Patterns of survival in patients with advanced Hodgkin's disease (HD) treated in a single centre over 20 years

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Summary A total of 164 consecutive adults with newly confirmed stage IIIB. IVA or IVB Hodgkin's disease (HD) commenced cyclical combination chemotherapy comprising mustine. vinblastine. prednisolone and procarbazine (MVPP) every 6 weeks (145 patients) or minor variants (19) at St Bartholomew's Hospital between 1968 and 1984. The median follow-up period is 14 years. Complete remission (CR) was achieved in 97 164 (59%) and partial remission (PR) in 23 164 (14%) with lesser responses or death being documented in 44. Achievement of CR correlated with stage. serum albumin and serum β_2 microglobulin level at presentation on univariate and multivariate analysis: 55 97 (58%) remain in continuous CR. the median duration of remission not having been reached. Twelve patients died in first remission: there have been 30 recurrences. one occurring after 13 years. Second remission was achieved in 17 30: 6 17 remain in continuous second remission and two have died in second remission. There have been nine second recurrences. third remission being achieved in 6 9. Two continue in third remission. two patients have died in third remission: 82 164 patients are alive with a minimum follow-up of 6 years. Eighty-two patients have died: 66 with evidence of HD. six with second malignancy. one each of haemorrhage and infection. eight of unrelated causes. the cause of death was unknown in one. The overall median survival from presentation is 14 years, being the same for patients in CR and PR with minimal residual abnormality (good partial remission. GPR). and being better for those for whom remission was achieved than those for whom it was not. The median survival following first recurrence is 4 years. being significantly longer for younger patients ($<$ 50 years). These results emphasise the importance of long-term follow-up to determine the clinical course of HD and are vital for planning experimental chemotherapy at the time of early treatment failure or recurrence.

The overwhelming improvement in the prognosis of advanced Hodgkin's disease (HD) brought about by the introduction of 'MOPP'–like cyclical combination chemotherapy appropriately led to this becoming established as the chemotherapy of choice for the ensuing two decades (DeVita *et al.,* 1970: Nicholson *et al.,* 1970: Sutcliffe *et al.,* 1978: Longo *et al.,* 1986: Hancock, 1986: McKendrick *et al.,* 1989: Selby *et al.,* 1990: Ranson *et al.,* 1991). In the meantime. the drawbacks of the treatment have become gradually apparent. It fails. to some extent. for at least one–third of the patients. either because remission. the major prerequisite for improving on the natural history is not achieved. or because recurrence occurs. It is unpleasant to receive and there are long-term complications of infertility (Chapman *et al.,* 1979: 1981: Horning *et al.,* 1981) and development of second malignancy (Coleman. 1986: Dorreen *et al.,* 1986: Tucker *et al.,* 1988: Kaldor *et al.,* 1990). Within the context of the only alternative being death following sequential single agent palliation. all of this was quite acceptable. The discovery of new drugs. the formulation of new combinations and the demonstration that bone marrow ablative therapy may be supported successfully. however. have inevitably raised questions as to whether the initial strategy should be modified. with the obvious objectives of decreasing the failure rate. or at least maintaining the proven level of success with less toxicity.

This analysis is presented to complement the relative paucity of reports on long-term follow-up of patients treated with a MOPP variant at the initial presentation with advanced HD. and provide a larger background against which to assess alternative approaches.

Materials and methods

Patients

A total of 164 consecutive previously untreated adults with advanced (stage IIIB. IVA. IVB) Hodgkin's disease were

referred to the department of Medical Oncology. St Bartholomew's Hospital. London between 1968 and 1984. and form the basis of this analysis. The diagnosis was confirmed in all instances by one of us (AGS) and re-reviewed to incorporate further subdivision of nodular sclerosing HD. and staging was according to the Ann Arbor classification (Carbone *et al.,* 1971). modified to include the use of computed axial tomography as an alternative to lymphography for the detection of intra-abdominal disease from 1980.

Clinical details of the patient population are shown in Tables I and II.

Serum. stored at $-20°C$ from 1978 onwards from initial presentation was available in 60 cases. These cases were not selected in any other way. A double antibody radioimmunoassay (Pharmacia) was used to quantify β_2 microglobulin levels in these specimens.

Treatment at presentation

Chemotherapy Between 1968 and early 1984. the treatment of choice was cyclical combination chemotherapy with mus-

Table I Patient population

			CS	PS
Male:Female		122:42		
Age years	Range	13–79		
	Median	36		
Stage	IIIB	61	33	28
	IVA	28	15	13
	IVB	75	64	11
Histology	NSI	47		
	NSII	46		
	LP	10		
	MC	37		
	LD	15		
	NHL and HD	1		
	Unclassified	8		
Total		164	112	52

NS = nodular sclerosing—subclassified into type I and II according to BNLI classification: LP = lymphocyte predominant: MC = mixed cellularity: LD = lymphocyte depletion: NHL = non–Hodgkin's lymphoma: CS = clinically staged: PS = pathologically staged.

Table II Sites of extranodal disease

Site	Frequency
Liver	37
Bone Marrow	17
Bone	12
Lung	8
Liver + bone marrow	8
Liver + lung	6
Liver + central nervous system	1
Bone + lung	3
Lung + liver + bone	2
Bone marrow + bone	2
Gut	2
Lung + thyroid	1
Central nervous system	2
Skin	1
Peritoneum	1

Cycles repeated every 6 weks, day 1 to day 1

Figure 1 MVPP treatment schedule.

