 patients receive 1-β-D-arabinofuranosylcytosine, bleomycin, vincristine, and methotrexate with leucovorin rescue, drugs that are not notably myelosuppressive. This use of nonmyelosuppressive agents on day 8 results in somewhat more rapid marrow recovery from day 1 drugs such that cycles are shortened to 21 days. All patients receiving ProMACE-CytaBOM also receive two double-strength tablets of trimethoprim-sulfamethoxazole twice a day as prophylaxis against *Pneumocystis carinii* pneumonia.

Table 11 *Return of the MACOP-B program to the use of combination chemotherapy without rest intervals between cycles by alternating myelosuppressive with nonmyelosuppressive drugs*

1	2	3	4	5	6	7	8	9	10	11	12
A[a]	V	A	V	A	V	A	V	A	V	A	V
C	M	C	B	C	M	C	B	C	M	C	B

Prednisone daily (75 mg)
Bactrim daily (p.o. twice a day)

[a] A, doxorubicin, 50 mg/m²; C, cyclophosphamide, 350 mg/m²; V, vincristine, 1.4 mg/m²; M, methotrexate, 400 mg/m² (plus leucovorin rescue); B, bleomycin, 10 units/m²; $N = 125$; complete remission, 84%; relapse, 21%; median follow-up, 18 months.

given as alternating monthly cycles, an encouraging step forward.

In order to compare the dose intensity of each of the three generations of combinations for diffuse aggressive lymphomas in some relevant way we have used the method of Hryniuk and Bush to calculate dose intensity of each drug and the average dose intensity of the combinations of drugs, but because there are nine different drugs in use in various ways in the combinations, we have constructed, as a standard of comparison, a hypothetical drug combination that would use all of the drugs in full doses continously. The dose intensity of drugs in the various treatment programs is calculated as the decimal fraction of the dose in the hypothetical combination over the same time frame. A zero is assigned to a drug that is omitted from a combination. A value of one has been assigned to methotrexate, in all studies analyzed, since it is used in doses that require leucovorin rescue, and for corticosteroids since they are always used in full clinical doses. When comparisons are made excluding methotrexate and prednisone from the combinations the average dose intensity is changed but the ranking of the programs is not altered. To examine the effect of the three major drugs used in the first generation programs, compared to second and third generation programs, we also calculated two- and three-drug average dose intensities for Adriamycin and cyclophosphamide separately from the nine-drug dose intensity and for Adriamycin, cyclophosphamide, and vincristine. These data are shown in Table 12 and Fig. 11.

As might be expected, more recent drug combinations have the highest average relative dose intensity (Table 12) and Fig. 11 shows that there is a strong correlation of the nine-drug relative dose intensity to outcome ($r = 0.82$; $P < 0.0008$). There is no discernible relationship of outcome to two- or three-drug relative dose intensity ($r = 0.11$; $P = 0.37$). For example, BACOP has the same two- and three-drug relative dose intensities as MACOP-B but results were poorer with BACOP. We are, it should be noted, in all cases sacrificing average dose intensity (the highest nine-drug relative dose intensity is 0.52 compared to the hypothetical combination) in order to combine active drugs. In other words, we are using combination chemotherapy today at the low end of the dose-response curve. Nonetheless, the third generation programs use more drugs, provide early exposure to non-cross-resistant agents with less marrow suppression, and have the highest dose intensity of all programs in common use.

Dosing effects are also easily discernible within some programs. For example, Fig. 12 illustrates the impact of dosing on outcome in the CHOP program. Overall, this first generation program produces about 30% long-term disease-free survival although in the earliest study the long-term disease free survival has declined to 21% (53). CHOP is a popular program in the practice of oncology because it is easy to administer. Fig. 12 shows that although it is possible to cure some patients (approximately 12%) with low doses of CHOP, a significantly greater fraction (41%) who receive full doses have long disease-free survival. In both cases the results appear inferior to newer programs, a fact that has not deterred the continued widespread use of CHOP.

If further reaffirmation of the importance of dose intensity is needed, the use of autologous bone marrow transplantation provides the proof (76–79). In patients with Hodgkin's disease and lymphocytic lymphomas who have failed all therapy, including treatment with radiation therapy and the programs reviewed above, 36 to 100% of small series of patients have been reported to attain complete remission, with extremely high doses of the various anticancer drugs to which they no longer responded when used in conventional doses. The doses used required autologous marrow transplantation to overcome the ablative effect on their bone marrow. Durable remissions have occurred, and relapse-free survivals are reported in the range of 19 to 64% (76–79).

