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A population-based study of intensive multi-agent chemotherapy with or without autotransplant for the highest risk Hodgkin's disease patients identified by the Scotland and Newcastle Lymphoma Group (SNLG) prognostic index. A Scotland and Newcastle Lymphoma Group study (SNLG HD III)

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Abstract

The aim of the study was to identify all patients with poor risk Hodgkin's disease (HD) using a numerical prognostic index in a defined population and to recruit them into a trial of intensive chemotherapy prednisolone, vinblastine, doxorubicin, chlorambucil, etoposide, bleomycin, vincristine, procarbazine (PVACE-BOP)×3 + autotransplant (Arm A) versus PVACE-BOP×5 (Arm B) in first remission. In 10 years, the Scotland and Newcastle Lymphoma Group (SNLG) registered 930 patients with HD of whom 178 (19%) were identified as 'poor risk' by the SNLG index and were aged 16–59 years. 126/178 (71%) entered the study. Of the 120 confirmed poor risk HD cases, all completed PVACE-BOP×3 with a 93% Complete Response/unconfirmed Complete Response (CR/CRu) rate. Only 65/107 in CR accepted the randomisation. With a median follow-up of 6 years, both arms of the trial have a similar time to treatment failure (TTF) (Arm A 79% ± 11 versus 85% ± 7 Arm B, $P = 0.35$). Advanced stage 'good risk' patients not included in the trial receiving standard therapy with CLVPP or ABVD had a 75% 5-year survival. The study demonstrates that PVACE-BOP therapy in the poorest risk group (58% had an IPI ⩾ 3) produces excellent CR rates (93%) and overall survival with minimal toxicity, and that the substitution of autotransplant in first CR does not improve outcome. The use of the objective SNLG index accurately helped in the selection of the poorest risk group in this population study. The placing of a randomised control trial within the context of a population-based study of HD enhances the validity of the outcome.

Keywords: Population study; Hodgkin's disease; Autotransplant; Chemotherapy; Randomised trial; Primary therapy

1. Introduction

In 1980, using MOPP-type chemotherapy [1] or CLVPP [2], it was possible to cure 50–60% of patients with advanced stage Hodgkin's disease (HD). The subsequent introduction and use of ABVD [3] has demonstrated excellent activity in advanced HD and has proved to be the most consistently applied chemotherapy over the last 15 years.

In the 1980s, the Scotland and Newcastle Lymphoma Group (SNLG) developed a numerical prognostic index (SNLG-PI) based on objective prognostic factors to identify more accurately the 40–50% of patients who would not be cured by conventional four drug schedules; this enabled the separation of patients with

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advanced stage disease into good and poor risk groups [4]. It was particularly valuable because it could be applied to patients with all stages of HD and has been confirmed by others [5] to separate patients treated by conventional four drug schedules into a survival population of poor risk (40% 10-year survival—all age groups) and good risk (75–80% 10-year survival). Thus, patients with a high chance of being cured by a four drug schedule could be excluded from entry into the proposed randomised trial of more intensive chemotherapy [6].

The trial reported here began in 1988 recruiting only those patients identified by the SNLG-PI to have a less than 50% probability of long-term survival on the then available chemotherapy. The population-based nature of the study group within the Northern part of the UK and Scotland has allowed assessment of all cases of HD occurring during the study period providing a denominator population against which the efficacy and toxicity of an intensive new schedule might be measured. The present report represents the only attempt, to date, not only to compare directly intensive chemotherapy with chemotherapy plus autotransplant in first remission in an objectively defined group of poor risk patients, but also to compare outcome to the overall denominator population from which the study population was drawn.

2. Patients and methods

2.1. The SNLG population

The population of Scotland is 5.5 million people and that of the former Northern Regional Health Authority of England 3.1 million. From 1988 to 1999, investigators in the West of Scotland were involved in an alternative study; therefore the study population from which the cases were drawn was 4.5 million. The SNLG is a population based group and the aim was to register all cases of Hodgkin's disease presenting in the co-operating centres, to assess the SNLG-PI on this population and enlist as many as possible of younger patients in the poor prognosis group into the trial.

2.2. Eligibility criteria

All patients had histologically-proven Hodgkin's disease. Central pathological review was undertaken by one of the authors. Eligibility criteria included a SNLG-PI of $\geqslant 0.5$ (i.e. identified 'poor risk' HD). Advanced stage 'good risk' patients (SNLG-PI <0.5) were excluded and received standard chemotherapy/radiotherapy. Patients had to be aged 16–60 years and be prepared to accept the possibility of autologous bone marrow transplantation. Patients who had received prior chemo/radiotherapy were excluded, as were those with co-existing malignancies apart from localised non-melanoma skin cancers. Patients at risk of pregnancy were asked to use contraception. Patients were also excluded if they were known to have significant heart, lung or renal disease which might be expected in itself to shorten survival or to significantly reduce tolerability for trial therapy. Local Ethical Committee approval was obtained at all centres and patients gave fully informed consent.

2.3. Histopathology

In the original protocol, central review was from sections stained with haematoxylin and eosin (H&E) stain. Latterly, the diagnosis was confirmed by the use of immunohistochemistry on paraffin sections where possible before trial entry. Subsequently, all trial entry specimens were reassessed by this method. The standard panel of antibodies was L26 (CD20, Dako), MB1 (CD45RA Novocastra), MT1 (CD43 Novocastra), CD3 (Dako), CD15 (Novocastra), BerH2 (CD30, Dako). For immunostaining of paraffin sections, a standard avidin-biotin peroxidase technique was employed. Subtypes were allocated according to the Revised European American Lymphoma (REAL) classification [7].