Figure 2 Dose:time curve of administered chemotherapy.

tine, vinblastine, prednisolone and procarbazine (MVPP), the intention being that responding patients should receive a minimum of six cycles at 6-weekly intervals (Figure 1). A total of 133 patients commenced MVPP during this time, with seven having chlorambucil substituted for mustine and the therapy being given at 4-weekly intervals (Ch1VPP), because of advanced age and frailty. Other minor modifications were made to the treatment for 13 patients, and one was treated for high grade non-Hodgkin's lymphoma because of concurrent HD and immunoblastic lymphoma.

For the latter part of 1984, all patients received Ch1VPP electively (n = 10).

With the passage of time, the total amount of treatment prescribed for each patient declined, as the results of trials became available. From 1968 until 1970 it was planned that all patients should receive 16 cycles of therapy, at increasing intervals over 3 years; from 1970 till 1974 patients entering complete remission were randomised to receive two drug (vinblastine and procarbazine, 13 patients) or four drug (MVPP, 11 patients) maintenance. For the final 10 years, six cycles was considered adequate.

Dose   The ratio of cumulative therapy administered to planned therapy over the first six cycles was retrospectively calculated in the patients for whom remission was achieved (Appendix). Delays in administration of chemotherapy were also evaluated in this group. The dose:time analysis showed that 85% of the patients received more than 85% of the therapy on time (Figure 2).

Radiotherapy   Twenty-four of 164 patients received irradiation electively in addition to the chemotherapy, eight prior to chemotherapy, becuase of pressing clinical problems (in these patients, the response to MVPP has not been distinguished from that of radiotherapy) and 16 after completion of chemotherapy, to sites of previous bulk disease or persistent residual abnormality. The response to radiotherapy has been documented separately for the latter.

Definition of response

This has been documented at the completion of six cycles of chemotherapy, unless death or obvious progression had intervened. The criteria upon which the description of the response are based changed over the 22 years of study, the precision with which 'complete remission' can be defined having increased. Consequently, the distinction between complete remission (CR) and partial remission (PR) has changed. To accommodate this, PR was subdivided as described below. It is important to note that GPR is not necessarily equivalent to the newly designated CR(u)(Lister et al., 1989).

Complete remission (CR)   A state when the patient is well, with no clinical or radiological (or other) evidence of Hodgkin's disease.
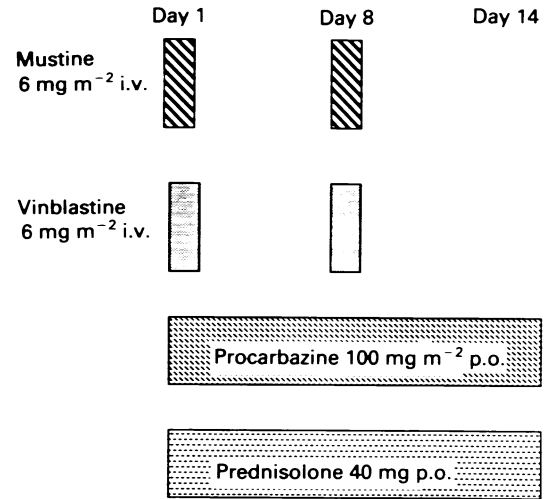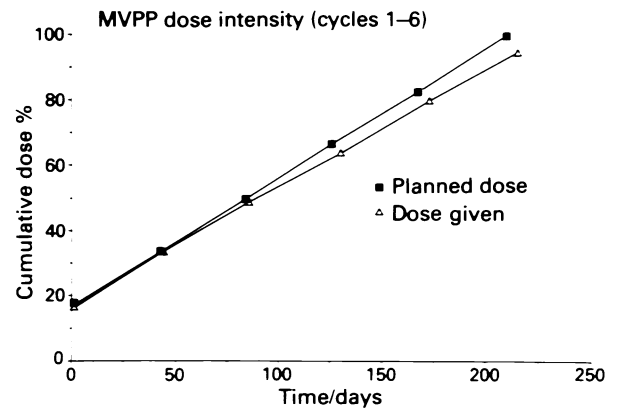
Partial remission.   [i] *Good partial remission (GPR).* A state when the patient is clinically well, but with persisting minimal residual abnormality at the completion of therapy. These patients were treated as if they were in clinical remission and observed without further therapy, as for complete remitters.

[ii] *Poor partial remission (PPR).* A state when the patient is well with residual abnormality, with a minimum reduction of more than 50% estimated volume of Hodgkin's disease.

Failure   Any response less than partial response.

Early death   Death occurring during the period of therapy, precluding an assessment of response.

Duration of remission

This has been defined as the period from documentation of remission to recurrence or, for patients in continuous remission, to time of last clinic attendance. For patients whose initial response was GPR, this period is the time to clinical progression/recurrence.

Treatment of recurrence

Recurrence after MVPP was usually retreated with combination chemotherapy, though the regimens have inevitably altered over the years. Recurrences which occurred during the early years of the study were retreated with MVPP,

MOPP or Ch1VPP. Non-cross resistant regimens such as adriamycin (doxorubicin). bleomycin, vinblastine and DTIC (ABVD) or etoposide, vincristine and adriamycin (EVA) were investigated from 1978 onwards (Sutcliffe et al., 1979; Richards et al., 1986). Irradiation, either singly or in combination with chemotherapy was used as necessary.

Precision of documentation of extent of disease and response to therapy declined with repeated recurrence, further response being described as remission (CR and GPR) or less.

Follow-up

The median follow-up for the study is 14 years, with a minimum follow-up of 6 years.

Follow-up information was complete and correct on 160 patients, either to death or until Autumn 1990.

