PAPERS AND ORIGINALS

Randomised trial of two-drug and four-drug maintenance chemotherapy in advanced or recurrent Hodgkin's disease

Medical Research Council's Working Party on Lymphomas

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Summary and conclusions

Between 1970 and 1975, 108 patients who presented with advanced or recurrent Hodgkin's disease and were free of disease after six courses of chemotherapy with mustine, vinblastine, procarbazine, and prednisone (MVPP) were allocated at random to one of two regimens of maintenance treatment: either intermittent treatment with vinblastine and procarbazine or intermittent treatment with MVPP. After a median follow-up period of nearly five years there was no significant difference between the two groups in either the rate of relapse or death rate. Six of the 55 patients given the two-drug regimen died compared with 10 of the 53 given the four-drug regimen. The four-drug regimen required hospital attendance and was less agreeable than the two-drug regimen.

The efficacy of maintenance chemotherapy with the two-drug regimen was no less than that with the four-drug regimen, but the two-drug regimen had several practical advantages.

Introduction

The usefulness of maintenance chemotherapy in advanced Hodgkin's disease remains uncertain, but in 1970 it was generally considered to be desirable. At that time the Medical Research Council instituted a randomised clinical trial to compare a two-drug regimen of maintenance chemotherapy (vinblastine and procarbazine (VP)) with a regimen using four drugs (mustine, vinblastine, procarbazine, and prednisone (MVPP)), one of which (mustine) had to be given by intravenous drip and sometimes produced severe nausea and vomiting. We report the results of the trial.

Patients and methods

The trial was restricted to patients with advanced or recurrent Hodgkin's disease. Patients were eligible for entry if they had not already received chemotherapy and presented either with advanced disease (stage IIIB, IVA, or IVB) or with relapse in an area that had been treated with radiotherapy. All patients were treated initially with six courses of MVPP, similar to the regimen described.[1] A course consisted of mustine (6 mg/m^2) and vinblastine (6 mg/m^2) given intravenously on days 1 and 8 and procarbazine (100 mg/m^2) and prednisone (40 mg) taken by mouth on days 1 to 14 inclusive. A gap of four weeks was left between courses. Sometimes the drug doses had to be reduced, particularly in the case of mustine, because of marrow suppression.

Hodgkin's disease was confirmed histologically and classified as described.[2] Patients were clinically staged at presentation according to the Ann Arbor classification,[3] the clinical history and results of physical examination, blood counts, liver function tests, chest radiography, and bipedal lymphangiography being used. Patients entered the trial only if at the time of randomisation all these findings had returned to normal.

Between May 1970 and June 1975, 108 patients completed six courses of MVPP and were in remission three months after the sixth course. These patients were entered into the trial and allocated at random to receive either MVPP or VP. Courses of VP were the same as with MVPP but with the omission of mustine and prednisone. Both treatments were given in 10 courses over three-and-a-half years after randomisation; a three-month gap was left after each of the courses 1-3, a four-month gap after each of the courses 4-6, and a six-month gap after each of the courses 7-9. Patients were entered into the trial from four centres: 41 patients from St Bartholomew's Hospital, London; 10 from Det Norske Radium Hospital, Oslo, Norway; 23 from Oxford; and 34 from the Royal Marsden Hospital, Sutton. All except one of the patients were followed up until 1 July 1977; the remaining patient emigrated 57 months after randomisation (to VP). All patients were followed up for at least two years, the median follow-up period being 4 years 11 months.

Members of the working party were Dr S T E Callender, Professor N F C Gowing, Professor G Hamilton Fairley (until October 1975), Dr I M E Hamlin, Dr J M Holt, Dr H Høst, Professor A Jones, Dr A H Laing, Dr J S MacDonald, Dr T J McElwain, Dr J S Malpas, Dr C R Newman, Dr C H Paine, Professor M J Peckham, Dr M C Pike, Dr A H T Robb Smith, Mr P G Smith, Dr A G Stansfeld, Dr S Sutcliffe, Dr A K Tucker, Dr N Wald, Dr W F White, and Dr F W Wright.
This report was prepared by Dr Nicholas Wald and Mr P G Smith.

