J. Egypt. Nat. Cancer Inst. Vol. 6, No. 1: 79 - 88, 1993.

IMPROVED FIVE YEAR SURVIVAL IN PATIENTS WITH ADVANCED HODGKIN'S DISEASE BY COMBINED MODALITY TREATMENT

INAS ABDEL-HALIM M.D., and NAZEM SHAMS M.D.

Radiotherapy and Surgery Departments, Faculty of Medicine
Mansoura University 1992

Abstract

Thirty five patients with advanced Hodgkin's disease (unfavourable stages II_B & III_A, and stages III_B, IV_A, IV_B) were evaluated. Twenty five patients were treated with combined chemotherapy (MOPP) and radiotherapy (in the form of total nodal irradiation, subtotal nodal irradiation, radiotherapy to residual or areas of initial bulkly disease). Complete remission (CR) was 84% and partial remission was 16%, relapse occured in 8 patients (32%) with relapse free survival ranging between 36-48 months; patients who relapsed were treated by ABVD, 62.5% of them entered in complete remission while 25% showed partial remission. The 5 year overall survival from the start of combined treatment was 85.7% for patients showing complete remission and 0% for patients with partial remission. The remaining 10 patients were treated with MOPP alone, 40% of whom achieved complete remission and partial remission occurred in 60% of patients.

Introduction

HODGKIN'S disease is one of the most therapy sensitive malignant lymphomas and in several long term studies more than 80% of the patients have been considered cured following radiotherapy, chemotherapy or usually a combination of both. Nevertheless, irrespective of age, initial presentation,stage or histologic subgroup, a few patients remain resistant to treatment. These patients can present either with initial resistance, an incomplete response to chemotherapy or earl and often multiple relapses (*Philip et al., 1986*).

Recent developments in the treatment of Hodgkin's disease have radically improved the prognosis of what had been considered until recently an inevitably fatal disease. Combination chemotherapy MOPP (*nitrogen mustard, oncovin, procarbazine and prednisone*) has greatly increased the incidence of complete response in patients with extranodal involvement and stage IV disease it provides definitely or potentially curative treatment for only about one third of patients (*Bonadonna et al., 1979*). Since maintenance chemotherapy has not been shown to improve significantly relapse free survival of patients entering complete remission with MOPP, multiple drug chemotherapy has been combined with radiotherapy with the primary intent to improve the duration of complete remission (*Coltman et al., 1976*).

Radiotherapy in advanced stages of Hodgkin's has been increasingly employed as an adjuvant to chemotherapy in residual or bulky disease (*Bonadonna et al., 1986*) or as combined modality (*Prosnitz et al., 1988*).

Chemotherapy-radiotherapy is confirmed to be a useful approach for advanced Hodgkin's disease, particularly in the presence of extranodal involvement, systemic symptoms and nodular sclerosis histology. The 5 year survival from starting combined treatment was 88.8% for complete responders and 0% for partial responders (*Bonadonna et al., 1979*). Combination of chemotherapy and radiotherapy in patients with advanced hodgkin's disease achieved complete response rates varying from 79% to 100% (*Delena et al., 1972*). So combined modality ;has shown a significant improvement in response rate, disease free and overall survival (*Longo et al., 1991*).

Combination chemotherapy is now considered standard treatment for patients with advanced stage of Hodgkin's disease since its introduction in the *Late 1960*, the combination of mustine hydrochloride, vincristine sulfate (*oncovin*), procarbazine and prednisone (MOPP) has been the combination most frequently used (*Longo et al., 1986*). Complete remission to MOPP alone in advanced Hodgkin's disease have been attained in 25-60% of patients (*Diggs et al., 1981*).

Four drugs chemotherapy combination using adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) achieved a similar CR rate to MOPP in patients with advanced Hodgkin's disease and represents a chemotherapeutic combination that is not cross resistant with MOPP and give a complete remission in patients who relapse after MOPP chemotherapy (*Strauss et al., 1980*), so chemotherapy with MOPP, CMOPP or ABVD like regimens had become standard therapy in advanced Hodgkin's disease (*Santoro et al., 1987 and Anderson et al., 1990*).