2.4. Pretreatment assessments

Pretreatment assessments included full clinical examination, with particular attention being made with reference to the presence or absence of systemic symptoms. Full blood count, including differential and a complete biochemical profile were performed pre-treatment. Radiological staging was done to Cotswold guidelines [8] with chest X-ray and computed tomography (CT)s of chest, abdomen and pelvis being the recommended minimum. Bulk disease (a single node $\geqslant 5$ cm) was to be recorded, with bulk disease in the mediastinum being defined as $>30\%$ of the intrathoracic ratio at T5/T6 level. Bone marrow aspirate and trephine were to be assessed for disease involvement prior to study entry. Pulmonary function tests were performed if the patient had pre-existing respiratory problems. All initial staging was repeated at the time of reassessment.

2.5. Calculation of prognostic index

The information required to calculate the SNLG-PI includes patient age, haemoglobin (g/dl), clinical stage, pretreatment absolute lymphocyte count and whether there is bulk disease (as defined above). The index is shown in Fig. 1 and a figure of $\geqslant 0.5$ indicates 'poor risk' disease and was the figure set for entry into the trial.

2.6. Study design

All patients entering the study received initially three cycles of prednisolone, vinblastine, doxorubicin, chlorambucil, etoposide, bleomycin, vincristine, procarbazine (PVACE-BOP) [9] in a continuous 28-day cycle over 12 weeks (Fig. 2). In those patients with bulk disease at diagnosis or residual disease following the initial 12-week period of chemotherapy, radiotherapy was administered to a dose of 30 Gy over 20 days to involved fields to all areas of bulk disease as defined in Fig. 1. Patients were eligible to be randomised if they had achieved a Good Partial Response/Complete Response (GPR/CR) at the end of 3 PVACE-BOPs plus radiotherapy. In patients who were randomised to receive autologous transplants the aim was to have the procedure completed within 8–12 weeks of finishing the radiotherapy and similarly for those receiving two further months of chemotherapy, this was to recommence not longer than 8 weeks after completing the radiotherapy. Bleomycin was omitted from courses 4 and 5 if the patients had received radiotherapy.

2.7. Patients not on trial

Details on all patients with HD from the population from which the patients came were collected. Patients with an SNLG-PI <0.5 were treated at the discretion of the physician in charge according to the stage of disease using local guidelines. The commonest therapies utilised for chemotherapy-requiring patients were CLVPP/MVPP or ABVD. Patients with index $\leqslant 0.5$ not on study were also followed up annually to death with treatment and outcome recorded.

2.8. Autotransplant procedure

Our group previously published the use of unmanipulated non-cryopreserved bone marrow autotransplants utilising melphalan/etoposide preconditioning [10]. This was the form of intensification and rescue used for the majority of the study, but following the introduction of peripheral blood stem cell transplants (PBSCT), centres were allowed to use these if preferred. The type of transplant was recorded. Bone marrow harvest was performed on day −2, followed by an infusion over 12 h of 1.6 gm/m^2 of etoposide and a single intravenous (i.v.) bolus of melphalan at a dose of 120 mg/m^2. Stem cells were returned 48 h later.

2.9. Dose adjustments during PVACE-BOP

2.9.1. Day 8

If the neutrophil count was $<1\times10^9$/l or platelets 75–100×10^9/l on day 8, it was recommended that the 'weeks' be changed round, i.e. omit the vincristine and doxorubicin, give bleomycin as for day 15 and start prednisolone for 14 days. Bleomycin to be given again

Calculation of the Prognostic Index for Hodgkin's Disease (Proctor et al. [4])

To calculate the index the patient's age, clinical stage, absolute lymphocyte count, haemoglobin and bulk disease are required.

The index (I) = 1.5858 - 0.0363 Age + 0.0005 (Age^2)
+ 0.0683 CS - 0.086 LC - 0.0587 Hb
+ additional factor if bulk disease is present*

Age is entered as an absolute figure in the equation

Clinical stage entered according to the key (Ann Arbor Classification)

IA, IIA, IIIA	= 1
IB, IIB	= 2
IIIB	= 3
IV	= 4

Absolute lymphocyte count is entered as a score

<1.0x10^9/l	= 1
1.0-1.5x10^9/l	= 2
1.5-2.0x10^9/l	= 3
>2.0x10^9/l	= 4

Haemoglobin (Hb) in g/dl is entered as an absolute figure in equation

* Bulk disease (a single node ≥ 5 cm or in the mediastinum > 30% of intrathoracic ratio add to index factor of 0.3

A total index score of ≥ 0.5 was the criteria for entry into the trial.

Fig. 1. The Scotland and Newcastle Lymphoma Group (SNLG) Hodgkin's Disease prognostic index applicable to all stages of disease. Index $\geqslant 0.5$ selects the worst 20% from the cohort.

on day 15 and the day 8 injections transferred to day 22. The aim was to ensure the dose intensity over a given 28-day period was maintained.

2.9.2. Dosage reductions other than day 8

If neutrophils $<1\times10^9$/l or platelets 75–100×10^9/l, doses were reduced to 75%.

At any point in the cycle, if neutrophils $<0.5\times10^9$/l or platelets $<75\times10^9$/l, it was recommended treatment be delayed for 1 week so the full doses could be given.

