COMBINATION CHEMOTHERAPY OF HODGKIN'S DISEASE WITH ADRIAMYCIN, BLEOMYCIN, VINBLASTINE, AND IMIDAZOLE CARBOXAMIDE VERSUS MOPP

GIANNI BONADONNA, MD,* ROBERTO ZUCALI, MD,† SILVIO MONFARDINI, MD,‡ MARIO DE LENA, MD,§ AND CARLO USLENGHI, MD‖

This paper reports the preliminary results of a controlled study randomizing MOPP vs. a new four-drug combination (ABVD) in advanced Hodgkin's disease. ABVD consists of 6 cycles of adriamycin, bleomycin, vinblastine, and imidazole carboxamide. The purpose for designing this new combination was two-fold: to compare the efficacy of ABVD with MOPP, and to demonstrate absence of cross-resistance between the two regimens. Of 60 patients entered into the study, 45 (MOPP 25, ABVD 20) are presently evaluable for the analysis of remission induction. No patient was previously treated with chemotherapy; 20% had relapsed after primary radiotherapy. Whenever possible, complete remission was defined also through rebiopsy of known organ involvement. Complete remission occurred in 76% of patients treated with MOPP and in 75% of those given ABVD, with no difference between the two regimens as far as stage (IIIB–III$_S$ and IV), histologic type, and prior irradiation were concerned. Crossover carried out for progressive disease or for relapse after initial remission showed absence of cross-resistance between MOPP and ABVD. Toxic manifestations after ABVD were in general well tolerated and reversible. The percent of optimal dose for each drug was as follows: adriamycin 87%, vinblastine 87%, bleomycin 96%, and imidazole carboxamide 96%. These preliminary results indicate that in terms of complete remission, ABVD could represent a successful alternative to MOPP to be used either in MOPP failures or in sequential combination with MOPP. However, the lack of long-term followup limits at the present time an adequate comparison between the two treatments.

Cancer 36:252–259, 1975.

THE QUADRUPLE COMBINATION KNOWN AS MOPP (mechloretamine, vincristine, procarbazine, and prednisone) has become in recent years the most widely used form of chemotherapy in advanced Hodgkin's disease. The incidence of complete remissions after six to eight cycles in patients untreated and previously treated with either radiotherapy or chemotherapy is well established.[7,14–16,19,22,27,30,31] The long-term results appear most encouraging in about half of complete responders.[16,19,27,31] MOPP has become almost the symbol of recent progress made in the control of neoplastic disease.

Several new combinations were subsequently designed with the intent to improve both the incidence of complete remission and the duration of response.[13,17,21,23,25,30] However, none of the current regimens has shown a definite therapeutic superiority when retrospectively compared to MOPP. The main characteristic of these otherwise effective combinations was that all have included one or more drugs already present in the original MOPP. Therefore, from the point of view of drug combination they could

Presented at the 65th Annual Meeting of the American Association for Cancer Research, Houston, TX, March 27–30, 1974.

From the Istituto Nazionale Tumori, Milan, Italy.

* Associate Director, Division of Clinical Oncology F.

† Clinical Assistant, Division of Radiology, Assistant Professor of Radiology, University of Milan.

‡ Clinical Assistant, Division of Clinical Oncology F.

§ Clinical Assistant, Division of Clinical Oncology F.

‖ Assistant Professor of Radiology, University of Milan.

Address for reprints: Dr. Gianni Bonadonna, Istituto Nazionale Tumori, Via Venezian 1, 20133 Milano, Italy.

The authors wish to knowledge the useful co-operation of Dr. Renato Musumeci for critically reviewing all lymphograms, and Dr. Pasquale Spinelli for performing peritoneoscopies.

Received for publication July 17, 1974.

be regarded somehow as MOPP modifications. A multiple drug combination designed to include some of the drugs known to be effective in Hodgkin's disease and not present in the classical MOPP would be very useful. First of all, such a new combination could be effectively employed in MOPP failures. Furthermore, it could be used in appropriate sequence with MOPP to increase the percentage of complete responders and, more important, the number of long-term survivors free of disease.

