

HODGKIN'S DISEASE

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Hodgkin's Disease

In 1832, when Thomas Hodgkin wrote about the anatomical distribution and clinical course of the illness which was later to bear his name, it was uniformly fatal.⁽¹⁾ Hodgkin's disease is now curable in the majority of patients, but debate and controversy remain about its aetiology and treatment. This review will focus on:

1. Chemotherapy for newly diagnosed patients with advanced stage disease.
2. The use of myeloablative therapy with autologous haemopoietic progenitor cell support.

With the development of the MOPP regimen,⁽²⁾ cure became a realistic possibility for a proportion of patients with advanced stage Hodgkin's disease. Since that time, a number of alternatives have been proposed in attempts to improve on the efficacy of MOPP and to decrease its short- and long-term toxicity. Different drugs, more drugs and so-called "Hybrid" regimens have been evaluated with some success. Treatments that include an alkylating agent are shown in Table 1, those without an alkylating agent are summarised in Table 2. More recently, intensive, weekly regimens of short duration have been developed at the Christie Hospital, Manchester, and at Stanford University; these are shown in Table 3.

Table 1. Treatment: Alkylating agent-containing regimens.

Regimen	Dose (mg/m ²)	Days
MOPP		
Mustine	6	1,8
VCR	1.4	1,8
PRO	100 po	1-14
PRED	40 po	1-14
ChLVPP		
CB	6 (total) po	1-14
VBL	6 (max 10)	1,8
PRO	100 po	1-14
PRED	40 po	1-14
LOPP		
CB	10 (total) po	1-10
VCR	1.4	1,8
PRO	100 po	1-10

PRED	25 po	1-14
MOPP-ABV Hybrid		
Mustine	6	1
VCR	1.4	1
PRO	100 po	1-7
PRED	40 po	1-14
ADR	35	8
BLEO	10	8
VBL	6	8
LOPP/EVA Hybrid		
VBL	10 (total)	1
CB	10 (total) po	1-7
PRO	50 po	1-7
PRED	50 po	1-7
VCR	2	8
ADR	50	8
ETO	200	8

Key

Mustine = Mechlorethanine; VLR = Vincristine;
 PRO = Procarbazine; PRED = Prednisolone; CB = Chlorambucil;
 BLEO = Bleomycin; VBL = Vinblastine; ADR = Doxorubicin;
 ETO = Etoposide

All drugs given intravenously unless oral (po) administration specified

Table 2. Treatment: Chemotherapy regimens without an alkylating agent.

Regimen	Dose (mg/m ²)	Days
ABVD		
ADR	25	1,15
BLEO	10 units	1,15
VBL	6	1,15
DTIC	375	1,15
EVA		
ETO	100	1,2,3
VBL	6	1
ADR	50	1q 28d

EVAP			
	ETO	150 po (200)	1-3
	VBL	6 (10)	1,8
	ADR	25	1,8
	PRED	25 po	1,8
VEEP			
	VCR	1.4 (2.0)	1,8
	EPI	50	1 q 21d
	ETO	100	1-4
	PRED	100 po	1-8
NOVP			
	MTR	10	1
	VCR	1.4	8 q 21d
	BVL	6	1
	PRED	100 po	1-5

Key (as for Table 1 with the following additions:
DTIC = Dacarbazine; EPI = Epirubicin; MTR = Mitoxantrone)

Table 3. Experimental 12-week regimens.

Drug	Dose (mg/m ²)	Days/weeks
VAPEC-B		
VCR	1.4	w 2,4,6,8,10
ADR	35	w 1,3,5,7,9,11
PRED	50mg/day po	w 1-6
	25mg/day	w 7-11
ETO	100 po	d 1-5, w 3,7,11
CY	350	w 1,5,9
BLEO	10	w 2,6,10
Stanford V (per cycle)		
ADR	25	d 1,15
VBL	6	d 1,15
Mustine	6	d 1
ETO	60 iv	d 15, 16
VCR	1.4 (max 2.0)	d 8, 22
BLEO	5u/m ²	d 8,22
PRED	40 po	for a total of 3 cycles over 12

weeks

Key (as for Tables 1 and 2)