2.10. Supportive care

The recommended antiemetic therapy was a 5HT antagonist. Co-trimoxazole (Septrin) (960 mg) was given as prophylaxis against pneumocystis 3× weekly during treatment from 1991. Growth factor support was not written into the protocol, but its use was allowed at the investigator's discretion and was to be documented.

2.11. Response criteria

Response was assessed after the third course of PVACE-BOP and repeated at the end of treatment.

A CR was defined as the disappearance of symptoms and physical signs and the complete resolution of abnormalities on X-rays, scans and in the bone marrow. An uconfirmed complete response (CR(u)) was documented when a residual mass of uncertain significance was observed. A GPR was defined as the disappearance of symptoms and a reduction of >75% diameter in measurable disease on scans and X-rays. A partial response (PR) was defined as the disappearance of symptoms and a reduction of >50% and <75% diameter in measurable disease on scans and X-rays.

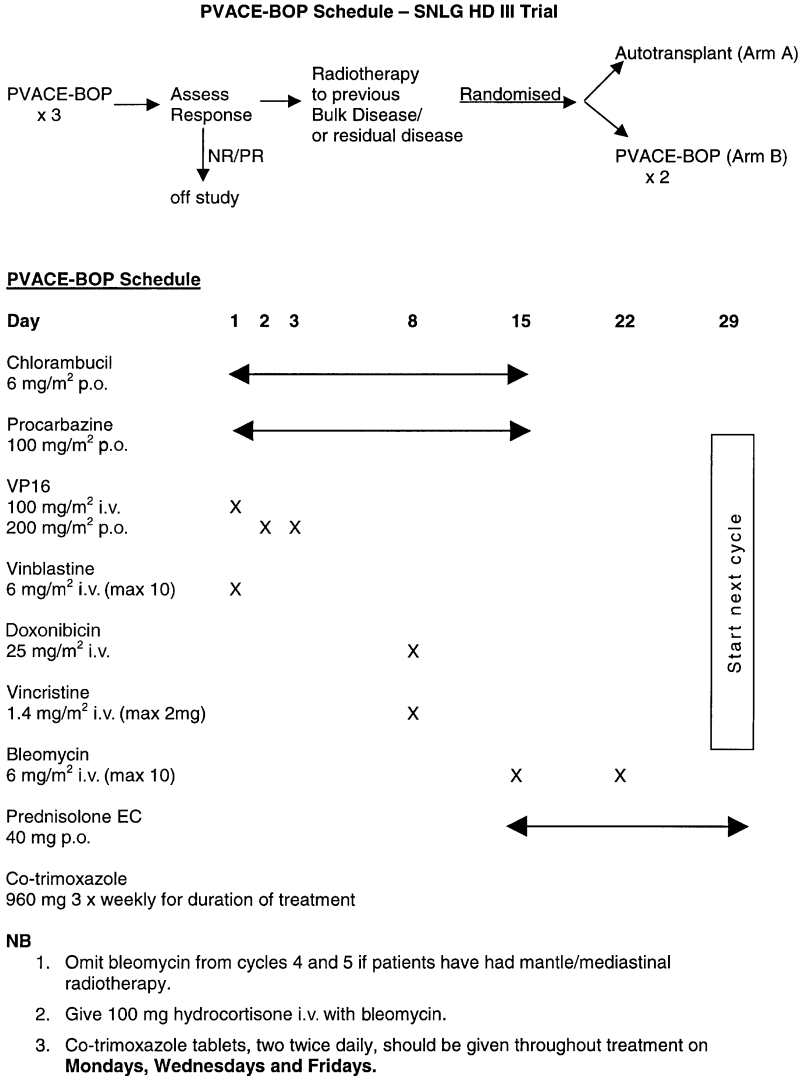

Fig. 2.

2.12. Toxicity

Treatment toxicity was assessed using the World Health Organization (WHO) criteria [11].

2.13. Statistical methods

The endpoints to be assessed were CR rate, overall survival and time to treatment failure. Survival was calculated using the Kaplan–Meier method [12]. Overall survival (OS) was from date of diagnosis to date of death. Time to treatment failure was defined as time from date of diagnosis to the date of the first observation of progressive disease, death due to any cause or discontinuation of trial treatment due to inadequate response.

3. Results

3.1. Patient population

Recruitment was from November 1988 to January 1999. Follow-up is to June 2000, i.e. minimum follow-up 16 months, median follow-up 6 years. 126 patients were entered into the study, 14% of the 930 patients registered with HD on the SNLG database over the trial recruitment period, but 71% of the poor risk patients (see Fig. 3). 6 were found to be ineligible: reasons for ineligibility were; not 'poor risk' (1) or ineligible on H&E review (5). Thus, 120 patients were assessable for the study, 69 males, 51 females, median age 27 years (range 16–59 years). Full clinical characteristics are shown in Table 1. One patient presented with concomitant