Statistical analysis

Proportions of patients achieving CR in different prognostic groups were compared using the χ^2 test with Yates's correction (Armitage, 1971). Duration of remission and overall survival were plotted using standard life table methods (Kaplan & Meier, 1958) and compared using the log rank method (Peto et al., 1977). The significance of prognostic factors in determining the achievement of CR was evaluated by logistic regression analysis, whereas duration of CR and overall survival differences were determined using a stepwise linear regression method based on Cox's proportional hazards model (Cox, 1972).

Results

Initial Presentation

Response to therapy Complete remission (CR) was achieved in 97 164 (59%) by the completion of six cycles of therapy. Nine of these patients had received adjuvant radiotherapy.

Partial remission (PR) was achieved in 23 164 (14%), with 18 23 being subclassified as GPR (18 164 = 11%), the other five being PPR. Four patients whose response was GPR after chemotherapy received irradiation with subsequent complete resolution of the abnormality in two. All five patients whose initial response was PPR received further therapy (non-cross resistant regimens in three, combined modality therapy in one and further MVPP in one), with complete resolution of the residual disease in two and minimal residual abnormality (GPR) in a third.

Twenty-nine patients (18%) had a response less than PR following six cycles of MVPP. Twenty-four of these pro-

ceeded to further therapy [MVPP MOPP (seven), alternative chemotherapy (16) or combined modality therapy (one)], CR being subsequently achieved in only one; a second patient was left with minimal residual disease (GPR) (Table III). One patient refused further therapy and two died of progressive disease before treatment was initiated. One patient died postoperatively, following restaging laparotomy and splenectomy.

The total number of patients in whom CR was achieved with first line (97) and second line (five) therapy was 102 164 (62%).

Fifteen patients died before completion of planned treatment, before response to treatment could be adequately assessed: three were known to have advancing disease at the time of death. There were nine deaths due to infective complications, one of cardiac failure, one from pulmonary embolus and one from cardiac tamponade due to haemopericardium.

The effects of presentation age, gender, serum albumin, erythrocyte sedimentation rate (ESR), alkaline phosphatase, lymphocyte counts, B symptoms, drug dose intensity, histology and serum β_2 microglobulin on achievement of remission were determined by univariate and multivariate analyses (the β_2 microglobulin results were from a smaller set of patients).

Prognostic factors significant for the achievement of CR by logistic regression analysis were albumin ($P = 0.0002$) and stage (IIIB vs IV. $P = 0.004$) (Table IV). The CR rate increased with increasing albumin, from 36% (13 36) for albumin < 33 g l, to 61% (46 76) for albumin 33–39 g l, to 81% (34 42) for albumin ≥ 40 g l. The CR rate for patients stage IIIB disease was 75% compared with 50% in patients with stage IV disease. Stage and albumin were independent, unrelated factors, significant on multivariate analysis.

Table III Response to second line therapy in non-remitters

Response to initial	Number	No. retreated and regimen	Response to second line CR	GPR	PPR	FAIL
MVPP						
GPR	18	4–RT	2	2		
PPR	5	1–MVPP	1			
		3–NCR	1	1	1	
		1–RT + CCNU				1
		Total (PPR group)	2	1	1	1
FAIL	29	24				
		7–MVPP				
		16–NCR		1	1	
		1–RT + MVPP	1			
		Total (Fail group)	1	1	1	

RT = radiotherapy; NCR = non-cross-resistant regimen

Table IV Prognostic factors for remission induction

Prognostic Factor	Variable	Remission rate% by groups	Significance -univariate (P)	Significance multivariate (P)
Albumin	< 33g l	36	< 0.001	0.0002
g l	33–39g l	61		
	> 40g l	81		
Stage	IIIB	75	< 0.001	0.004
	IV	50		
β_2	$< 3 > \mu$g ml	64	0.002	0.02
microglobulin	$3 + $ g ml	29		
μg ml	$< 40:40 + $		0.04	NS
Age	years			
Sex	M:F		NS	
ESR	$< 40:40 + $		NS	
Alkaline phosphatase	Normal vs abnormal		NS	
Lymphocyte count	$< 0.75 \times 10^9$ l $> 0.75 \times 10^9$ l		NS	
B symptoms	$+ :-$		NS	
Histology			NS	

NS = not significant

On a reduced set of 60 patients with known β_2 microglobulin values, selected only for the fact that serum had been stored at presentation, using the logistic regression method. β_2 microglobulin was the only significant factor for achievement of CR ($P = 0.02$). The CR rate in patients with serum β_2 microglobulin levels in the normal range (0–3μg/ml) was 23/36 (64%), in contrast to 7/24 (29%) in individuals with elevated levels (>3μg/ml). This difference is highly significant on univariate ($P = 0.002$) and multivariate analysis ($P = 0.02$).

Age is significant by univariate analysis ($P = 0.04$), but is correlated with albumin and is not significant in the multivariate analysis. Lymphocyte count, histology, ESR, alkaline phosphatase and sex did not correlate with achievement of CR.

First remission – CR   Fifty-five of 97 patients entering CR with six cycles of therapy remain in continuous remission, the median duration of first remission not having been reached (Figure 3). Twelve patients died in first remission. Recurrence has been documented in 30 between 0 and 13 years. Patients in GPR had a significantly higher 'recurrence' rate compared with patients who achieved CR ($P < 0.001$) (Figure 3), recurrence being documented in 15 18.

In these (remitters) patients, retrospective calculation of the cumulative dose administered [Appendix] demonstrated on univariate analysis, a significantly higher risk of recurrence, if there was a reduction of more than 15% of the planned cumulative dose over the first six cycles ($P = 0.009$).