d = day; w = week

Until relatively recently, MOPP or variations of it, such as MVPP,⁽³⁾ were the standard treatment. Overall, approximately 50% of patients were cured,^(4,5) outcome being influenced by prognostic factors such as age, stage, the presence of B symptoms, performance status, bulk of tumour and number of extra-nodal sites (in patients with stage IV disease). The severe nausea and vomiting associated with Mustine was a drawback; thus, replacing it with Chlorambucil in the regimens ChlVPP or LOPP⁽⁶⁾ represented a significant improvement in terms of acute toxicity. However, the long-term problems of infertility and secondary acute myelogenous leukaemia (AML) (see below) remained. Alternative treatments such as the ABVD regimen were therefore developed.⁽⁷⁾ The advantage of ABVD is that it does not cause infertility, and secondary myelodysplasia has not been observed. It is, however, associated with nausea and vomiting; there is also the possibility of pulmonary toxicity due to Bleomycin and heart failure due to Adriamycin, especially when this treatment is used in conjunction with “mantle” irradiation. Nonetheless, the success of ABVD led to the investigation of alternating chemotherapy comprising MOPP and ABVD, given as a total of twelve monthly cycles. The original study from Milan showed alternating MOPP/ABVD to be better than MOPP alone in terms of progression-free survival.⁽⁸⁾ Subsequent large, randomised studies by Cancer and Leukaemia Group B (CALGB) and the European Organisation for Research and Treatment of Cancer (EORTC) confirmed the superiority of the alternating regimen.^(9,10) However, there was no difference in survival in either study, almost certainly because “salvage therapy” at recurrence is effective. In the CALGB study, MOPP was compared to both ABVD and to the alternating regimen; progression-free survival was in fact better with ABVD alone and with the alternating regimen.⁽¹⁰⁾ A study by the British National Lymphoma Investigation (BNLI) similarly compared LOPP to an alternating regimen LOPP/EVAP and, once more, the latter was found to be better in terms of both progression-free and overall survival.⁽¹¹⁾

Since then, various “Hybrid” regimens have been developed, essentially using half of one treatment protocol with part of another following the original report from Vancouver.⁽¹²⁾ Several randomised studies have compared alternating MOPP/ABVD with a Hybrid MOPP/ABV regimen; no difference in outcome was found.^(13,14) A BNLI study with essentially the same structure also found no difference between an alternating LOPP/EVAP regimen and the Hybrid regimen LOPP/EVA.⁽¹⁵⁾ However, a randomised study which compared MVPP with the Hybrid regimen ChlVPP/EVA conducted at the Christie Hospital, Manchester, and at St. Bartholomew’s Hospital (SBH) in London showed a higher complete remission rate (68% versus 55%) and a lower failure rate (2.4% versus 12.5%) with the Hybrid treatment.⁽¹⁶⁾ There were also fewer treatment-related deaths in the Hybrid arm of the study. The actuarial five-year progression-free survival for all patients was 80% for treatment with the Hybrid, compared to 66% for MVPP ($p = 0.005$). The Hybrid treatment has therefore been adopted as the control arm

of a new study at these two hospitals, in which this regimen is being compared to an experimental sequential 12-week regimen, VAPEC-B, which was originally investigated in patients with recurrent disease with encouraging results.⁽¹⁷⁾ The latter is similar to a weekly treatment programme Stanford V,⁽¹⁸⁾ which is also given for just three months (Table 3).

Debate continues about the role of irradiation following chemotherapy for patients with advanced disease. Most physicians agree that sites of previous bulky disease, i.e., a mediastinal mass greater than one-third of the intrathoracic diameter or any mass greater than 10 cm in diameter, should be irradiated on completion of chemotherapy, because recurrence after chemotherapy tends to occur in unirradiated sites.⁽¹⁹⁾

Prognostic Factors

Multivariate regression analyses have identified the following to be correlated with a worse prognosis: older age, male gender, the presence of B symptoms, a lymphocyte count less than $0.75 \times 10^9/l$ at presentation, involvement of multiple extranodal sites, low haemoglobin, low serum albumin, increased ESR, a large mediastinal mass, high serum lactic dehydrogenase (LDH) and inguinal lymph node involvement.⁽²⁰⁻²²⁾

Toxicity

All of the treatments mentioned above are toxic, specifically causing loss of hair, nausea and vomiting, mucositis, myelosuppression and peripheral neuropathy. There has also been concern for some time about two late effects associated with alkylating agent-containing regimens such as MOPP, namely, infertility and secondary AML. Infertility affects both men and women; sperm storage is recommended prior to starting treatment in younger men. Storage of ovarian tissue is still at an experimental stage. Myelodysplasia associated with cytogenetic abnormalities of chromosomes 5 or 7 often precedes frank AML. As compared to de novo AML, secondary leukemias only rarely respond to treatment. There is also an increased incidence of solid tumours (especially breast and lung cancer). These are thought to be associated with radiotherapy and independent of chemotherapy.