Results

Of the 108 patients, 55 were allocated to treatment with the two-drug (VP) regimen and 53 to treatment with the four-drug (MVPP) regimen. There was no appreciable difference between the groups in the distribution of factors of possible prognostic importance (table I). In the analysis 10 patients who either relapsed before receiving their first course of treatment or received a different treatment from the one allocated were included in the group to which they had initially been randomised (see footnote to table I).

TABLE I—*Clinical and histological details of patients allocated to maintenance treatment with either VP or MVPP. Figures are numbers of patients*

	VP group	MVPP group
Sex distribution:		
Male	40	35
Female	15	18
Age (years):		
<20	6	2
20-39	30	36
40-59	16	13
⩾60	3	2
Presenting disease:		
Advanced	23	19
Recurrent	32	34
Clinical stage:		
IIA	4	2
IIB	0	1
IIIA	9	8
IIIB	14	15
IVA	9	7
IVB	19	20
Histological type:		
Lymphocyte-predominant	7	3
Nodular sclerosis	22	27
Mixed cellularity	19	15
Lymphocyte-depleted	5	6
Not classified	2	2
Total	55	53

Four patients (three allocated to MVPP, one to VP) relapsed between time of randomisation and first maintenance course of chemotherapy; four patients randomised to MVPP were treated with VP; one patient randomised to VP was given MVPP; one patient randomised to MVPP was given no maintenance treatment. For analysis all these patients are included in treatment group to which they were allocated at random.

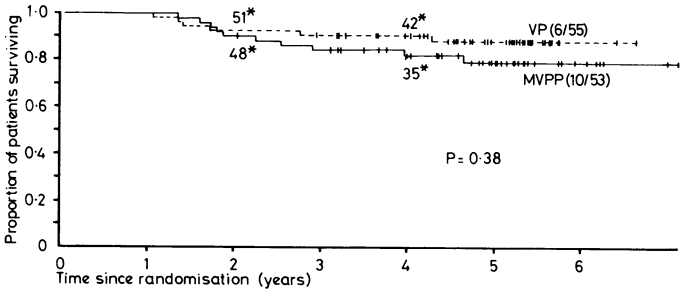

FIG 1—Actuarial estimates of survival in patients allocated to VP or MVPP regimen. Steps indicate when patients died. Vertical bars indicate when patients who were still alive were last followed up. Figures marked with asterisk are numbers of patients surviving in each treatment group two and four years after randomisation. Numbers of deaths in each group given in parentheses.

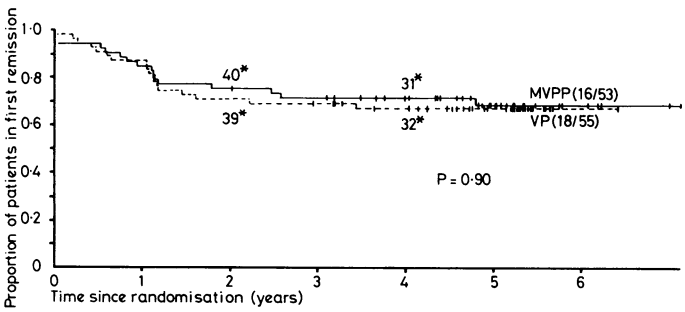

FIG 2—Durations of first remission after randomisation to the two treatment groups. Steps indicate when patients relapsed. Vertical bars indicate when patients still in first remission were last followed up. Figures marked with asterisk are numbers of patients still in first remission two and four years after randomisation. Numbers of patients who relapsed given in parentheses.

Figure 1 gives the actuarial estimates of the proportions of patients alive at different times after randomisation to the two treatment groups. Six of the 55 patients allocated to the VP regimen and 10 of the 53 allocated to the MVPP regimen died. This difference is not significant and there was no convincing evidence of any difference in survival times between the two groups. Actuarial estimates of the proportions of patients surviving for at least five years after randomisation were 88% with the two-drug regimen (95% confidence interval 77-90%) and 80% with the four-drug regimen (95% confidence interval 66-89%). Of the 16 patients who died, 14 died of Hodgkin's disease and two (both in the MVPP group) of acute myeloblastic leukaemia, one at 21 months and the other 48 months after randomisation. Fig 2 shows the durations of remission after randomisation. Eighteen patients relapsed in the VP group and 16 in the MVPP group, and again there was no material difference in the durations of remission between the two groups.