Next Generation of Combination Chemotherapy in Lymphomas

The most important point to emerge from the analysis of the relationship of dose intensity to outcome is that we have not

Table 12 *Two-, three-, and nine-drug relative dose intensities of nine primary treatment programs for diffuse aggressive lymphomas (see text)*

Regimen[a]	Duration of treatment (mo)	% of long-term survival	% of standard	RDI 9 drugs	RDI 3 drugs	RDI 2 drugs	Drug exposure first 2 wk
1. MACOP-B	3	69	1	0.51	0.78	0.74	5/6
2. ProMACE/CytaBOM (1, 8)	4.5	70	0.94	0.48	0.50	0.46	8/8
3. ProMACE/MOPP (1, 8)	6	58	0.86	0.44	0.52	0.56	6/7
4. ProMACE/MOPP	8	48	0.84	0.43	0.50	0.60	5/7
5. M-BACOD	7	48	0.82	0.42	0.51	0.54	5/6
6. BACOP	6	35	0.76	0.39	0.75	0.69	3/5
7. MOPP	6	35	0.71	0.36	0.58	0.44	4/4
8. COMLA	9	<33	0.55	0.28	0.24	0.17	2/4
9. CHOP	6	<30	0.51	0.26	0.46	0.50	4/4

[a] COMLA, cyclophosphamide-vincristine-methotrexate-leukovorin-1-β-D-arabinofuranosylcytosine; M-BACOD, methotrexate-bleomycin-adriamycin-cyclophosphamide-vincristine-dexamethasone.

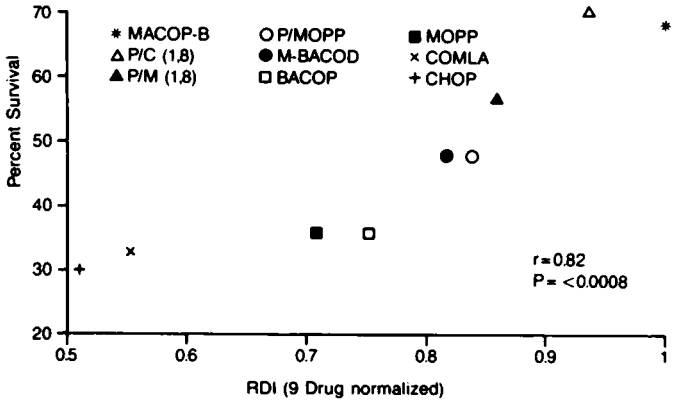

Fig. 11. Relationship between normalized nine-drug relative dose intensity and disease-free survival in diffuse large cell lymphomas. The nine most extensively studied treatment programs for diffuse large cell lymphomas use nine different drugs in some permutation. Each of the nine regimens was evaluated for its relative dose intensity based upon delivery of full doses of all nine drugs. Of course, none of the programs achieved such an ideal since they use from four to eight drugs. The regimen that had the highest relative dose intensity was MACOP-B. Its dose intensity was arbitrarily rated as 1 and the other regimens were normalized to MACOP-B, thus giving a normalized 9-drug relative dose intensity. The long-term survival of each regimen was plotted against the normalized nine-drug relative dose intensity. A statistically significant relationship was found between dose intensity and disease-free survival. *COMLA*, cyclophosphamide-oncovin-methotrexate-leukovorin-1-β-D-arabinofuranosylcytosine; P/C (1, 8), ProMACE-CytaBOM (1, 8); P/M (1, 8), ProMACE-MOPP (1, 8); P/MOPP, ProMACE-MOPP; M-BACOD, methotrexate-bleomycin-adriamycin-cyclophosphamide-vincristine-dexamethasone.