Combined modality treatment (Radiotherapy plus chemotherapy) in advanced Hodgkin's disease produced statistically fewer events and better disease free survival than chemotherapy alone (Pavlovsky et al., 1992).

Patients and Methods

Thirty five patients with Hodgkin's disease stage IIB, IIIA (*unfavourable, age >35 years or mixed cellularity histology, B symptoms, bulky disease > 5 cm*) IIIB, IVA and IVB referred to radiotherapy departement, Mansoura University between January 1985 to December 1990 were included in this study. The main characteristics of patients groups are presented in table (1).

Clinical staging was performed in all patients according to the Ann Arbor staging classification.MOPP regimen was administered, every 28 days and the doses were:

Mustine hydrochloride
6 mg/m2 day 1&8I.V.

Oncovin 1.4mg/m2 day 1&8 I.V.

Procarbaxine (*Natulan*) 100 mg/m2 P.O. days 1-14 inclusive Prednisone 40 mg/m2 P.O. days 1-14 inclusive, for 6 cycles CMOPP as MOPP but mustine is replaced by cyclophosphamide (C) 600 mg/m2 in young patients due to the mutagenic effect of mustine.

The dosage of ABVD regimen was as follows:

Adriamycin 25mg/m2 day 1 & 14 I.V.
Bleomycin 10mg/m2 day 1 & 14 I.V.
Vinblastine 6 mg/m2 day 1 & 14 I.V.
Imidazole carboxamide
735 mg/m2 day 1 & 14 I.V.

Repeated every 4 weeks, and was given to relapsed patients after previous MOPP with or without radiotherapy.

The patients were divided into 3 categories for purposes of analysis according to treatment modality. The first group (*20 patients*) received MOPP plus radiotherapy (RTh) in one of the following forms: total nodal irradiation (TNI) which was employed in the presence of paraaortic lymph node involvement plus supradiaphragmatic lymph nodes otherwise subtotal nodal irradiation (*upper mantle and paraaortic + splenic fields*) was utilized in doses ranging from 3000-3500 cGy/3-4 weeks using Cobalt 60 machine, F.S.D range from 80-100 cm according to field size, the technique used was two paralle opposing anteroposterior fields. The second group included 5 patients received MOPP plus local radiotherapy to residual or initial bulky disease in dose range from 2000-2500 weeks. The third group included 10 patients received MOPP alone.

Criteria for response

Complete remission (CR); disappearance of all symptoms attributed to Hodgkin's disease in all measurable disease as

determined by physical examination, x-rays, bone marrow biopsy and blood biochemical studies as complete blood picture, liver and kidney functions.

Partial remission (PR) disappearance of constitutional (B) symptoms and reduction by >50% in the sum of the product of the largest perpendicular diameters of all measurable disease.

Statistical analysis was performed by One way Anova test using computer.

Results

In this study, the 35 patients included 23 males and 12 females. Ages of the 35 patients ranged between 5-67 years. Histological subtypes were lymphocytic predominance in 5 patients (14. 3%). Mixed cellularity in 21 patients (60%) and nodular sclerosis in 9 patients (25.7%). Ten patients were stage IIB, 5 patients were IIIA, 10 patients were IIIB, 4 patients were VIA, and 6 patients were IVB (as shown in table (1). Table (2) represents the response rate in terms of complete and partial remission to different treatment modality in correlation with staging, pathological subtype and systemic symptoms. No statistically significant correlation was found between response rate to combined MOPP/RTh and pathological subtype or systemic symptoms. But there is statistically significant correlation between response rate to combined treatment and staging of the disease ($p = <0.05$).

Table 1. : The main characteristic of 8 / 35 patients with advanced Hodgkin's disease

Main pretreatment characteristic	No. of patients
* *Stages*	
II B	10
III A	5
III B	10
IV A	4
IV B	6
* *Disease extent*	
Nodal disease	28
Extranodal + nodal disease	7
* *Symptoms*	
A	10
B	25
* *Histological types*	
Lymphocytic predominance	5
Mixed cellularity	21
Nodular sclerosis	9
* *SEX*	
Males	23
Females	12
* *Age 5-67 years* (mean age 34 years)	

Table (3) represents the comparative response rate (CR,PR) to chemotherapy alone and to combined MOPP/RTh. The complete remission to combined modality was 84% and partial remission was 16%. In patients who received MOPP alone. CR occurred in 40% of patients and PR

Table 2. : Correlation between response rate to different treatment modality and stage of disease, pathological subtypes and presence of systemic symptoms.