New effective drugs have recently appeared on the horizon of cancer chemotherapy. Among them, adriamycin (ADM), bleomycin (BLM), and nitrosourea derivatives (BCNU, CCNU, Me-CCNU) were all found to produce objective response, through a wide range of treatment schedules, in 40 to 60% of patients with advanced Hodgkin's disease.[2-5,10,11,28] Moreover, Frei et al.[18] reported in 1972 that 5-(3,3-dimethyl-1-triazeno) imidazole-4-carboxamide (DTIC) administered intravenously in 5-day courses at the initial dose of 250 mg/m^2 induced complete plus partial remissions in 10/18 (56%) previously treated patients with Hodgkin's disease, with a median duration of 4 months. The therapeutic effects of DTIC in refractory Hodgkin's disease were also confirmed in our Institute, with the observation of objective response in 5/6 patients. DTIC is nonmyelosuppressive in the majority of patients adequately treated, and when combined with ADM is synergistic in experimental systems without producing additive toxicity.[29] The favorable effects of the combination of DTIC with ADM in human sarcomas were reported by Gottlieb et al.[20]

On the base of favorable results obtained in our Institute with a quintuple drug treatment including mechloretamine (HN_2), adriamycin (ADM), bleomycin (BLM), vincristine (VCR), and prednisone (MABOP),[13] a new combination was designed in 1973 with ADM, BLM, vinblastine (VLB), and DTIC (ABVD). ADM, BLM, and DTIC are known to be individually non-cross-resistant to drugs included in MOPP; also, VLB appears to show little cross-resistance with VCR in humans.[8] The purpose of combining these four drugs was two-fold: 1) to compare in terms of remission induction the efficacy of ABVD with MOPP; 2) to demonstrate the absence of cross-resistance between the two combinations.

This paper reports the preliminary results of this prospective controlled study.

PATIENTS AND METHODS

Patient Sample

A total of 60 patients (30 in each treatment group) was entered into this study between April, 1973 and January, 1974. At the present moment, 45 are considered evaluable for the analysis of remission induction (MOPP 25, ABVD 20). The remaining patients are not considered evaluable since they have not yet completed the induction phase. The distribution of patients by age, sex, histologic type, stage, and previous therapy is presented in Table 1. The

TABLE 1. Main Features of Evaluable Patients

		MOPP (25 cases)	ABVD (20 cases)
Mean age (yr)		38 (6–60)	37 (5–67)
Median time from diagnosis to treatment (mo)		2	2
Sex			
Males		12	14
Females		13	6
Histology			
Lymphocyte predominance		1	1
Nodular sclerosis		12	10
Mixed cellularity		7	7
Lymphocyte depletion		5	2
Stage			
Clinical		1 (4%)	2 (10%)
Pathologic		24 (96%)	18 (90%)
IIB	untreated	2	1
	prior RT	0	0
IIIB–III$_S$ (A + B)	untreated	8/11	10/11
	prior RT	3/11	1/11
IV (A + B)	untreated	8/12	5/8
	prior RT	4/12	3/8

Lukes and Butler histopathologic classification was used.[24] A total of 11 patients (MOPP 7/25, ABVD 4/20) had received radiotherapy (RT) prior to combination chemotherapy and had relapsed to primary irradiation program. No patient was previously treated with chemotherapy.

History, physical examination, complete blood-counts, liver function tests, skin tests, chest roentgenogram with tomography in the presence of mediastinal adenopathies, skeletal survey, bipedal lymphangiography, liver-spleen scans, and bone marrow biopsy with Jamshidi needle were done routinely. Staging was performed in accordance with the Ann Arbor classification.[9] In 8/42 patients (19%), peritoneoscopy was carried out in place of laparotomy. For the sake of simplicity, patients relapsing after RT were staged as the untreated patients in relation to their lymphatic or extralymphatic involvement.

Treatment Program

MOPP was administered according to the classical dose schedule as originally described by De Vita et al.[14] In the absence of progressive disease, ABVD was also administered in monthly cycles for a total of six treatments. ABVD consisted of ADM (25 mg/m^2, i.v.), BLM (10 mg/m^2, i.v.), VLB (6 mg/m^2, i.v.), and DTIC (150 mg/m^2, i.v.). The first three drugs were administered on day 1 and 14, while DTIC was given during the first 5 days of each cycle. No treatment was given from day 15 to 28. In the first three patients (all untreated) of this series, ADM, BLM, and VLB were repeated on day 8 during cycles 1 and 2. Because of consistent leukopenia (WBC 2500–2000/mm^3) present in all patients on day 8, in subsequent cycles as well as in all other patients the second administration of these drugs was always done on day 14. Table 2 presents the dose adjustments used during both treatments. Virtually all patients were treated and managed on an outpatient basis.