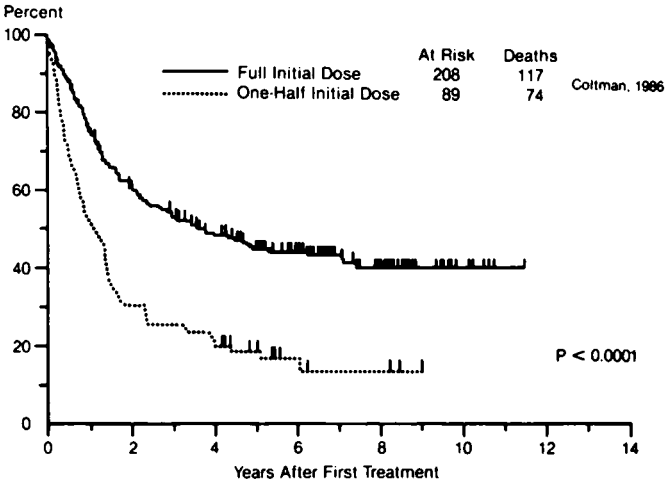

Fig. 12. Effect of dose of CHOP on treatment outcome in Southwest Oncology Group studies in advanced stage diffuse large cell lymphoma. The Southwest Oncology Group has conducted a number of studies of the treatment of diffuse large cell lymphoma using CHOP combination chemotherapy and variations on CHOP. A provision in the protocols allows physicians, at their discretion, to deliver CHOP at one-half the protocol dose if the patient is over age 65 or has other clinical problems that the physician thinks might affect tolerance to chemotherapy. This curve depicts the percentage of all patients surviving as a function of time for those patients receiving initial full dose CHOP *versus* those receiving initial half-dose CHOP. There is a statistically significant survival advantage to those receiving full dose CHOP.[3]

explored to the fullest extent the dose-response curve of combination chemotherapy in drug-responsive human tumors. All current programs in lymphomas use less than full doses of each active agent. This has been viewed as a requirement of extended treatment with drug combinations, with dose intensity declining as more marrow-suppressive drugs are added and the duration of treatment programs is extended, as exemplified in the study of MOPP *versus* MOPP-ABVD mentioned above. These data provide insight to several approaches to improving our capacity to treat effectively with greater attention to dose intensity.

Two general approaches have already been described, that of increasing dose intensity by alternating hybrid half-cycles of known drug combinations or alternating, on a weekly basis, myelotoxic and nonmyelotoxic drugs. The former was done to introduce more non-cross-resistant agents into treatment programs sooner, but a side benefit has been the preservation of dose intensity with less myelotoxicity. The latter approach avoids rest intervals thereby increasing dose intensity. The dose-limiting toxicity is shifted from the bone marrow to the mucous membranes.

There are others ways to improve combination chemotherapy that have not been fully explored. The clinical data reviewed and the data in rodents suggest that patients who have failed one or more drug programs that contain alkylating agents will respond to alkylating agents, or to other drugs as single agents like procarbazine, emphasizing that the doses of these drugs in the combination programs had not been optimized but also providing a way to select the drugs to intensify at the clinical level. Experience in the Ridgway osteogenic sarcoma supports the contention, for example, that if the dose of L-PAM, the better drug in the two-drug combination shown in Table 3, is reduced because of toxicity from 6-MP, the end result is compromised. In the clinic, results with high dose alkylating agents in autologous bone marrow transplant programs and the Stanford data on alkylating agent salvage of MOPP treatment failures also support the view that significant alkylating agent underdosing is taking place in combination chemotherapy programs. Future trials should test not only the use of drugs in combination that more closely approximate their full therapeutic doses but also the impact of increasing dose intensity of the most active agent in the drug combination program while retaining the combination and doses of other agents in the program. By using the best available clinical data, the most effective drug can be selected such as exemplified above. There are now data suggesting that if compromises must be made to increase dose intensity (of individual drugs or entire combina-

[3] C. A. Coltman, personal communication.

tions), it may be possible to do this by reducing the duration of treatment without sacrificing cure, although this requires further study in lymphomas. If so, combination programs using drugs at full therapeutic doses given over 3 rather than the usual 6 to 12 months might be more tolerable and acceptable to patients. Studies of this sort are just beginning in the clinics and require only the testing of well worn principles of treatment, not new therapeutic tools.

If dose intensity is a treatment variable with an important impact on outcome, as the data suggest, then the question of the use of supportive procedures such as autologous bone marrow transplantation, without total body radiation as a requirement for cytoreduction, as part of the primary treatment program, rather than reserving it for patients who have failed all existing therapies, should be considered. Although this approach is rigorous, if it resulted in the salvage of one-fourth to one-third of the newly diagnosed patients, such an approach could be justified. The recent introduction of genetically engineered bone marrow colony-stimulating factors, granulocyte-colony-stimulating factor and granulocyte-macrophage-colony-stimulating factor, also promises to provide a unique opportunity to improve dose intensity of combination chemotherapy in a way similar to autologous bone marrow transplantation by preventing leukopenia normally seen after exposure to chemotherapy. Studies testing this hypothesis are under way at several institutions including our own.