However, the duration of remission was the same for patients who received maintenance chemotherapy after six cycles when compared with patients treated with six cycles
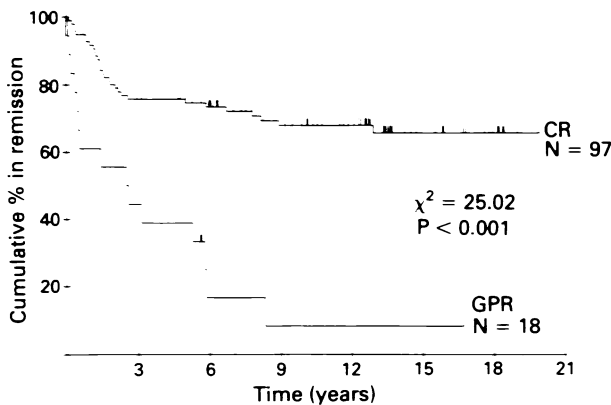
only. There was no significant difference in remission duration of patients receiving two drug maintenance, compared to patients receiving four drug maintenance. (This has been previously reported as part of a multicentre Medical Research Council trial – MRC Working Party on Lymphomas, 1979.)

There is no significant difference in the duration of remission of patients who had additional irradiation, compared with patients who had chemotherapy alone.

Presentation age, gender, albumin, serum β_2 microglobulin, erythrocyte sedimentation rate (ESR), alkaline phosphatase, lymphocyte counts, B symptoms did not correlate with remission duration on univariate analyses.

Recurrent disease

Thirty patients had recurrent disease. Second CR was achieved in 17 30 and PR in two, with what was considered appropriate therapy (Table V). Overall, salvage therapy with non-cross-resistant regimens was more effective than MVPP type regimes at inducing second remission (Table VI)). The median duration of second remission is 4.3 years. Nine of those 17 who achieved second remission have had a second recurrence, third remission being reinduced in six, the median duration of third remission being 4.4 years.

Fifteen of the 18 patients in GPR have had recurrent progressive disease. Complete remission was induced in nine patients with appropriate salvage therapy (Table V) and GPR in a further three.

Response at first recurrence correlated with duration of first remission – remission (CR and GPR) was induced in 54% of patients whose first remission was less than 1 year, 63% when remission was between 1 and 2 years and 88% when remission greater than 2 years (Table VI). There was no correlation between age, gender, albumin level or extranodal disease at recurrence and achievement of second remission (or duration of second remission). Over a 15-year period, a significantly greater proportion of patients with recurrence within 2–3 years of second remission had duration of first remission of less that 12 months ($P = 0.01$). However, there was no overall correlation between duration of first remission and duration of second remission.

Figure 3   Duration of remission–CR v GPR.

A – Uncensored
B – Censored for 2nd malignancy deaths only
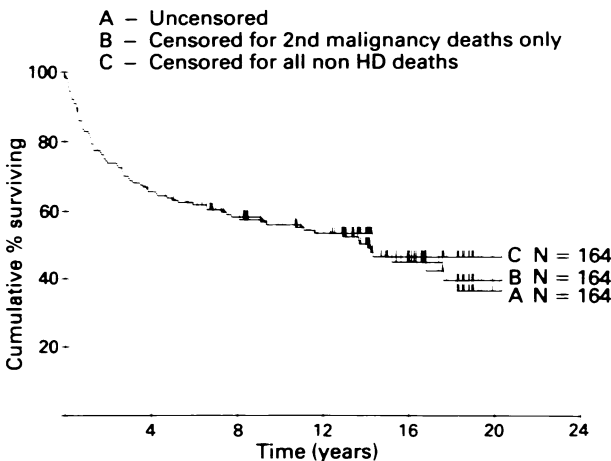C – Censored for all non HD deaths

Figure 4   Survival of patients with advanced Hodgkin's disease A = uncensored; B = censored for second malignancy deaths only; C = censored for all non-Hodgkin's disease deaths.

Table V   Response to salvage therapy in patients with recurrent disease

Response to initial therapy	Salvage regimen	Number retreated	Response to salvage		
			CR	GPR	PPR
CR	MVPP Type	12	5		
	NCR	5	4	1	
	RT	8	7		
	Combined modality	2	1		1
	No treatment	3			
	Total	30	17	1	1
GPR	MVPP type	8	4	2	1
	NCR	5	4	1	
	Surgery	1	1		
	No treatment	1			
	Total	15	9	3	1

NCR = non-cross-resistant therapy: ABVD = Sutcliffe *et al.* (1979) EVA = Richards *et al.* (1986).

Table VI   Efficacy of salvage therapy related to time to recurrence

Time Interval	Total	MVPP	NCR	RT	Other
<1 year	7 13	3 8	1 1	2 2	1 2
1–2 years	10 16	4 6	5 5	2 3	0 3
>2 years	14 16	6 7	5 5	3 3	–
Total	31 45	12 21	11 11	7 8	1 5

Survival from initial presentation

Eighty-two of 164 patients are still alive, the overall median survival being 13.7 years (Figure 4). Eighty-two patients have died; 66 patients had active HD at the time of death, 42 never having been in clinical remission (CR or GPR). The median survival of the non-remitters, excluding early deaths, is 0.4 years (0.2 years, including early deaths) (Figure 5a). Though the numbers are small, the survival of patients who achieve clinical remission with second line therapy or require more than six cycles of MVPP is significantly worse than patients who achieve clinical remission with initial chemotherapy ($P = 0.004$). The survival of patients in CR is the same as for patients in GPR, despite a significantly higher rate of recurrent disease in the latter (Figure 5b).