Parameters	MOPP/RTh			MOPP alone	
	CR	PR	P Value	CR	PR
1- Staging			P=<0.05		
II B	9	1			
III A	4	1			
III B	8	2			
IV A	--	--		4	--
IV B	--	--		--	6
2- Pathological subtype			P=>0.05		
*Lymphocytic predominance	3	--		2	--
* Mixed cellularity	11	4		--	6
* Nodular sclerosis	7	--		2	--
3- Systemic symptoms			P=>0.05		
A	4	1		2	2
B	17	3		2	4

Table 3. : Response rate to PTh/MOPP in 35 patients with advanced Hodgkin's disease.

Treatment Modality	Total	CR	PR	Relapse
Prior RTh + MOPP	20	17(85%)	3(15%)	6(30%)
MOPP alone	10	4(40%)	6(60%)	8(80%)
MOPP + RTh to residual or initial bulky disease	5	4(80%)	1(20%)	2(40%)
Total	35	25	10	16

in 60% there is statistically significant correlation in response rate to treatment between patients receiving combined chemotherapy radiotherapy and patients receiving MOPP alone. The relapse free survival in patients who received combined MOPP/RTh treatment ranged between 36-48 months (means 42 ± S.D 14.9). Table (4) represents the response rate to ABVD regimen in patients with relapse after previous treatment, in patients who received combined treatment 62.5% achieved complete remission and 25% of them showed P R with ABVD while in patients relapsing after MOPP alone CR after ABVD was 50% and PR 25%. Treatment tolerance was in general fairly good, no increased incidence of bacterial or viral infection was observed. During the entire period of therapy, myelosuppression represented the most common side effect during the chemotherapy the incidence of severe myelosuppression as determined at the time of intravenous drug injection was neglegible, subsequent radiotherapy was found to be slightly more toxic to the bone marrow. The complication of radiation in childhood patients was low due to careful administration and appropriately fractionated radiation dose. The degree of alopecia, nausea and vomiting was mild

Table 4. : Response rate to ABVD after MOPP ± RTh.

Treatment Modality	No. of patients received ABVD	Response rate after ABVD		
		CR	PR	Relapse
Prior RTh + MOPP	5	17(85%)	3(15%)	6(30%)
MOPP alone	8	4(40%)	6(60%)	8(80%)
MOPP + RTh to residual or initial bulky disease	3	4(80%)	1(20%)	2(40%)
Total	16	25	10	16

Table 5. : Complications following combined Radiotherapy and Chemotherapy.

Complications	No. of patients	%
Leucopenia	4	16%
Thrombocytopenia	3	12%
Peripheral neuropathy	2	8%
Radiation Pneumonitis	--	--
Herpes Zoster	--	--
Second malignancies (Leukaemia)	--	--

and no severe cases of neurotoxicity. Leucopenia and thrombocytopenia occurred in many patients (16% & 12% respectively) but levels returned to normal in most instances by 3 weeks and cumulative toxicity was not seen (Table 5). The cumulative 5 year survival curve of all patients receiving combined Rth and chemotherapy (CR versus PR) is shown in figure (1).