In the presence of progression during induction or relapse before 8 weeks from the sixth cycle (induction failure), crossover was carried out. Although this report will deal only with remission induction, it is worth mentioning that the subsequent treatment program in responsive patients includes low-dose (3000–3500 rads) high-energy RT delivered to involved as well as to adjacent lymph-node-bearing areas (extended-field RT in Stage IIB and total nodal irradiation in Stage IIIB–III$_S$) in patients with lymphatic extension. In these patients no further treatment is given after completion of RT. In those with extralymphatic disease RT is delivered to sites of major pretreatment involvement (including lung, liver, and bone), followed by six more cycles of either MOPP or ABVD administered every 2 months.

Assessment of Results

Before starting a new cycle, chest roentgenogram and followup films of retroperitoneal nodes were carried out in practically all patients. One month after the end of the sixth cycle or after disappearance of all visible signs of disease for at least 1 month, skeletal survey and liver scan (or liver-spleen scan in non splenectomized patients) were repeated. At the same time needle biopsy of either bone marrow and/or liver (peritoneoscopy with four biopsies) was also performed if these two sites were known to be involved.

A patient was considered in a state of com-

TABLE 2. Dose Reduction Schedule Before Starting Each Course

WBC count per mm^3	Platelet count per mm^3	Dose adjustment MOPP ABVD
>4000	>130,000	100% of all drugs
3999–3000	129,000–100,000	100% VCR, DTIC, BLM, PRED. 50% HN_2, ADM, VLB, PROC.
2999–2000	99,000–80,000	100% BLM, PRED 50% VCR, DTIC 25% HN_2, ADM, VLB, PROC.
1999–1500	79,000–50,000	100% BLM, PRED. 25% VCR, DTIC NO HN_2, ADM, VLB, PROC.
<1500	<50,000	100% BLM, PRED all other drugs withheld

Pred.—prednisone; PROC—procarbazine.

plete remission (CR) when all symptoms and signs of disease, including roentgenographic, radioisotopic, and biochemical studies had returned to normal. Furthermore, a second biopsy of accessible extralymphatic sites of known involvement such as liver and bone marrow had to be interpreted as negative. One patient in whom there was a complete disappearance of systemic symptoms and lymphadenopathies after 6 cycles of MOPP, although osteoblastic bone lesions remained unchanged, was judged to be a complete response. Partial remission (PR) was defined a 75% or greater (but not complete) reduction in the product of the longest perpendicular diameters of all evidence of disease. Patients with regression of less than 75% or no change in measured tumors by the end of sixth cycle, or with relapse (regrowth of tumor masses and/or appearance of new lesions) during induction or within 2 months from its completion (i.e. before starting RT) were all categorized as induction failures (IF).

RESULTS

Comparison of Response

The comparison of response after primary treatment in relation to stage is presented in Table 3. There is no statistical difference in terms of CR, PR, and IF between MOPP and ABVD. All clinical evidence of disease had disappeared in most patients of both treatment groups after the end of the fourth cycle. In the present series ABVD was usually able to produce a more rapid regression of measurable disease than MOPP; in 7/15 complete responsers a complete disappearance of lesions was observed by the end of second cycle. In both treatment groups the last parameter to return to normal was usually the lymphogram.

In all patients considered clinically in complete remission, the second biopsy of bone marrow and liver was interpreted as negative. The sites of incomplete or no remission were observed in extra-lymphatic structures in 3/12 patients treated with MOPP (liver 1, lung 2) as compared to 1/8 of those given ABVD (liver 1). These findings occurred at the level of adenopathies in 4/25 MOPP patients and in 4/20 ABVD patients, respectively. In a total of 6/8 patients the incomplete regression was observed in retroperitoneal nodes.

The comparison of treatment results in relation to histologic subtypes revealed no significant difference between the two treatment groups. However, it is of note that both patients with lymphocytic depletion achieved CR after ABVD as compared to 2/5 after MOPP. The comparison of response in relation to prior radiotherapy also failed to show a particular difference between MOPP and ABVD, and confirms that the percentage of CR is not influenced by previous irradiation.