Fifty-five of the 97 patients entering CR are alive without ever having had a recurrence, 6/97 are alive having had one recurrence, four having had two recurrences and one having had three recurrences. Thirty-one of the 97 remitters are dead, 12 never having had a recurrence, 15 with recurrence once, three twice and one three times (Figure 6).

Sixteen patients died without clinical evidence of Hodgkin's disease at the time of death, 12 never having recurrent disease, four following recurrence and being in second (two) or third remission (two).

There was no significant difference in survival of patients treated with MVPP compared with patients treated with ChlVPP.

The stepwise linear regression method was used to detect any differences in survival correlating with age, sex, stage, histology, albumin, alkaline phospatase, absolute lymphocyte count or ESR. The only factors which significantly affect survival adversely on univariate and multivariate analysis are advanced age, histology (lymphocyte deplete) and low absolute lymphocyte count ($<0.75 \times 10^9/1$) (Table VII). Albumin failed to reach statistical significance (despite its importance for achievement of CR) though it correlates highly with lymphocyte deplete histology (mean albumin in patients with lymphocyte deplete histology is 31 g/l compared to 37 g/l in patients with other histology ($P = 0.001$, t-test) and low absolute lymphocyte count. Similarly, stage correlates with age (mean age in stage IIIB patients was 34 years, compared to 42 years for stage IV patients ($P = 0.001$, t-test)). Stage and albumin did not, therefore reach statistical significance in the multivariate analysis.
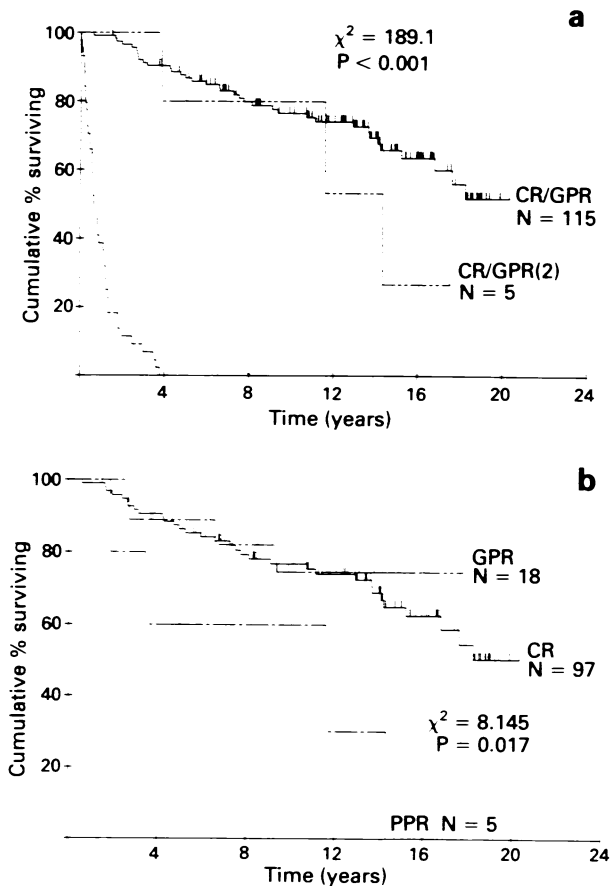

Figure 5 a. Survival of remitters *v* non-remitters *v* patients who achieve remission with second line therapy. b. Survival of patients in CR *v* GPR *v* PR.
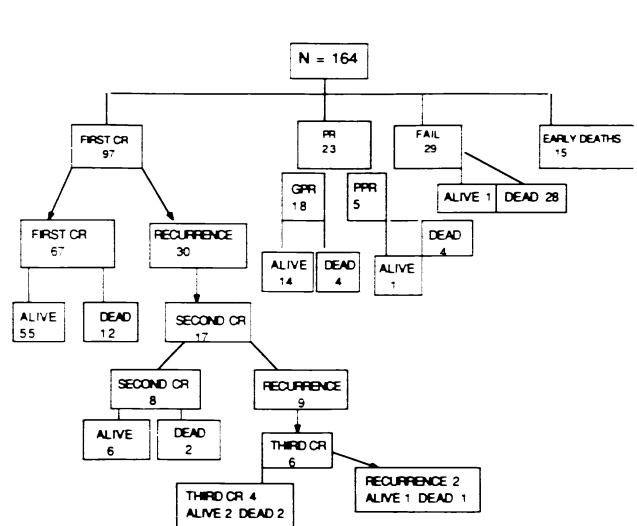

Figure 6 Flow diagram of patterns of remission and recurrence.

Table VIIa Univariate analysis of prognostic factors for survival

Variable	Significance-P value
Albumin	0.002
Age <45:46 +	<0.001
Lymphocyte count <0.75:0.75 $\times 10^9$ 1	0.009
Histology LD:rest	<0.001
$\beta_2$microglobulin	0.003
Stage IIIB:IV	0.01
Maintenance chemotherapy	0.1
ChlVPP:MVPP	0.4
Chemotherapy:combined modality	0.66

Table VIIb Multivariate analysis of prognostic factors for survival

Prognostic factor	All deaths		Non HD deaths censored		Non HD and second malignancy deaths censored	
	RR	P	RR	P	RR	P
Age (<45:>45years)	3.1	0.0001	2.4	0.002	2.4	0.003
Histology (LD vs rest)	2.3	0.03	2.6	0.01	2.6	0.02
Lymphocyte count (<0.75 vs >0.75 $\times 10^9$ 1)	1.9	0.03	1.9	0.04	2.1	0.03

Sex, stage, albumin, $\beta_2$microglobulin, alkaline phosphatase and ESR were not significant on multivariate analysis. RR = relative risk; LD = lymphocyte depletion histology.