Therapeutic Implications of the New Biology of Lymphomas

The use of biologics, particularly monoclonal antibodies and molecular probes to determine the lineage of lymphoma cells, has already provided more precise diagnostic information (80–90). With few exceptions, however, determining lineage specificity does not explain differences in response rates. With the exception of peripheral T-cell lymphomas associated with human T-cell leukemia/lymphoma virus I infections, phenotyping has not defined clinically useful prognostic subsets in adult lymphomas (90–92). At NCI, for example, diffuse large cell lymphomas of T- or B-cell origin are equally curable (93).

A major problem faced by therapists is the determination of whether or not a patient is in complete remission after therapy. Phenotyping and genotyping can determine clonal excess in peripheral blood or bone marrow lymphocyte populations in patients who appear to be in remission (81, 83, 94, 95). In a study by Smith *et al.* (94), analysis of the proportion of κ to λ light chain-bearing lymphocytes in the peripheral blood showed that, of patients who are in remission more than 18 months, those diagnosed as "diffuse histiocytic" lymphomas had normal ratios and 64% of those with nodular poorly differentiated lymphomas had abnormal ratios, data that fit with the relative likelihood of relapse after current chemotherapy in these tumor types. These kinds of data should be useful in more accurately determining the end point of treatment in the future, particularly if more intense but shorter duration treatment programs are used.

There are cytogenetic abnormalities in most lymphomas with distinct chromosome translocations (96–98). Although there is no known prognostic significance to these findings *per se*, more studies need to be carried out in uniformly staged patients treated with state-of-the-art chemotherapy to determine the true prognostic importance of these data.

Biologics are under intense scrutiny as therapeutic tools in patients with lymphoma. Monoclonal antibodies have attracted considerable attention as therapeutic tools. Currently the most common use is for purging autologous bone marrow in patients about to undergo high dose chemotherapy with autologous bone marrow transplantation (99, 100). Currently clinical data do not substantiate any benefit for purging but the studies suffer from small numbers (76, 100). The lymphomas were also the first human tumor treated with monoclonal antibodies (101–103). Much excitement was created by the induction of a single complete remission in a patient who had evolved from a low grade follicular B-cell lymphoma to an intermediate grade diffuse lymphoma when treated successfully with antibody to the idiotype of the tumor (102). This patient remains in complete remission some 5 years after treatment (104). Attempts to repeat these results by the original group (105) and others (106, 107) have produced only temporary responses. The main reason for failure to attain durable remission in most cases now appears to be due to point mutations in the variable region of the immunoglobulin gene (108–110), thereby altering the idiotype, although some failures have been due to the unanticipated presence of more than one clone of malignant cells (biclonal lymphomas) (111–113). Despite the clonal variation that has been seen in the cells of patients with follicular lymphoma, there appears to be potential for therapeutic efficacy with anti-idiotype-directed monoclonal antibodies that has not yet been fully evaluated. The anti-idiotype antibodies seem to have the greatest clinical effect when given to patients with a substantial number of T-lymphocytes infiltrating the lymphoma involved (104). It is conceivable that the antibodies might be more effective if given in conjunction with cytotoxic cells bearing the Fc receptors that might mediate tumor cell killing or together with lymphokine-activated killer cells and interleukin 2. The monoclonal antibody T101 specific for a M_r 65,000 protein expressed on all peripheral T-cells and some normal B-cells has been used to treat and image B-cell chronic lymphocytic leukemia and cutaneous T-cell lymphoma, malignancies that nearly always react with T101 (103, 114). Antibodies to the transferrin receptor react with a subset of cells in many lymphomas and there appears to be correlation between the expression of this receptor and the proliferating fraction of the lymphoma on flow cytometric analysis (115). Radiolabeled antiferritin polyclonal antibodies, raised in multiple species, have also been used in patients with Hodgkin's disease with the report of temporary partial remissions in about one-third of previously treated patients (116). These observations raise the possibility of attacking only the proliferating population of tumor cells with an immunological approach to complement cytotoxic chemotherapy, in that it could be administered during a phase of treatment in which the patient was recovering from acute marrow toxicity of chemotherapy. A number of other studies are under way, or proposed, using monoclonal antibodies to specific cell surface determinants, including the use of antibodies reactive with Reed-Sternberg cells in Hodgkin's disease (117, 118) and to other determinants in B- and T-cell lymphomas (91, 119).

In general, the results of monoclonal antibody studies have been at best short-term, partial or less than partial responses (120). Imaging studies have shown that the vast majority of label localizes in the reticuloendothelial cells. However, despite problems of poor localization, immunomodulation, the secretion by the tumor of the specific antigen, and variability in antibody affinity, there is much potential for this therapeutic modality (120). Although the development of human monoclonal antibodies has been slow, the application of molecular genetic techniques to engineer monoclonal antibodies with high affinity mouse variable region genes and high efficiency human

heavy chain constant regions may lead to improved results (121, 122).