Data about crossover for remission induction failure are presently available only for five patients (MOPP two, ABVD three). In one patient with Stage IIIB disease, complete clinical remission was achieved with four cycles of ABVD. Then a progressive relapse occurred only in the mediastinum, despite two more cycles of therapy. One month after the sixth cycle of ABVD, MOPP was started, followed by rapid objective response. A second patient with Stage IV achieved an almost complete clinical remission after six cycles of ABVD. During the time of re-evaluation, there was a relapse of the retroperitoneal adenopathies which showed a prompt objective and subjective response starting from the first cycle of MOPP. As far as results of ABVD as secondary treatment are concerned, one patient with Stage IIB disease initially treated with MOPP, with almost complete remission of lymphoadenopathies, showed by the fifth cycle new manifestations of disease, which failed to regress after the sixth cycle. Crossover to ABVD produced a complete remission after only one cycle. A good partial remission is being obtained in a patient with Stage IV not achieving complete regression after 6 cycles of MOPP. In another patient with Stage IV showing only a minimal re-

TABLE 3. Comparison of Response in Relation to Stage

Stage	MOPP No	CR	PR	IF	ABVD No	CR	PR	IF
IIB	2	1		1	1	1		
IIIB–III$_B$ (A + B)	11	9	2		11	8	1	2
IV (A + B)	12	9	1	2	8	6	2	
TOTAL	25	19 (76%)	3 (12%)	3 (12%)	20	15 (75%)	3 (15%)	2 (10%)

sponse after two cycles of MOPP followed by rapid progression, a transient tumor regression was observed also after two cycles of ABVD. Since the patient died about 1 month from the last dose of ABVD, he was categorized as an induction failure after both treatments.

Three patients died during the induction phase. The cause of death was due to viral hepatitis in one patient while in partial remission after four cycles of MOPP, and to progressive disease in two other cases (one in each treatment group). As already mentioned before, one patient failed to show a consistent response to secondary therapy with ABVD. The second patient died in another hospital with a superimposed bronchopneumonia, and therefore a crossover to MOPP was not performed.

The manifestations of toxicity are reported in Table 4. A various degree of nausea and vomiting occurred in both groups after each drug administration without being significantly relieved by injection of sedatives. In general, patients tolerated fairly well both types of treatments. The prompt disappearance of symptoms and signs of disease was usually followed by improvement in their performance status. Bone marrow suppression represented the main dose-limiting factor, and therefore a temporary reduction of myelosuppressive agents was required. The incidence of transient leukopenia, as determined on the day of drug administration, was higher after MOPP than after ABVD. However, only 1 patient given MOPP showed a WBC less than 2000/mm^3. In both treatments thrombocytopenia occurred in the minority of patients; in no instance was the platelet count determined below 80,000/mm^3. Incidence and degree of myelosuppression were not statistically different between the groups of splenectomized and nonsplenectomized patients, as well as between previously irradiated and previously nonirradiated patients. No infections or hemorrhagic manifestations related to drug administration were observed. Transient normochromic normocytic anemia developed in 2 patients of each group. In 2 patients of the MOPP group a temporary drastic reduction of the dose of VCR was necessary because of severe paresthesias. The incidence of temporary loss of hair was higher in the group given ABVD as compared to MOPP. Due to the action of ADM, 15 patients developed an almost complete alopecia, while in 5 instances loss of hair was completely absent. Skin changes due to BLM, although noted in a total of 40%, consisted only in few hyperpigmented stria on the back (6 patients) and in a moderate thickening of the skin in both hands (2 patients). Interstitial pulmonary lesions were suspected in 4 patients, and for this reason the administration of BLM was temporarely interrupted. However, the classic signs of pulmonary toxicity[12] were in no instance confirmed through repeated chest roentgenograms, and BLM could be resumed without untoward effects. In a total of 4 patients, amenorrhea was observed during the induction phase. All three menstruating females given ABVD showed cessation of menses. At the time of this writing, it is not yet possible to state whether this side effect is temporary or permanent.

TABLE 4. Toxic Manifestations

	MOPP (25 cases)	ABVD (20 cases)
Leukopenia*	56%	45%
Thrombocytopenia†	16%	15%
Paresthesias	72%	5%
Loss of hair	48%	75%
Skin changes		40%
Amenorrhea	1/8‡	3/3‡

* WBC < 4000.
† Platelets < 130,000.
‡ Menstruating females.