On the reduced set of 60 patients with known β_2 micro-globulin levels, age and lymphocyte count were again significant. Serum β_2 microglobulin was significant on univariate ($P = 0.003$, Figure 7), but not on multivariate analysis.

On the basis of these prognostic factors, patients can be divided into two distinct groups—a good prognostic group, in which none of the patients have any of the adverse factors (age less than 45 years, lymphocyte count more than $0.75 \times 10^9/l$ and histology apart from lymphocyte depletion), and a poor prognostic group, where patients have one or more of the adverse factors. The difference between the two groups is statistically very significant ($P < 0.001$) (Figure 8).

Survival following recurrence

The median survival from first recurrence is 4 years, being better when second remission was achieved than the rest. The median survival of patients who achieve second CR is 12 years. Advanced age correlated adversely with survival, (age greater than 40, $P = 0.04$; age greater than 45, $P < 0.009$; age greater than 50, $P = 0.009$). Extranodal disease at time of recurrence was a significant adverse prognostic factor on univariate but not on multivariate analysis. Gender, albumin level at recurrence or duration of first remission were not significant in correlating for better survival.

Causes of death

Eighty-two of the original 164 patients have died, 15 before completion of planned chemotherapy and 51 with refractory or recurrent disease. Thus 66/82 (80%) of the deaths occurred in patients with evidence of active disease. There were 16
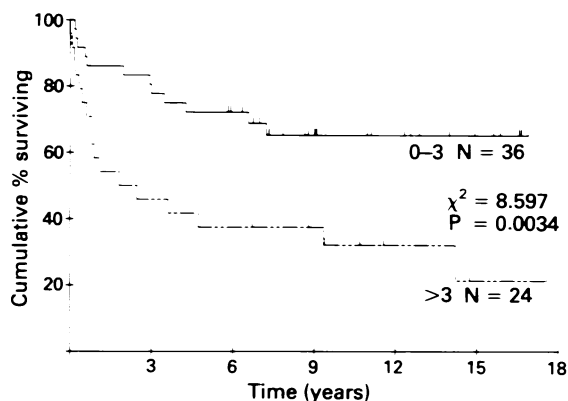
deaths in patients who had no evidence of active disease at the time of death, six of which were due to second malignancy.

The causes of death are shown in Table VIII. Details of deaths of patients who died with no evidence of HD are in Table IX.

Second malignancies Second malignancies have been recorded in 10 patients (Table X), six having died as a result. The commonest second malignancy has been non-Hodgkin's lymphoma; there has been only one documented case of acute myeloid leukaemia. Of the 67 patients in continuous first remission, seven have developed a second malignancy. Three of the seven had maintenance chemotherapy (24 patients had maintenance chemotherapy in total); three others had irradiation in addition to the chemotherapy (21 remitters received irradiation overall). There was one second malignancy in second remission and one in third; one patient developed acute leukaemia with concurrent progressive disease at second recurrence.

Discussion

This analysis provides further evidence of the enormouse long-term survival advantage conferred on patients with advanced Hodgkin's disease by the achievement of complete remission with MOPP-like cyclical combination chemotherapy, with more than 50% of them predicted to be alive 20 years later, and only one recurrence having been seen to date, after 10 years. In contrast, the survival of those for whom no remission was achieved was as bad as the natural history of the disease.

From this perspective, the first urgent priority is an improvement of the complete remission rate. This was lower (59%) with MVPP than has been recorded by others with

Figure 7 Survival of patients with normal *v* elevated β_2-micro-globulin levels at presentation.
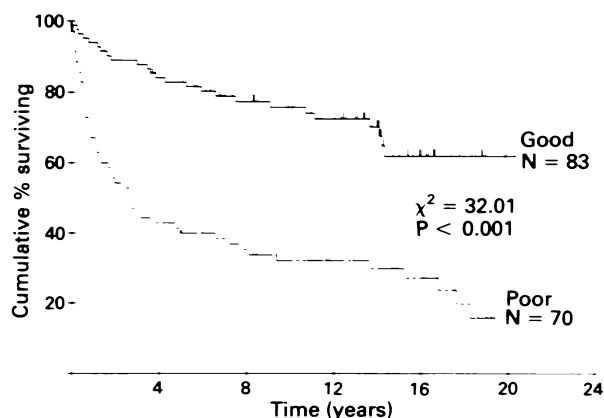

Figure 8 Survival of patients with Hodgkin's disease, by prognostic group. Good prognostic group:age <45 years and lymphocyte count more than $0.75 \times 109/1$ and histology apart from lymphocyte depletion. Poor prognostic group:either age >45 years or lymphocyte count <$0.75 \times 109/1$ or lymphocyte deplete histology.