Table II shows the relapse rates and death rates in the two groups each year after randomisation. Because of the small differences in rates between treatment groups the rates are shown for the two groups combined. During the first year there were no deaths in either group, but the next year the death rate was 8·7/100 person-years at risk. In subsequent years it declined significantly (P = 0·01), and three years after randomisation the average yearly death rate was only 1·7/100 persons. The relapse rate was highest in the first two years, averaging 16·0/100 person-years at risk, but then fell dramatically (P = 0·00003), only two patients having their first relapse after more than three years in remission, a rate of 1·4/100/year. Fig 3 shows the durations of survival after first relapse in the two treatment groups. Patients who relapsed while receiving MVPP had a poorer prognosis after relapse than did those receiving VP but the difference was not significant (P = 0·23).

Fig 4 shows the durations of first remission after randomisation according to six factors of possible prognostic importance. For analysis the two treatment groups are combined. Women relapsed less rapidly than men, though not significantly so, and patients aged under 40 were less likely to relapse than older patients, though again the difference was not significant. Histological type had no demonstrable effect on the duration of remission but clinical stage did: patients with stage IV disease were more likely to relapse than those with stage II or III disease. There was no material difference

TABLE II—*Yearly first-relapse rates and death rates in the two treatment groups after randomisation*

Time since randomisation (years)	First relapse: Person-years at risk	First relapse: No of first relapses: MVPP group	First relapse: No of first relapses: VP group	First relapse: No of first relapses: Total	First relapse: Relapses/100 person-years at risk†	Deaths: Person-years at risk*	Deaths: No of deaths: MVPP group	Deaths: No of deaths: VP group	Deaths: No of deaths: Total	Deaths/100 person-years at risk‡
0–	99·3	8	7	15	15·1	108·0	0	0	0	0
1–	82·3	5	9	14	17·0	103·8	5	4	9	8·7
2–	76·5	2	1	3	3·9	96·6	3	1	4	4·1
3–	67·9	0	1	1	1·5	84·9	1	0	1	1·2
4–	53·3	1	0	1	1·9	65·2	1	1	2	3·1
⩾5	21·3	0	0	0	0	29·0	0	0	0	0
Total	400·5	16	18	34	8·5	487·4	10	6	16	3·3

*Numbers are larger than for first relapse as patients are included up to death rather than to first relapse.
†Trend in relapse rate since randomisation: $\chi^2_1 = 17·39$; P = 0·00003.
‡Trend in death rate (starting at one year) since randomisation : $\chi^2_1 = 5·98$; P = 0·014.

in the duration of remission between patients with advanced Hodgkin's disease and those with recurrent disease. Patients with systemic symptoms (Ann Arbor classification B) relapsed more rapidly than those without such symptoms (classification A) but the difference was not significant. Finally, there was no significant difference in the lengths of remission between patients treated at different centres.

The durations of remission in patients receiving MVPP and VP were compared within the subdivisions of the six factors shown in fig 4, and in no instance was there a significant difference. The number of patients who had died by July 1977 was too small to examine the influence of the six factors on survival.

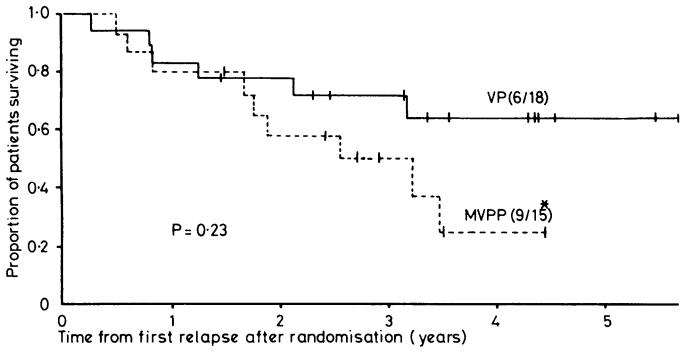

FIG 3—Durations of survival after first relapse in the two treatment groups. Steps indicate when patients died. Vertical bars indicate when patients who were still alive were last followed up. Numbers of deaths given in parentheses. *Excludes one patient who died without record of relapse.

Discussion

There was no evidence of any benefit associated with four-drug maintenance chemotherapy as compared with two-drug chemotherapy among patients with advanced or recurrent Hodgkin's disease who achieved remission after six courses of combination chemotherapy. The initial results of one study suggested that some form of maintenance chemotherapy is of value,[4] but longer follow-up of the patients failed to confirm this[5]; and another study failed to show any benefit associated with maintenance treatment.[6] Our results therefore need to be interpreted in the light of the possibility that maintenance chemotherapy may not be necessary at all. If a decision is made to offer patients maintenance treatment the simpler, two-drug regimen seems to be preferable as it does not require hospital admission for administration.