Table 5 presents the percentage of optimal dose per m^2 of body surface administered during the six cycles in each treatment group. It appears evident that although some dose reduction was necessary after the first cycle, this was not progressive through the induction phase. Patients, with the exception of those on the sixth cycle of MOPP, received more than 81% of optimal dose. The average total dose fails to show a significant difference in the two treatments as far as highly myelosuppressive agents (HN_2 and procarbazine vs. ADM and VLB) and moderately myelosuppressive agents (VCR vs. DTIC) are concerned.

DISCUSSION

The results of this study, though based on a limited series of patients, suggest that the quadruple cyclic combination called ABVD is similar to MOPP in terms of remission rate in advanced Hodgkin's disease. Furthermore, there is also a preliminary indication that there is no crossresistance between the two treatments. Complete response after primary treatment was achieved at various levels of metastatic involvement; whenever possible, clinical findings were confirmed through a second

TABLE 5. Percentage of Optimal Dose per Cycle

	Cycles						Average total course
	1	2	3	4	5	6	
MOPP							
HN2 + PROC	100	90	87	89	90	73	89
VCR	100	92	81	93	88	73	88
PRED	100			100			100
ABVD							
ADM + VLB	84	88	84	93	86	85	87
DTIC	100	100	94	97	95	92	96
BLM	100	100	94	97	100	87	96

biopsy. At the time of writing, it is too early to provide adequate information about the duration of complete remission. For this reason, in the absence of long-term followup, this study remains preliminary in nature, since it provides only comparative remission rates. Furthermore, the duration of CR, which is now the most important parameter of comparability of new combinations with MOPP, is presently not available. Toxicity, as expressed by incidence of side effects and percentage of optimal dose administered per cycle, appears reversible and tolerable in both treatments groups. ABVD also appears fairly simple to administer; virtually all patients were treated on an outpatient basis.

Cyclic combination chemotherapy is now accepted as the most successful therapeutic modality to induce a prompt and complete remission in advanced (Stages IIIB–IV) Hodgkin's disease of adults and children.[32] Several studies have recently shown the useful results of combined drug treatment also in earlier stages (IIB–IIIA) when given either alone[19,31] or after high-energy irradiation.[26] Which is the combination of choice? So far, as mentioned before, none of the multiple drug treatments designed in various centers throughout the world has yielded better results than those achieved with MOPP. Therefore, this combination should be regarded at the present moment as the most simple and effective drug therapy to be used in clinical practice. However, MOPP has failed to control successfully for long periods of time all patients with advanced Hodgkin's disease. Therefore, there is a need in our opinion for another effective and tolerable drug combination, to be employed especially in MOPP failures. For this reason, this combination should include drugs non-cross-resistant to MOPP. The problem of whether further intensive treatment or maintenance single agent chemotherapy can statistically influence the duration of remission and the long-term survival in complete responders as compared to no further therapy remains open to discussion.[19,31] Certainly, the definition of complete response through histologic rather than only clinical parameters can be of help in clarifying this controversy.

Concerning the sequence of combined treatment modality for advanced Hodgkin's disease with nodal extension, we still prefer to administer chemotherapy before radiotherapy. As outlined in a previous publication,[13] effective chemotherapy can control and possibly destroy distant microscopic foci of disease located outside the irradiation fields. Furthermore, a partial remission in the lymph nodes after chemotherapy can become more easily complete after subsequent radiotherapy, rather than before. Hematosuppression usually recovers more quickly after multiple drug treatment than after total lymphoid irradiation. Our present program includes radiotherapy also in Stage IV patients who were found responsive to induction chemotherapy. Low-dose radiotherapy is delivered primarily to sites of major pretreatment involvement, in accordance with the findings observed by Frei et al.[19] The incidence of secondary neoplasms in occasional patients given combination chemotherapy or chemotherapy plus intensive radiotherapy[1,6] should not prevent, in our opinion, the appropriate use of effective and tolerable combined modalities in good-risk patients with advanced Hodgkin's disease.