Table VIII Causes of death

Hodgkin's disease present	66(15)[a]
Second malignancy	6(10)[b]
Cerebrovascular accident	2
Myocardial infarction	3
Infection	3
Coma	1
Unknown	

[a]Early deaths; [b]total second malignancy

Table IX Causes of deaths in remission

Patient	Age at death	Which remission	Cause	Time from Diagnosis (years)
1DG	51	First	Coma	8 months
2AN	62	First	NHL CVA	3
3DS	61	First	CVA	7
4EA	54	First	Oat cell carcinoma of bronchus	7.5
5GH	76	First	Bronchopneumonia old age (age 76 years)	8
6PL	47	First	Adenocarcinoma of lung	9 years
7CG	34	Third	Myeloproliferative disorder	11
8BAJ	72	First	Carcinoma of the prostate	11
9BC	42	Third	Myocardial infarction	13
10AG	58	First	Unknown	13.8
11CRW	80	First	Bronchopneumonia	14
12AE	46	First	Myocardial infarction	14.3
13WPG	65	Second	? second malignancy (Histology inconclusive)	15.3
14JAB	72	First	Myocardial infarction	17.5
15RDH	60	First	Carcinoma of the oesophagus	18
16COL	49	Second	Non-Hodgkin's lymphoma	20

Table X Second malignancies

Second malignancy	Remission status	Treatment	Time from diagnosis (years)
NHL	Second CR	MVPP. COPP. CVPP	13.8
NHL	First CR	MVPP MRT	12.6
NHL	First CR	MVPP maintenance	10.5
Carcinoma of oesophagus	First CR	MVPP MRT	10
Squamous cell carcinoma of skin and carcinoma of the prostate	First CR	MVPP MRT	9.4
Myelodysplastic syndrome	Third CR	MVPP maintenance	9.4
Adenocarcinoma of lung	First CR	MVPP + TNI	9
Oat cell carcinoma of lung	First CR	MVPP	6.4
Acute myeloid leukaemia	Progressive disease at second recurrence	MVPP	3.1
NHL	First CR	MVPP maintenance	2.8

NHL = non-Hodgkin's lymphoma; MRT = mantle radiotherapy; TNI = total nodal irradiation; COPP = cyclophosphamide. vincristine. procarbazine and prednisolone; CVPP = cyclophosphamide. vinblastine. procarbazine and prednisolone.

MOPP or similar regimens (Longo et al.. 1986; Selby et al.. 1990; Ranson et al.. 1991). although some of the difference may be accounted for by variations in the patient populations. particularly with respect to age and general debility (as reflected by hypoalbuminaemia). additional therapy or differences in the criteria for documenting complete remission. Regardless of this. however. it is clear that either persisting with the same treatment beyond six cycles. or changing it at that time to an alternative is not a fruitful approach since this only increased the complete remission rate to 62%. and more important. the survival of this 6% was markedly inferior to that of the initial 59%. Failure to demonstrate significant efficacy of the ABVD programme (Santro & Bonadonna. 1979) for patients with refractory disease at St Bartholomew's Hospital. in contrast to the experience in Milan (Santoro et al.. 1979; 1982). may well relate solely to the fact that it was 'left too late'. The equivalent efficacy of the ABVD and MOPP in inducing remission provided the rationale for testing non-cross-resistant and hybrid combinations (Santoro et al.. 1982; Klimo & Connors. 1985). Most. but not all. recent data have supported this approach for improving responsiveness. the most spectacular results coming from Vancouver. with a reported complete remission rate of 88% (Klimo & Connors. 1988) after hybrid chemotherapy and involved field irradiation where necessary. Failure to achieve complete remission in this way. of course. leaves little room for manoeuvre and raises the question of whether bone marrow ablative treatment is indicated for some patients in this setting. The present consensus seem to be that it is only likely to benefit those who are at least showing some evidence of response (Jagannath et al.. 1989; Carella et al.. 1988); dose escalation per se does not universally overcome intrinsic resistance. Clearly some indication from the presentation features of probability of conventional treatment failing would be most helpful. The data above indicate that advanced age and hypoalbuminaemia are the major adverse factors. neither of which would be likely to predispose well to intensification of therapy. It is more likely that the rate of response will be a useful indicator. but the logistics of repeated detailed re-evaluation during therapy are daunting.

Presentation serum β_2 microglobulin levels. available in a smaller set of patients. correlated with achievement of complete remission; it remained statistically significant on mul-

tivariate. analysis though albumin and stage were not. Amlot and Adinolfi (1979) found correlation between presentation β_2 microglobulin levels and initial stage in patients with Hodgkin's disease. This trend was also confirmed by Hagberg et al. (1983) and Child et al. (1980). However. there was no correlation with achievement of remission or survival. Prognostic effect of β_2 microglobulin on response to therapy and also on subsequent survival has been documented in non-Hodgkin's lymphoma and myeloma. but not in Hodgkin's disease (Legros et al.. 1987; Han et al.. 1989; Hagberg et al.. 1983). The cause of elevated β_2 microglobulin levels is still speculative. It has been suggested that there is increased shedding due to decreased cell surface expression or due to increased cell turnover. Swan et al. (1989) suggested that patients with high β_2 microglobulin had absent cellular expression of Class I Major Histocompatibility Complex (MHC). Therefore the prognostic value of serum β_2 microglobulin may provide a crude and indirect assessment of the importance of tumour MHC expression.

The freedom from recurrence pattern for those entering complete remission is very similar to that reported in the literature. with most recurrences occurring during the first 3 years. and approximately two-thirds still free of disease 10-15 years from presentation. Limited support for the importance of dose-intensity comes from the finding that reduction of more than 15% of the planned cumulative dose over the first six cycles correlated with a high risk of recurrence. This interpretation is of course complicated by the inevitable problem of retrospective analysis. Further. the fact that the MVPP programme is given every 6 weeks compared with 4 weeks for MOPP. and yields identical results in terms of freedom from recurrence suggests that there may well be a threshold above which the dose intensity effect becomes irrelevant. Whether the somewhat lower remission rate in this study compared with 4-weekly MOPP may reflect the effect of lower dose intensity is a matter of speculation. Preliminary results from a Cancer and Leukaemia Group B (CALGB) study suggest an advantage for ABVD in both inducing and maintaining remission (Canellos et al.. 1988; Anderson et al.. 1990) are interesting and await confirmation. Significant improvement in the complete remission. freedom from progression. relapse-free survival and overall survival with alternating MOPP ABVD over MOPP alone has been reported from Milan. though at a cost of increased treatment related toxicity (Bonadonna et al.. 1986).