Because of the small size of this trial the results need to be interpreted with caution. The same reservation applies to the two American studies mentioned above. One of these included 75 patients[4] and the other 57,[6] and neither offered conclusive evidence for or against maintenance chemotherapy. In our trial the difference between the proportions of patients expected to survive five or more years after randomisation was only 8% (88% in the VP group and 80% in the MVPP group surviving five years), and the 95% confidence interval on this difference (−6% to 23%) was wide enough to include the possibility that MVPP might be better than VP.

All the patients in the trial were followed up for at least two years, and the rate of first relapse among patients who had not relapsed by that time was low and seemed likely to remain so (table II). Patients who did relapse, however, experienced a high mortality, half of them dying within three years later (fig 3); and only one patient in the study died without record of a relapse. Any difference in mortality between the two treatment groups in the next few years is therefore likely to occur only among patients who had already relapsed. In view of the low relapse rate after the first two years of the trial mortality will probably remain low in patients who did not have a relapse, and as there were only 18 patients who did relapse and were still alive by July 1977 (12 in the VP group, 6 in the MVPP group) large differences in survival between the two treatments will probably not emerge in the next few years.

A possible argument for use of the VP regimen is that since drug resistance might be less with two drugs than with four, relapse might be easier to treat, and our results suggest that this may be so; patients relapsing during treatment with VP tended to survive longer than those relapsing in the MVPP group. The difference was quite pronounced but the numbers were small and it was not statistically significant (fig 3).

Of the 16 patients who died, two died of myeloblastic leukaemia. This was highly significantly ($P<0.001$) more than would be expected (0·03) if the 108 patients in the trial had experienced the same mortality rates from leukaemia as the general population of England and Wales. Both deaths occurred in patients with advanced Hodgkin's disease (stages IIIB and IVB) who had received no chemotherapy or radiotherapy before the six courses of MVPP which preceded randomisation. Inducing leukaemia is a recognised complication of treating Hodgkin's disease with intensive chemotherapy,[7 8] a risk that appears to be even greater in patients who have also received radiotherapy. The average yearly risk of dying from leukaemia among patients in our trial was about 0·4% after randomisation, which is similar to that reported by Coleman *et al.*[7] There is no doubt that intensive chemotherapy has prolonged the lives of patients with advanced or recurrent Hodgkin's disease, and this outweighs the risk of leukaemia associated with treatment. That both patients who died of leukaemia received the four-drug maintenance regimen may well have happened by chance, but it seems reasonable to suppose that the risk of leukaemia may increase with the amount of chemotherapy given, which is an additional argument against the use of four-drug maintenance treatment.

Patients were entered into the study only if they were in clinical remission at the time of randomisation, which was three months after completing six courses of chemotherapy. Survival