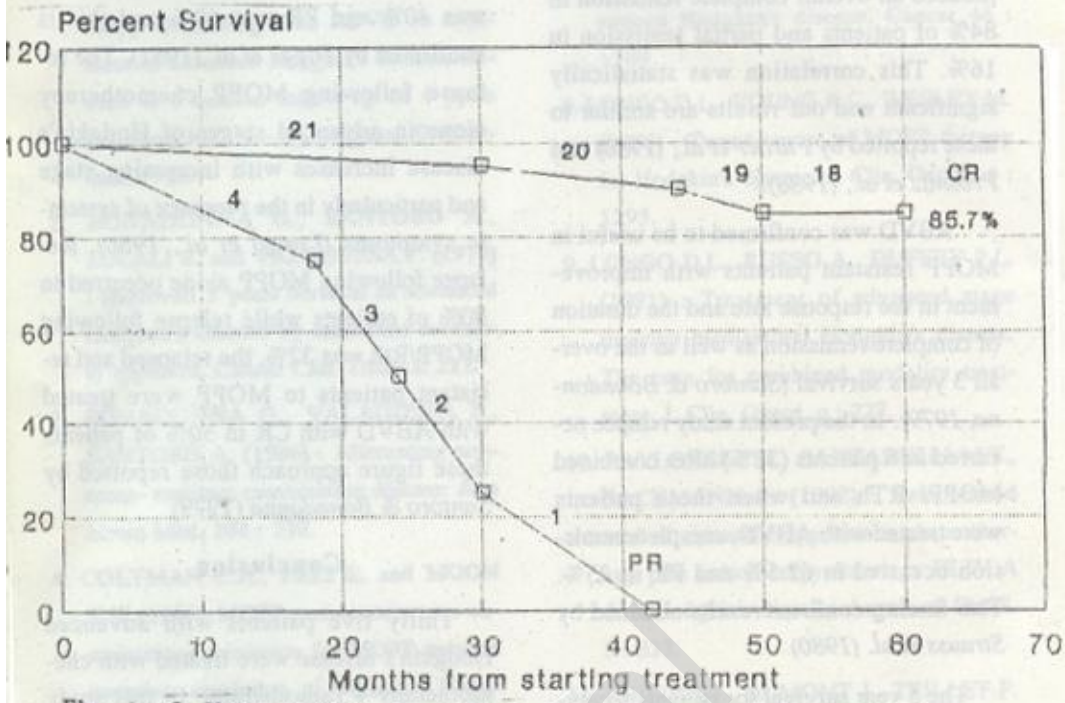

Fig. 1: 5 Year survival in patients who have recevied combined treatment [CR versus PR]

Discussion

The therapeutic effect of combined modality chemotherapy / radiotherapy approach has been evaluated in advanced stages of Hodgkin's disease. Radiotherapy plus 6 cycles of MOPP markedly improved 5 year survival, in the current study a statistically significant correlation was noticed between response rate to combined treatment (in terms of complete and partial remission) and staging of the disease while there was no statistically significant correlation between response rate and pathological subtypes and systemic symptoms (A & B symptoms). These findings were previously confirmed by *Bonadonna et al., (1979)* who emphasized that irrespective of the combination utilized in treatment of advanced Hodgkin's disease, the duration of CR was not

unfavourably influenced by the presence of systemic symptoms and histopathological subtypes.

In this study, the combined program induced an overall complete remission in 84% of patients and partial remission in 16%. This correlation was statistically significant and our results are similar to these reported by *Farber et al., (1980)* and *Prosnitz et al., (1988).*

ABVD was confirmed to be useful in MOPP resistant patients with improvement in the response rate and the duration of complete remission as well as the overall 3 years survival *(Santoro & Bonadonna, 1979).* In the present study relapse occurred in 8 patients (32%) after combined MOPP/ RTh and when these patients were treated with ABVD, complete remission occurred in 62.5% and PR in 25%. This finding confirms results obtained by *Strauss et al. (1980).*

The 5 year survival for patients receiving combined MOPP/RTh who achieved complete remission in the study was 85.7% as compared to patients with partial remission, this is agreable with the results of *Stein et al. (1982)* and *Longo et al. (1991).* The difference in respone rate (CR and PR)to treatment between patients treated with chemotherapy (MOPP) alone and patients receiving MOPP/RTh is striking and clearly shows the superiority of sequential chemotherapy and radiotherapy approach in advanced Hodgkin's disease and this difference was statistically significant.

In this study, the CR to MOPP alone was 40% and PR was 60% and this is confirmed by *Diggs et al. (1981).* The relapse following MOPP chemotherapy alone in advanced stages of Hodgkin's disease increases with increasing stage and particularly in the presence of systemic symptoms *(Longo et al., 1986).* Relapse following MOPP alone occurred in 80% of patients while relapse following MOPP/Rth was 32%, the relapsed and resistant patients to MOPP were treated with ABVD with CR in 50% of patients these figure approach those reported by *Santoro & Bonadonna* (1979).