In conclusion, the results presented in this paper indicate that the development of an effective multiple drug treatment independent from MOPP can be achieved by the association of some of the new compounds known to be active in Hodgkin's disease such as ADM, BLM, and DTIC. Although this multiple drug treatment (as other similar treatments) was designed more

on an empirical rather than a solid scientific bases, it produced a percentage of complete responders comparable to that observed in a randomized study with the classic MOPP. It should be emphasized once more that ABVD was not designed with the intention to compete with MOPP. Rather, its main purpose is to serve as an effective alternative treatment in MOPP failures. It needs to be emphasized that potentially severe, and to a certain extent unpredictable, side effects occur from both ADM and BLM. The unique toxicities of two of the agents in the ABVD combination would probably render difficult and even hazardous a long-term therapy at full dosage. For this reason, the primary use of this combination in young untreated patients would, at present, not be preferable to MOPP.

If the promising results emerging from our preliminary study are confirmed on a larger series of patients, followed for an adequate period of time, the next logical step would be to combine sequentially both MOPP and ABVD in an attempt to increase the percentage of complete responders, as well as to decrease the incidence of patients destined to relapse.

REFERENCES

Arsenau, J. C., Sponzo, R. W., Schnipper, L. E., Bonner, H., Young, R. C., Canellos, G. P., Johnson, R. E., and De Vita, V. T.: Non lymphomatous malignancies complicating Hodgkin's disease.—Possible association with intensive therapy. *N. Engl. J. Med.* 287:1119–1122, 1972.

2. Blum, R. H., and Carter, S. K.: A clinical review of bleomycin, a new antineoplastic agent. *Cancer* 31:903–914, 1973.

3. Blum, R. H., and Carter, S. K.: Review of adriamycin, a new anticancer drug with significant clinical activity. *Ann. Intern. Med.* 80:249–259, 1974.

4. Bonadonna, G., Monfardini, S., De Lena, M., Fossati Bellani, F., and Beretta, G.: Clinical trials with adriamycin—Results of three years study. *In* International Symposium on Adriamycin. Berlin, Springer, 1972; pp. 139–152.

5. Bonadonna, G., De Lena, M., Monfardini, S., Bartoli, C., Bajetta, E., Beretta, G., and Fossati Bellani, F.: Clinical trials with bleomycin in lymphomas and in solid tumors. *Eur. J. Cancer* 8:205–215, 1972.

6. Bonadonna, G., De Lena, M., Banfi, A., and Lattuada, A.: Secondary neoplasms in malignant lymphomas after intensive therapy. *N. Engl. J. Med.* 288:1242–1243, 1973.

7. Canellos, G. P., Young, R. C., and De Vita, V. T.: Combination chemotherapy for advanced Hodgkin's disease in relapse following extensive radiotherapy. *Clin. Pharmacol. Ther.* 13:750–755, 1972.

8. Carbone, P. P., Bono, V., Frei, E., III, and Brindley, C. O.: Clinical studies with vincristine. *Blood* 21:640–647, 1963.

9. Carbone, P. P., Kaplan, H. S., Musshoff, K., Smithers, D. W., and Tubiana, M.: Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res.* 31:1860–1861, 1971.

10. Carter, S. K., Schabel, F. M., Brader, L. E., and Johnston, T. P.: 1,3 bis-(2-chloroethyl)-1-nitrosourea (BCNU) and other nitrosoureas in cancer treatment—A review. *Adv. Cancer Res.* 16:273–332, 1972.

11. De Lena, M., and Beretta, G.: Comparative toxic and therapeutic effect of adriamycin and bleomycin in malignant lymphoma. *Tumori* 58:78–88, 1972.

12. De Lena, M., Guzzon, A., Monfardini, S., and Bonadonna, G.: Clinical, radiologic, and histopathologic studies on pulmonary toxicity induced by treatment with bleomycin (NSC-125066). *Cancer Chemother. Rep.* 56:343–356, 1972.

13. De Lena, M., Monfardini, S., Beretta, G., Fossati Bellani, F., and Bonadonna, G.: Clinical trials with intensive chemotherapy and radiotherapy in Hodgkin's disease. *Natl. Cancer Inst. Monogr.* 36:403–420, 1973.

14. De Vita, V. T., Serpick, A. A., and Carbone, P. P.: Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann. Intern. Med.* 73:881–895, 1970.

15. De Vita, V. T., and Carbone, P. P.: Chemotherapeutic implications of staging in Hodgkin's disease. *Cancer Res.* 31:1838–1844, 1971.