Limited clinical experience is available in the treatment of lymphomas with lymphokines such as interferon, interleukin 2, or tumor necrosis factor. Therapeutic efficacy of interferon is greatest in the uncommon hairy cell leukemia (123). Nearly three-fourths of the patients achieve good partial remissions and normalization of blood counts with continued therapy (124–127). Interferon also has clinically useful effects in low grade follicular lymphomas although the data are preliminary (128–132). Some patients can attain apparent complete remissions with interferon alone, although in most cases they are not durable when treatment is discontinued. Its effectiveness is equivalent to some new anticancer drugs and it seems likely to find use in conjunction with other treatments, perhaps even preceding chemotherapy, to reduce tumor cell mass and mutability. Perhaps the greatest potential use of interferons for lymphoma therapy is their use in conjunction with monoclonal antibodies, lymphokines, or adoptively transferred cells. Interferons, especially γ-interferon, can increase the expression of certain cell surface antigens on tumor and normal cells (133, 134), an effect that might potentiate the efficacy of antibodies. In addition, *in vivo* synergy, *vis-à-vis* antitumor effects, has been observed between γ-interferon and tumor necrosis factor. There is also interest in extending the use of interferon-activated monocytes to the therapy of hematopoietic tumors (135).

Interleukin 2 has been used alone and in combination with cells activated *in vitro* by interleukin 2 as a form of adoptive immunotherapy (136). Studies in nine patients with advanced drug-resistant B-cell derived follicular mixed (three patients) and diffuse large cell lymphomas (six patients) at NCI have met with some preliminary successes. Of the nine patients treated, one has attained a complete remission lasting 8 months and four have had partial remissions.[4] Effectiveness of interleukin 2 and lymphokine-activated killer cells against advanced cases of B-cell lymphoma would provide an attractive adjuvant treatment to eradicate minimal residual malignant cells in patients who have achieved complete remissions with combination chemotherapy.

Other lymphokines that may mediate antitumor effects of lymphomas include: lymphotoxin (137), a glycoprotein related to tumor necrosis factor that appears capable of lysing certain cell lines from patients with relapsed diffuse large cell lymphomas; cytolysin, the protein from cytotoxic T-lymphocytes responsible for mediating tumor lysis (138); and leukoregulin, the cytostatic lymphokine released from lymphocytes upon exposure to tumor cells that interferes with tumor cell, but not normal cell proliferation (139). The effect of lymphotoxin can be augmented by interferons (140). The clinical development of these factors and exploration of their use in combinations and integrated with chemotherapy and radiation therapy is an important goal for therapeutic research over the next few years.

One of the difficulties we face with biologics is their integration into existing clinical protocols. In animal systems, the inverse relationship between cell number and curability, first noted with chemotherapy, is even more dramatic with most biologics. Considering the differences in toxicity between biologics and chemotherapy it is reasonable to assume that biologics should be used soon after identification of clinical activity in phase II trials, especially in patients who attain a complete remission after combination chemotherapy and have a high risk of relapse.

[4] Unpublished observations.

Conclusion

Looking back, the most important aspect of chemotherapy of lymphomas has not been the development of any individual treatment program, but rather the demonstration that chemotherapy could cure a significant fraction of patients with a common malignancy affecting a major organ system in adults. Although these treatments are cumbersome and complicated, one-half of all adults with lymphomas are now curable with treatment programs that involve combination chemotherapy alone or in conjunction with radiotherapy. However, the experimental method, so useful in the laboratory, has proved difficult to apply in clinical trials. Only after long years of analysis has it become apparent that controllable variables like dose intensity have not been carefully managed, and this failure may well account for the plateau effect in long-term survival noted in recent sequential studies of the chemotherapy of lymphomas. A requirement for publication of clinical trials in the future should be the provision of adequate data on total dose and dose rate for each drug used in the study to allow more accurate interpretation of dose intensity as a treatment variable. Furthermore, analysis of these data should provide new insight for the design of future clinical trials.

Moving forward, we are faced with the interesting challenge of integrating new agents, some naturally occurring or genetically engineered biologics and other synthesized biochemicals that mimic sequences of protein or DNA, into existing clinical trials to accelerate their movement from bench to bedside. Considering the plethora of new ideas and new agents that require testing, physicians should be encouraged to become partners in this effort by considering all patients with lymphomas in the United States candidates for clinical trials.

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