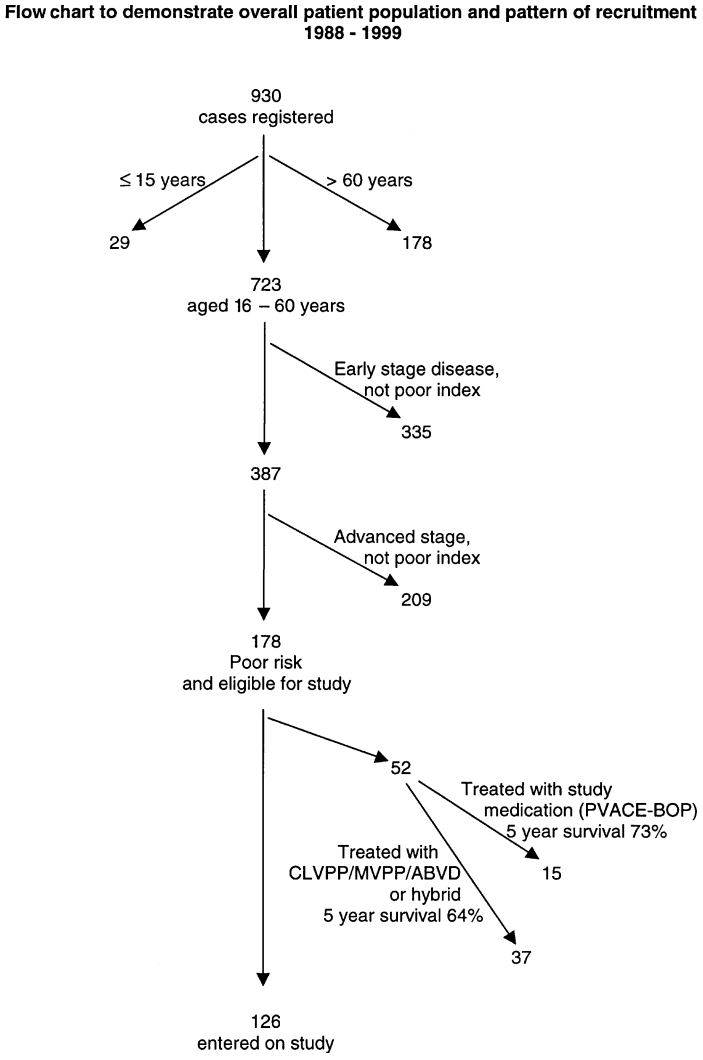

Fig. 3. 126/178 poorest risk patients recruited to the study from the overall population (71%). 209 patients stage III and IV (not high risk on the Scotland and Newcastle Lymphoma Group (SNLG) index) were excluded from the study and received standard CLVPP, MVPP or ABVD±radiotherapy. Survival for this 'good risk' advanced stage group was maintained at 75%. 52 patients were poor risk, but not randomised. 15 received the protocol therapy off study (5-year survival 73%), 37 received the four drug schedules (5-year survival 64%).

Table 1
Patient characteristics—120 eligible patients[a]

Clinical characteristics	
Median age 27 years (range 16–59 years)	
Gender	
Male	69
Female	51
Stage	
IIA	7
IIB	30
IIIA	8
IIIB	23
IVA	6
IVB	46
ECOG	
0	17
1	45
2	37
3	14
4	5
Unknown	2
International Prognostic Index (IPI)	
0	6
1	14
2	31
3	32
4	19
5	17
6	1
Bulk disease	
Present	98
Absent	22
LDH	
Normal	39
Raised	42
Not done	39
Albumen	
>40	36
<40	84
Hb (g/dl)	
>12	24
<12	96
Lymphocyte count ($\times 10^9$/l)	
>1	62
<1	58
Pathology	
Histological subtypes	
LP	1
MC	25
NS	88
LD	3
Unclassifiable	3

LDH, lactate dehydrogenase; NS, nodular sclerosing; LP, lymphocyte predominant disease; ECOG, Eastern Co-operative Oncology Group; MC, mixed cellularity; LD, lymphocyte depleted.

[a] Note that 80% of patients were Hodgkin's Disease International Prognostic Index (IPI) $\geqslant 2$.

autoimmune haemolytic anaemia and another with immune thrombocytopenic pupura.

7 patients had early stage (IIA), bulky disease, but were identified as poor risk by the SNLG-PI. The remainder had advanced stage disease. During the study, the International Hodgkin's Disease prognostic Index was published [13] and this has been applied to the eligible patients; 100/120 (83%) had $\geqslant 2$ risk factors and 69/120 (58%) had >3 risk factors, thus verifying the 'poor risk' nature of the study population.

3.2. Pathology

The majority of patients (88, 73%) had the nodular sclerosing (NS) subtype and, as expected, their median age was younger than the other subgroups (Table 2). The study only included 1 patient with lymphocyte predominant disease (LP). In 3 patients, the subtype was 'unclassifiable', although the diagnosis was confirmed to be HD. This was due to the small size of the specimen in 2 cases and because the diagnostic specimen was a bone marrow trephine in the third instance.

As part of the ongoing research programme within the SNLG, additional histocytochemistry was performed on the diagnostic specimens in retrospect. 9 patients would not be classified by these more modern techniques as having HD, but are included in the results of the trial as they were passed as eligible on H&E review. These 9 patients all diagnosed pre-April 1995 had previously been assessed as mixed cellularity (MC) (7), NS (2), but on full review were found to be T cell-rich B cell lymphoma (4 patients), anaplastic large cell lymphoma (4 patients) and diffuse large B cell lymphoma (1 patient).

3.3. Dose administration

All patients completed the first three courses of PVACE-BOP, and 13 were taken off study due to insufficient response (4 with no response and 9 with PR). 42 patients refused randomisation having originally consented to the study. Attempts were made to obtain reasons for this. In the early years of the study, when the effect of transplantation on fertility was unknown, some females refused for this reason. Following the publication of a regional study demonstrating that ABMT with melphalan/etoposide conditioning was associated with preserved fertility in women [14], consent levels improved. In total, 65 patients proceeded to 'randomisation' (Fig. 4) and their details are shown in Table 3. Not all patients accepted the treatment allotted (3 received PVACE-BOP instead of the ABMT and 3 received ABMT instead of PVACE-BOP), but patients are analysed by an 'intention to treat'.