16. De Vita, V. T., Canellos, G. P., and Moxley, J. H. III: A decade of combination chemotherapy of advanced Hodgkin's disease. *Cancer* 30:1495–1504, 1972.

17. Durant, J. R., and Lessner, H. E.: Development of four-drug BCNU combination chemotherapy regimens. *Cancer* 32:277–285, 1973.

18. Frei, E., III, Luce, J. K., Talley, R. W., Vaitkevicius, V. K., and Wilson, H. E.: 5-(3,3-dimethyl-triazeno) imidazole-4-carboxamide (NSC-45388) in the treatment of lymphoma. *Cancer Chemother. Rep.* 56:667–670, 1972.

19. Frei, E., III, Luce, J. K., Gamble, J. F., Coltman, C. A., Jr., Costanzi, J. J. Talley, R. W., Monto, R. W. Wilson, H. E. Hewlett, J. S. Delaney, F. C., and Gehan, E. G.: Combination chemotherapy in advanced Hodgkin's disease—Induction and maintenance of remission. *Ann. Intern. Med.* 79:376–382, 1973.

20. Gottlieb, J. A., Baker, L. H., Quagliana, J. M., et al.: Chemotherapy of sarcomas with a combination of adriamycin and dimethyl triazeno imidazole carboxamide. *Cancer* 30:1632–1638, 1972.

21. Jacquillat, C., Weil, M., Desprez-Curely, J. P., et al.: Chimiotherapie de la maladie de Hodgkins par les association thérapeutiques. *Bull. Cancer (Paris)* 58:221–234, 1971.

22. Lowenbraun, S., De Vita, V. T., and Serpick, A. A.: Combination chemotherapy with nitrogen mustard, vincristine, procarbazine, and prednisone in previously treated patients with Hodgkin's disease. *Blood* 36:704–717, 1970.

23. Luce, J. K., Gamble, J. F., Wilson, H. E., et al.: Combined cyclophosphamide, vincristine and prednisone therapy of malignant lymphoma. *Cancer* 28:306–317, 1971.

24. Lukes, R. J., and Butler, J. J.: The pathology and nomenclature of Hodgkin's disease. *Cancer Res.* 26:1063–1081, 1966.

25. McElwain, T. J., Wrigley, P. F. M., Hunter, A., Crowther, D., Malpas, J. S., Peckham, M. J. Smithers, D. W., and Fairley, G. H.: Combination chemotherapy in advanced and recurrent Hodgkin's disease. *Natl. Cancer Inst. Mongr.* 36:395–402, 1973.

26. Moore, M. L., Bull, J. M. Jones, S. E. Rosenberg,

S. A., and Kaplan, H. S.: Sequential radiotherapy and chemotherapy in the treatment of Hodgkin's disease—A progress report. *Ann. Intern. Med.* 77:1–9, 1972.

27. Moore, M. R., Jones, S. E., Bull, J. M., William, L. A., and Rosenberg, S. A.: MOPP chemotherapy for advanced Hodgkin's disease—Prognostic factors in 81 patients. *Cancer* 32:52–60, 1973.

28. O'Bryan, R. M., Luce, J. K., Talley, R. W., Gottlieb, J. A., Baker, L. H., and Bonadonna, G.: Phase II evaluation of adriamycin in human neoplasia. *Cancer* 32:1–8, 1973.

29. Skibba, J. L., Beal, D. D., Ramirez, G., et al.: N-demethylation of antineoplastic agent 4(5)-(3, 3-dimethyl-1-triazeno) imidazole-5(4) carboxamide by rats and man. *Cancer Res.* 30:147–150, 1970.

30. Stutzman, L., and Glidwell, O.: Multiple chemotherapy agents for Hodgkin's disease—Comparison of three routines: a cooperative study by Acute Leukemia Group B. *JAMA* 225:1201–1211, 1973.

31. Young, R. C., Chabner, B. A., Canellos, G. P., Schein, P. S., and De Vita, V. T.: Maintenance chemotherapy for advanced Hodgkin's disease in remission. *Lancet* i:1339–1343, 1973.

32. Young, R. C., De Vita, V. T., and Johnson, R. E.: Hodgkin's disease in childhood. *Blood* 42:163–173, 1973.