Conclusion

Thirty five patients with advanced Hodgkin's disease were treated with chemotherapy + radiotherapy. In this study sequential chemotherapy / radiotherapy is confirmed to be a useful approach. The combined treatment improves response rate in term of complete remission and 5 year survival. The efficiency of ABVD was confirmed to be the second useful line in improving the response rate as well the survival in relapsed patients. In conclusion to avoid prohibitive bone marrow toxicity the doses of radiation should be moderate to low and the number of cycles of induction chemotherapy could also

be reduced at least in patients achieving prompt remission.

References

1. ANDERSON J.R., CANELLOS G.P., ROPERT K.J. (1990) : MOPP vs ABVD vs Mopp alternating with ABVD as treatment in advanced Hodgkin's disease. Results at a median follow up of 4 years (Meeting June 6 - 9). Lugano. Switzerland, P. 26.
2. BONADONNA G., SANTORO A., ZUCALI R. and VALAGUSSA P. (1979) : Improved 5 years survival in advanced Hodgkin's disease by combined modality approach. Cancer Clin. Trials 2: 217.
3. BONADONNA G., VALAGUSSA P., SANTORO A. (1986) : Alternating noncross- resistant combination disease: Ann Intern Med. 104 : 739.
4. COLTMAN C.A., FREI E. and MOON T.E. (1976): MOPP maintence versus unmainatined remission for MOPP induced complete remission of advanced Hodgkin's disease. Proc. Am. Soc. Clin. Oncol. 17 : 289.
5. DELENA M., MONFARDINI S., BERETAA G. (1972) : Clinical trials with intensive chemotherapy and radiotherapy in Hodgkin's disease. International symposium on Hodgkin's disease NCT. 36:403.
6. DIGGS CH., WIERNIK P. and SUTHERLAND J. (1981) : Treatment of advanced untreated Hodgkin's disease with SCAB, An alternative to MOPP. Cancer 47 : 224.
7. FARBER C.R., PROSNITZ C.R., CODMAN E.C. (1980) : Curative potential of combined modality therapy for advanced Hodgkin's disease. Cancer 46 : 1509
8. LONGO D.L., YOUNG K.C., WESLEY M. (1986) : Twenty years of MOPP therapy for Hodgkin's disease. J. Clin. Oncol., 4 : 1295.
9. LONGO D.L., RUSSO A., DUFFEY P.L. (1991) : Treatment of advanced stage massive mediastinal Hodgkin's disease. The case for combined modality treatment. J. Clin. Oncol. g : 227.
10. PAVLOVSKY S., SANTARELLI M.T., SACKMANN F. (1992) : Randomized trial of chemotherapy versus chemotherapy plus radiotherapy for stage III-IV A & B Hodgkin's disease. Annals of Oncol. 3 : 533.
11. PHILIP T.J., DUMONT J., TEILLET F. (1986) : High dose chemotherapy and autologous bone marrow transplantation in refractory Hodgkin's disease. Br. J. Cancer 53 : 737.
12. PROSNITZ L.R., FABER L.R., KAPP D.S. (1988) : Combined modality therapy for advanced Hodgkin's diseaase: 15 years follow up data. J., Clin. Oncol. 6: 603.
13. SANTORO A. and BONADONNA G. (1979) : Prolonged disease free survival

in MOPP resistant Hodgkin's disease after the ABVD. Cancer Chemotherapy Pharmacol. 2 : 101.

14. SANTORO A., BONADONNA G., VALAGUSSA P. (1987) : Long term results of combined chemotherapy radiotherapy approach in Hodgkin's disease. Superiority of ABVD plus radiotherapy versus MOPP puls radiotherapy. J. Clin. Oncol. 5 : 27.

15. STEIN R.S., GOLOMB H.M. and WIERNIK P.H (1982) : Anatomic substages of Hodgkin's disease follow up of a collaborative study. Cancer treatment reports 66 : 733.

16. STRAUSS D.J., MYERS J., PASS S. (1980): The eight drug radiation therapy program MOPP/ ABVD/RTh for advanced Hodgkin's disease. Cancer 46 : 233.