Table 2
Histological subtypes[a]

Histological subtype	Gender		Median age (range) (years)	Clinical Stage		
	Male	Female		II	III	IV
Nodular sclerosing	48	40	25 (16–59)	29	23	36
Mixed cellularity	17	8	33 (16–59)	6	7	12
Lymphocyte depleted	1	2	40 (39–47)	1	0	2
Lymphocyte predominant	1	0	42	0	0	1
Unclassifiable	2	1	32 (23–43)	1	1	1

[a] Final histological review diagnosis on study patients, by gender and clinical stage.

3.4. Dose intensity of PVACE-BOP and melphalan/etoposide autotransplant preconditioning

An analysis was conducted by Dr Hasenclever on behalf of our study group to assess the relative dose intensity of PVACE-BOP versus accelerated BEACOPP and ABVD, utilising his mathematical model [15]. In addition, an assessment of the melphalan/etoposide autotransplant protocol was assessed in a similar way. The dose intensity is represented by an arbitrary weighting given to each drug and varies with the drug dose. The result indicated PVACE-BOP ≡6 units, escalated BEACOPP ≡6 units, ABVD ≡4.5 units and melphalan/etoposide autotransplant preconditioning ≡9.3 units. The latter is equivalent in intensity to the pre-transplant conditioning CVB, but is less than that of classical BEAM preconditioning. Thus, it was clear that in the design of the trial patients had not been disadvantaged by having one arm of greater intensity than another.

3.5. Toxicity

Details of the toxicity of PVACE-BOP are shown in Table 4. 470 courses were assessed. The principal toxicity was haematological. 236 courses (50%) were given without delay or 'changing weeks'.

3.6. Non-haematological toxicity

Prior to the introduction of pneumocystis prophylaxis with co-trimoxazole, 2 patients developed this infection. No patient contracted the disease following the introduction of the prophylaxis. 5 patients suffered severe constipation requiring hospitalisation and there were 12 episodes of WHO Grade 3 infection. One patient died of pneumonitis with normal blood counts 8 weeks after his third PVACE-BOP whilst awaiting a bone marrow transplant, but despite a post-mortem no organism was ever identified.

Herpes zoster infection occurred in 10 patients whilst on treatment. Other significant toxicities were: deep vein thrombosis (2 patients), 'procarbazine rash' (1), severe (grade III) mucositis (1), and transitory abnormal liver function tests (2).

Table 3
Patient characteristics—randomised patients

	Autologous transplant arm (34 patients)	Further chemotherapy arm (31 patients)
Median age (range) (years)	31 (16–59)	25 (16–51)
Gender		
Male	20	16
Female	14	15
Stage		
IIA	2	4
IIB	9	9
IIIA	2	1
IIIB	8	5
IVA	1	3
IVB	12	9
International index		
0	1	2
1	6	3
2	9	10
3	10	6
4	5	5
5	3	5
Bulk disease[a]		
Present	31	23
Absent	3	8
LDH		
Raised	11	11
Normal	9	7
Not done	14	13

LDH, lactate dehydrogenase.
[a] Bulk disease defined as a single node >5 cm or C/T ratio >33%.

3.7. Haematological toxicity

Predictably with such an intensive protocol, grade 4 neutropenia occurred in 44% of courses. At the start of the study, there were no growth factors licensed for use, so the recommendation was to 'move weeks' rather than delaying treatment. Later in the study, growth factors were allowed and their use was recorded. WHO Grade 4 thrombocytopenia occurred in less than 2% of courses and severe anaemia was not a major problem.

One patient developed acute myeloid leukaemia (AML) within 4 months of stopping treatment. She did not have the cytogenetic abnormalities associated with secondary AML, but after an initial response to treatment she eventually relapsed and died of the disease. Patients are under annual review and at a median follow-up of 6 years, there is no evidence of marrow failure in routine blood counts in randomised patients.

3.8. Delays and dose reductions

389 of 470 courses (83%) were given on time, with most delays occurring prior to the third course of chemotherapy (Table 4). Dose reduction occurred, most often with chlorambucil and procarbazine (dose reduction in 14 courses), and doxorubicin (17 courses). One patient had their vincristine dose reduced in subsequent courses due to parasthesia in course 1 and a further patient had no procarbazine after course 1 due to a drug-related skin eruption.

3.9. Radiotherapy

All but 1 of the 89 patients with bulk disease who responded to treatment received radiotherapy as scheduled. This was localised in 6 cases (neck 2, axilla 2, pelvis 2). Three patients received abdominal radiotherapy alone (1 inv Y, 2 paraaortic nodes) and 32 received mantle radiotherapy (including 3 with abdominal irradiation as well), 46 had radiotherapy to the mediastinum (includes 13 to neck as well). A further patient received radiotherapy to neck and lumbar spine. Radiotherapy was given prior to further chemotherapy or transplant.