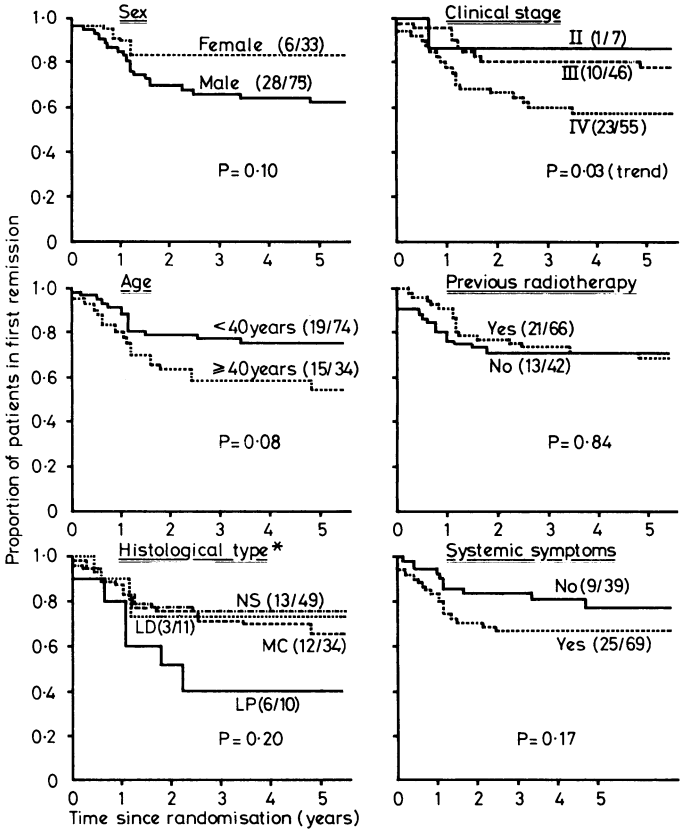

FIG 4—Durations of remission after randomisation according to clinical and histological characteristics. Steps indicate when patients relapsed. Numbers of patients who relapsed given in parentheses.
*Histological type: NS = nodular sclerosis; LD = lymphocyte-depleted; MC = mixed cellularity; LP = lymphocyte-predominant.

and remission rates therefore relate only to patients who achieved remission. Since patients were not uniformly notified to the trial co-ordinating centre at the time of first diagnosis we cannot give the survival or disease-free periods of the original population of patients. Nevertheless, of the patients in the present study whose remission was successfully induced with MVPP, 84% (95% confidence interval 76-90%) were alive 5 years after randomisation to the two maintenance regimens. This and the observation that the relapse rates and death rates of patients in the trial declined significantly with time after randomisation suggest that a high proportion of patients who did not relapse within two years of starting maintenance treatment may have been "cured."

Data from the participating centres were collected by Mrs Catherine Harwood. The working party was disbanded in December 1975.

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Transurethral resection of large prostates

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Summary and conclusions

A total of 102 men (mean age 70) underwent transurethral resection of the prostate. The weight of the resected prostate ranged from 40 to 152 g. Two deaths occurred in patients aged 85 and 92 years, both of whom were generally unfit. The average postoperative stay in hospital was 8·3 days.

The proportions of patients with incontinence, infection, and stricture were similar to those in other series of resections and open prostatectomies, suggesting that resection of the larger prostate is safe and an acceptable alternative to an open operation.

Introduction

Prostatic adenomas of small or average size may be removed by adequately trained staff as safely and effectively by the transurethral route as by open operation.[1] The superiority of transurethral resection in terms of the length of stay in hospital and degree of discomfort to the patient is a strong argument in favour of training and employing more specialist urologists.[2] Despite the increasing popularity of transurethral resection, however, particularly large prostates are still assumed to be better dealt with by an open operation, partly because of the tedium and difficulty of doing a long resection but also for fear of greater complications postoperatively.

To see whether larger prostates may be equally well resected we analysed a consecutive series of 102 transurethral resections of benign prostates weighing 40 g or more.

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Patients and methods

We studied 102 patients—that is, all those in whom one of us (RHW) resected 40 g or more during April 1971 to March 1976. Their mean age was 70 years; table I shows the age distribution. The patients were graded according to their preoperative fitness as follows.[1] Grade 1: fit men aged under 70 years with no known cardiovascular or respiratory disease and not diabetic. Grade 2: men aged 71-80 years and younger men with diabetes, hypertension, or chronic lung disease; also those with a history of myocardial infarction or cerebrovascular accident more than six months previously. Grade 3: men aged over 80 years or very unfit, and those with recent myocardial infarction or cerebrovascular accident. Table II shows the distribution of the patients between these three categories.

TABLE I—*Age distribution of all 102 patients studied*

Age (years)	50-	60-	70-	80-	90-100
No of patients	11	42	37	10	2

TABLE II—*Classification of patients as grade 1, 2, or 3 according to preoperative medical state*

Clinical grade	1	2	3
No of patients	40	41	21

Most of the operations in this series were performed under general anaesthesia; a few patients had a spinal anaesthetic. The instrument used was a 26F Thackray or Storz loop resectoscope; if the urethra was tight for this an Otis internal urethrotomy was performed. In all cases we believed that all adenomatous prostatic tissue had been removed.

Most of the resections were of prostates weighing 40-60 g, but several were considerably larger. Table III shows the distribution of

TABLE III—*Distribution of weights of resected prostates*

Weight (g)	40-	50-	60-	70-	80-	90-	100-	110-	120-	130-	140-	150-160
No of patients	40	34	10	5	5	6	1					1