Survival from recurrence was surprisingly good. and once again correlated most closely with the response to salvage therapy. and was characterised for most by repeated recurrences with a diminishing likelihood of response. The response rate was better following longer first remissions. The absence of an absolute correlation between duration of first remission and duration of second remission is surprising. although the majority of patients with second recurrence within 2-3 years of apparently successful re-induction therapy had had initial remission lasting less than 1 year. This weak correlation. the fact that the median duration of second remission was 4 years coupled with a median survival of 4 years from recurrence and 12 years from second remission makes selection of the most appropriate management at recurrence difficult. particularly as advancing age (above 40 years) was the only adverse feature identified. It is not yet clear whether survival following recurrence after non-cross-resistant alternating or hybrid chemotherapy will follow the same pattern as following MOPP or MVPP. Further newer combinations have been shown to be promising (Richards et al.. 1986).

The published experience with bone marrow ablative therapy is certainly encouraging. either if used at recurrence or as consolidation of remission (Carella et al.. 1988; Gribben et al.. 1989; Jagannath et al.. 1989; Jones et al.. 1990). However. much more data will be required to demonstrate its general applicability and efficacy. It is less. rather than more. likely to be relevant to most of the patients who have a recurrence when over 45 years of age. and this is the group in greatest need of help. It will clearly take many years to prove

a survival advantage for such treatment at first recurrence or in second remission: the only valid endpoints of present studies in the near future will have to be freedom from recurrence and toxicity, with the hope that if the former is substantially improved, it will convert into longer survival. Whether it will be possible to answer the question without randomised trials is arguable. Minimisation of the short-term toxicity of treatment, possibly with the use of haemopoietic growth factors would clearly be most helpful and widen the range of people in whom therapy could be tested. While it can be postulated that the successful induction of a second remission is not an argument for very intensive consolidation, it might well be considered the treatment of choice following subsequent recurrences. The necessity of identifying the most appropriate patients to receive experimental therapy is obvious.

The pattern of survival for the whole population was obviously dominated by failure of the treatment, with 80% of the deaths so far having occurred in people with active disease. It has previously been reported that almost all of the men and at least half of the women who survive are sterile (Sherins & DeVita 1973; Chapman et al., 1979; 1981; Waxman et al., 1982) and with longer follow-up it is clear that the incidence of second malignancy continues to increase (Tester et al., 1984; Dorreen et al., 1986; Coleman, 1986; Tucker et al., 1988; Kaldor et al., 1990; Somers et al., 1990). Second malignancies accounted for 10% of the deaths in remitters, being the single most important cause of mortality after HD. The risk of second malignancy seems to be increased in patients who receive additional therapy—6 7 remitters who develop second malignancy had had extra chemotherapy as maintenance or additional irradiation. Three other patients who developed second malignancy following recurrence had been retreated with combination chemotherapy. The increased risk of secondary malignancy with increasing therapy is well recognised, particularly following irradiation (Coleman, 1986; Somers et al., 1990). Data on more than 12,411 patients treated for HD in different centres were pooled and analysed in 1989 (Somers et al.,

1990). The cumulative incidence of second malignancy over a 20-year follow-up period approaches 18.6%, with 'solid tumours' accounting for the majority of late malignancies. In this group of patients treated with MVPP with a minimum follow-up of 6 years there has only been one instance of frank acute myeloid leukaemia which occurred at the same time as progressive Hodgkin's disease at second recurrence. and one myelodysplastic syndrome in third remission. In the NCI series (Longo et al., 1986), there were 13 cases of acute leukaemia, from a total cohort of 198 patients, 12 of which occurred in patients who had received both MOPP and irradiation. In contrast to these results, Kaldor et al. (1990), in a case controlled study of 163 cases of leukaemia following therapy for Hodgkin's disease, found no increased risk in patients receiving additional irradiation. In the same study, treatment with more than six cycles significantly increased the risk of secondary acute leukaemia. The Stanford data suggest that the risk of acute leukaemia reaches a plateau at 10 years, at 3.3%, though the risk of secondary non-Hodgkin's lymphoma continues to increase. The cumulative actuarial risk of all second cancers from the Stanford series is 17.6% at 15 years (Tucker et al., 1988). The cumulative risk of acute leukaemia in this present series is thus lower than that reported with a number of series using MOPP. Whether this is a consequence of the 'lower' intensity with which MVPP is administered, being 6-weekly instead of 4-weekly, needs to be determined.

The long-term toxicity of the newer treatments, either without alkylating agents, or including them in lower doses in the form of hybrid or alternating programmes, may well be much less than that of MOPP alone. Much will have been gained even if this is the only achievement of modifying the initial therapy. Reducing its duration was certainly a benefit. Neither the failure of MOPP like therapy to eliminate HD from some patients nor its late toxicity, even fatal for others, should be allowed to detract from the significant benefit it has brought to the majority of those who received it. The challenge is to look forward and do better.

Appendix

Dose reduction

Percentage of planned dose administered

$$= \frac{\frac{T}{P} \text{Mustine} + \frac{T}{P} \text{Vinblastine} + \frac{T}{P} \text{Procarbazine} + \frac{T}{P} \text{Prednisolone}}{4} \times 100$$

T = total dose administered. P = planned dose.

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