3.10. Bone marrow transplant

In total, 40 patients received a stem cell transplant following treatment with PVACE-BOP (32 randomised). No patient died of the procedure. Time to transplant from the end of initial therapy was a median

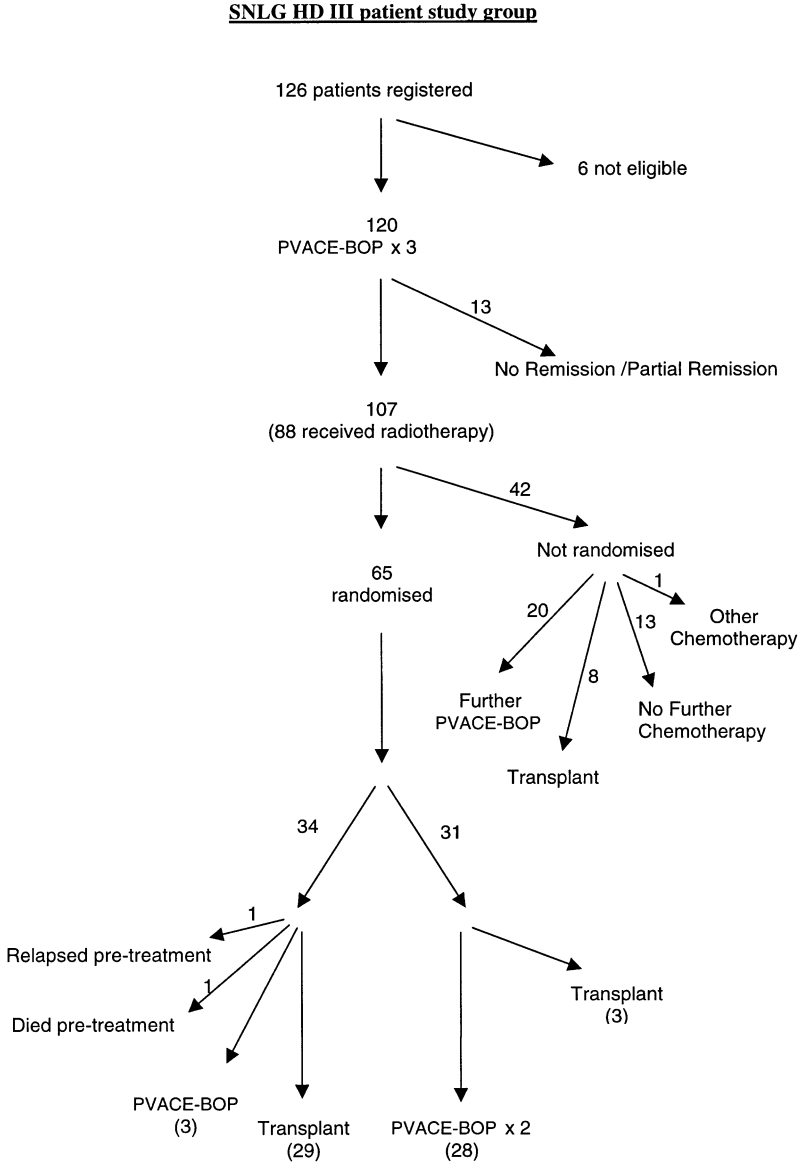

Fig. 4. The flow diagram demonstrates the details of treatment designation highlighting the problem of refusal of randomisation in a substantial minority.

Table 4
PVACE-BOP toxicity (maximum toxicity per course)

	WHO Grade 4 neutrophils	Platelet toxicity WHO Grade 4	Haemoglobin WHO Grade 2	Course 'changed week order'	Delays
Course 1 (120)	48	1	38	32	15
Course 2 (120)	59	1	37	43	14
Course 3 (120)	54	4	38	44	26
Course 4 (58)	27	0	11	21	8
Course 5 (52)	19	2	13	13	18
Total (470)	207	8	137	153	81
% of courses affected	44%	2%	29%	33%	17%

WHO, World Health Organization.

of 8 weeks (range 2–35 weeks) and toxicity was as expected, with the median days in hospital being 22 (range 16–38 days), median days on i.v. antibiotics 9 (range 0–22 days), median days to neutrophil count $>0.5\times10^9$/l 14 (range 6–30 days) and to platelet count $>50\times10^9$/l 41 (range 10–280 days). Only 3 of the study patients received a PBSC transplant, so we were unable to compare the toxicities of the two procedures.

3.11. Response, survival and pattern of failure

All 120 eligible patients were assessable for response and all completed their initial three courses of PVACE-BOP. 4 patients had no response/static disease, giving a response rate of 97%. None of these patients was salvaged by subsequent therapies. A further 9 patients achieved a partial remission and were taken off study; all received salvage therapy and 4 survive (1 post-allogeneic transplant and 2 postautologous transplant).

Of the 107 patients remaining on study, 100 achieved a CR/CR(u) and 7 GPR, and all except one of the 89 patients with 'bulk' or residual disease received radiotherapy as per protocol. However, a further patient had his radiotherapy delayed by 6 months as he absconded from follow-up.

With a median follow-up of 6 years, the OS for eligible patients is 78%±4 (Fig. 5); there were no significant differences between the treatment arms in the time to treatment failure (TTF) for the 65 randomised patients (Fig. 6), 5 year TTF in the autotransplant group (Arm A) 79%±11 versus 85%±7 in the further chemotherapy arm (Arm B) (log rank test, chi-squared 0.85, with one degree of freedom, $P=0.35$).

3.12. Relapses

In the 65 randomised patients, 2 relapsed prior to the randomised treatment (1 in each arm) and 1 patient died of pneumonitis in CR pretransplant. 5 patients relapsed in the transplant arm (at 12, 16, 29, 52 and 67 months). Only 2 patients relapsed in the chemotherapy arm, both

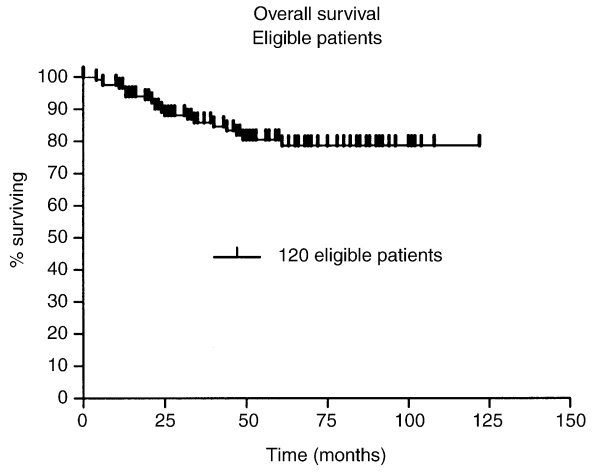

Fig. 5. In the initial index study, this group of patients, The Scotland and Newcastle Lymphoma Group (SNLG)-PI≥0.5, have a survival on the four-drug schedule of <50% [4].

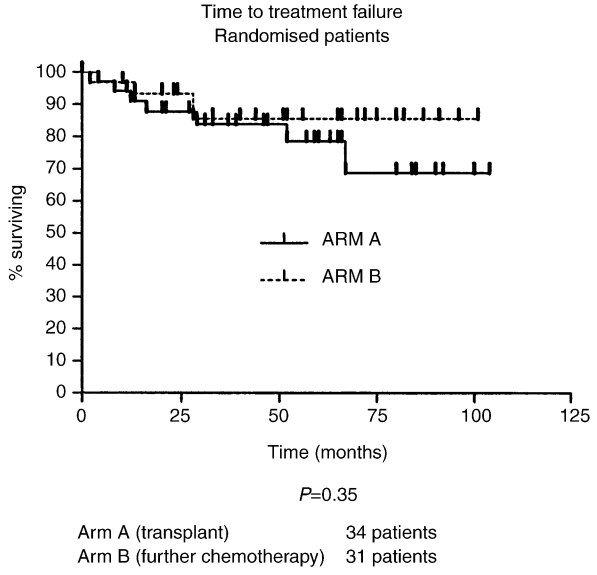

Fig. 6. With a median follow-up of 5 years, there is no significant difference in terms of survival. Both arms show substantial improvement over treatments in use when the IP index was constructed.

at 28 months. The patient with AML accounted for the other 'event' in this arm.

Of the 42 non-randomised patients who had achieved CR, 7 relapsed, 2 on treatment. The other 5 patients relapsed at 9, 16, 16, 17 and 19 months, respectively. In summary, a total of 20 eligible patients died; the cause of death was refractory disease in 8 patients, relapse in 10, and malignancy (AML, breast cancer) in 2.

3.13. Fertility

With regard to fertility, all men on the study were advised to use sperm banking if they wished to have a family in the future. Formal post-treatment sperm counting was not part of the study. Fertility has been generally preserved for the women on the study with pregnancies occurring in both treatment arms. All females <40 years having PVACE-BOP$\times$3 plus melphalan/VP16 autotransplant who wished to become pregnant were able to conceive naturally with some multiple births [14], as previously reported.

3.14. Outcome in patients not HD following immunohistochemistry review

These 9 patients all had advanced stage disease (7 stage IV B and 2 stage IIIB) and 7 had 'bulky' disease. 6 patients achieved a CR with 3$\times$PVACE-BOPs of whom 4 are alive in CCR1 (follow-up 39–92 months), 1 is in CR2 and the other died of their disease. 3 patients achieved a PR only and all eventually succumbed to their disease (survival 6–44 months).

3.15. Second malignancy

Apart from the patient with AML mentioned above, there has been only 1 other case of second malignancy in a woman aged 49 years at the time of trial entry who developed breast cancer 3 years post-treatment. She had not received thoracic radiotherapy and we feel the tumour was probably unrelated to treatment.

4. Discussion

4.1. Evolution of chemotherapy in poor risk HD

In the multidrug treatment of advanced HD the first generation schedules (MOPP [1], CLVPP [2]) achieved a 50–60% 5-year survival. ABVD, a second generation schedule, is presently regarded as the 'gold standard' for advanced HD with increased efficacy over first generation schedules and more acceptable long-term toxicity [3].

In the mid- to late-1980s, a third generation series of hybrid and alternating schedules appeared with the aim of enhancing the improvement in treatment results seen with ABVD. This resulted in a lack of uniformity of approach to the treatment of HD. Concerns about the safety of some schedules arose when a major intergroup study using a hybrid schedule was prematurely terminated because of leukaemia/marrow dysplasia rates [16]. Since then investigators have tended to move back to using ABVD.

More recently, a fourth generation of continuous or high intensity, relatively short schedules has emerged (Stanford V [17,18], BEACOPP and escalated BEACOPP [19]). The Stanford V schedule uses 3 months continuous therapy$\pm$radiotherapy and emerged from a phase 2 single institution study. Following the pilot study [17], this schedule is currently being tested in a randomised setting. A series of studies from the National German Hodgkin's Study Group has demonstrated the excellent remission rates from the BEACOPP [19] schedule on a large patient cohort and currently a trial of BEACOPP versus escalated BEACOPP is underway. The SNLG study reported here is the first to compare prospectively a multi-agent continuous schedule against auto transplant in first remission and place such a study in the overall context of an unselected population of patients with HD to assess relative outcome according to the new CONSORT guidelines [20].

When different treatment schedules for advanced HD are compared, the emphasis is usually on the therapy given, with relatively little attention given to the patient population treated. Reported remission rates and survival curves for all studies depend on patient selection. Currently, most studies use classical Ann Arbor stage alone for selection of patients to enter chemotherapy trials. It is accepted that in non-Hodgkin's lymphoma this is sub-optimal and an International Prognostic Index (IPI) exists to help further definite those poor risk patients [21]. There have been a number of studies looking at the production of a Hodgkin's disease prognostic index for clinical use over the last 15 years, one of which is the SNLG numerical prognostic index [4]. Our Group was sufficiently convinced that this index provides an objective measure of risk for trial purposes that it was used as the key parameter for entry into the present study. During the course of the study, the development of the IPI for HD [13] has provided an extremely valuable model against which the risk stratification in HD can be measured. This index was derived primarily from Stage III B and IV patients receiving 'state of the art' schedules. The authors do not recommend that the IPI be used for selection for trial entry, but rather to provide a benchmark for comparison between studies. The SNLG prognostic index developed on all patients regardless of stage compares well with the IPI, and any discrepancy is largely explained by the fact the SNLG index identifies a proportion of early stage cases whom

we would regard as 'poor risk'. Such patients were not included in the development of the IPI. Of the patients selected for the present study as poor risk on the SNLG index, 58% had an IPI score of $\geqslant 3$.

4.2. The population-based study perspective

The SNLG prospectively collects details on more than 90% of patients diagnosed to have HD within a defined population using the population adjusted clinical epidemiology (PACE) process [6]. Detailed registration forms are completed on all patients irrespective of entry into trial, and this allows the results from the study population to be put into the context of patients treated with conventional therapy concurrently across the geographical area of the study.

During the study period, there were 930 patients entered on the SNLG register of HD of whom only 178 in the appropriate age group had an SNLG poor risk index and were thus eligible for study. A proportion (209/387, 54%) were advanced stage, but did not have a poor prognostic index and were thus ineligible for the trial; in all other studies these patients would have been eligible for a randomised trial comparing intensive chemotherapy schedules. They were excluded from HD III because outcome on CLVPP or ABVD±radiotherapy was predicted to be 75% survival at 5 years. This has remained the case for these patients over the period of the study.

Only 65 patients from 105 in CR at the time of first assessment proceeded to randomisation. There is no significant difference between the TTF and OS in either arm. Thus, autotransplant cannot be recommended for HD as part of primary treatment as toxicity from an autotransplant in terms of hospitalisation is much greater. As this study has run for 10 years and as a result of the lack of emergence of any obvious trend towards improved outcome with the autotransplant, it was clear that the numbers required to demonstrate any significant clinical difference would never emerge. The results of the current prospective European Bone Marrow Transplant study of autotransplant versus chemotherapy in first remission may help to clarify the situation further.

A recent analysis performed using a mathematical dose intensity model [15] demonstrated that it is possible to give an intensity rating to individual drug and dose schedules. This model suggests that one course of PVACE-BOP is equivalent to one course of Stanford V which is equivalent to one course of accelerated BEACOPP, and that the dose intensity of ABVD is approximately two-thirds of these schedules. However, the number of courses used in studies varies, with three for Stanford V, five for PVACE-BOP and eight for accelerated BEACOPP. In order to work out the true efficacy of these chemotherapy schedules and the optimal number to be given in practice, we need to assess their impact by definition of risk in the patient populations. The level of intrinsic toxicity of the schedule and, in particular, its leukaemogenic potential is critical.

Table 5
Five-year time to treatment failure (TTF) by International Prognostic Index (IPI) for Hodgkin's Disease[a]

IPI	Number of patients	HD III 5-year TTF (%)	Predicted 5-year TTF (by IPI) (%)
0, 1	20	89	84, 77
2	31	78	67
3	32	77	60
4	19	60	51
$\geqslant 5$	18	72	42

[a] In each of the International Prognostic Index (IPI) categories [13], the outcome identified in that study has been improved in the present study by 10–30% in the various subgroups.

5. Conclusions

PVACE-BOP as used in our present study (3 months continuous chemotherapy/radiotherapy to bulk disease/two further courses of chemotherapy) demonstrates a substantial improvement, in our population, over results from patients given hybrid schedules at the beginning of the 1990s. In the IPI poor risk groups, an increase in TTF of up to 30% has been demonstrated in each of the categories (Table 5). The poorest risk groups within patients with advanced stage HD, for our population, now have a similar survival to those at standard risk. It will be noted from Fig. 3 that those patients who did not receive the PVACE-BOP schedule, but were in the poor risk group had a poorer outcome when not entered onto the trial medication. The question now arises as to whether this more intensive therapy might improve results in the standard risk patient over what might be expected with ABVD. This is to be investigated in a randomised trial in our Group.

Poor prognosis HD is most effectively treated by one of the fourth generation chemotherapy schedules. We would suggest that PVACE-BOP can now join these schedules having demonstrated a 93% CR rate in the worst possible group of patients and a 5-year survival of 78%.

The SNLG index was developed on patients treated on first and second generation drug schedules in the 1980s. It has been useful in identifying patients for the current study, but a new index is required to identify patients who are at risk of not responding to fourth generation intensive schedules. Studies of the impact on outcome of serum factors such as sCD30, Interleukin 10 (IL10), β2m, etc., currently in progress might help to further identify these patients.

Finally, the use of the patient population based approach (PACE) [6] undoubtedly enhanced the input into this therapeutic trial with 71% of the target population entering from our geographical area. The added advantage was the ability to track the overall population and put the results of the trial into a reality-based context.

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