As mentioned above, pulmonary toxicity can occur, particularly in patients who have received Bleomycin-containing treatments such as ABVD followed by irradiation. Cardiac toxicity has been described in patients receiving combined modality therapy that includes Adriamycin, but this is rare. Most treatments for Hodgkin's disease include prednisolone, which can lead to avascular necrosis of the femoral head.

Management

After appropriate staging investigations have been completed, the diagnosis, treatment and chance of success need to be explained to the patient, preferably with a member of the family or close friend present. In 1996, treatment for Hodgkin's disease is almost always given with curative intent. This should be made clear from the outset, but the possibility of failure needs to be mentioned. A plan needs to be made, outlining the likely duration of treatment, to include radiotherapy in addition to chemotherapy in patients with bulky disease at presentation, together with an explanation of the side effects.

Most younger people with Hodgkin's disease can be treated on an out-patient basis and continue to live and work relatively normally throughout this time. However, especially with the new Hybrid regimens, myelosuppression does occur and may require admission to hospital for episodes of infection. The importance of contacting the hospital immediately in this situation should be emphasized; the possible need for blood transfusions should also be mentioned. In patients with bone marrow infiltration, profound cytopenia may occur with the initial cycles. The potential late effects of the treatments should also be mentioned, and sperm storage undertaken if appropriate.

Specific treatment will depend on whether the person is being treated in the context of a clinical trial or not; consideration also needs to be given to the question of fertility. When this is of paramount importance, many physicians still prefer to use ABVD.

High-Dose Treatment with Autologous Bone Marrow or Peripheral Blood Progenitor Cell Support

The rationale for using high-dose treatment in Hodgkin's disease is based on the dose-response relationship for drugs such as Cyclophosphamide, BCNU and Etoposide. Most high-dose regimens for Hodgkin's disease have not used whole body irradiation since a substantial number of patients will already have received appreciable doses of radiotherapy to the mediastinum. Most studies have been conducted in heterogeneous groups of patients, some with demonstrably resistant disease, others with recurrent disease at varying time points. Review of the literature (Table 4) shows very variable results, which are influenced by numerous prognostic factors and by patient selection.⁽²²⁻³⁰⁾ However, a BNLI study in which 40 patients were randomised between high-dose treatment with the 'BEAM' regimen and less intensive therapy with 'mini-BEAM' did show a significant difference in progression-free survival in favour of the more intensive treatment.⁽²⁸⁾

Table 4. Myeloablative therapy with autologous haemopoietic progenitor cell support.

Regimen	Drugs	Dose and Schedule (mg/m ²)
CBV	Cyclophosphamide BCNU Etoposide	1.5G daily x 4 days 300 day -5 125-150 bd days-5 to -3
CBVP	Cyclophosphamide BCNU Etoposide	1.8G daily, days -6 to -3 500 day -2 2,400 by 45 hr infusion preceding C, B and Cisplatinum 50/day, days -6 to -3
BEAM	BCNU Etoposide	300 day -6 200 bd, days -5 to -2

	Ara-C	200 bd, day -5 to -2
	Melphalan	140 day -1
BEAC	BCNU	300 day -7
	Etoposide	100 bd, days -6 to -3
	Ara-C	100/day, days -6 to -3
	Cyclophosphamide	35 mg/kg/day, days -6 to -3

Nonetheless, the specific indications for high-dose treatment have not been clarified. With the general perception amongst physicians and their patients being that high-dose treatment is “better treatment”, it will now be difficult to conduct randomised comparisons of high-dose treatment against conventional salvage therapy in specific situations. The consensus of opinion is that patients in the following situations should be considered for high-dose therapy:

- 1) Early recurrence, i.e., within twelve months of completing initial treatment.
- 2) Residual disease despite two different chemotherapy regimens and radiotherapy.
- 3) Second or subsequent recurrence.
- 4) Resistant, progressive disease.

With regard to the last of these, a small number of patients will respond and remain in remission. This is clearly different from the situation in high-grade lymphoma, where lack of response to conventional treatment generally implies no meaningful response to high-dose treatment.

In recent years, transplant programmes have moved away from using autologous bone marrow towards peripheral blood progenitor cells (PBPCs) because of considerably faster blood count recovery times with the latter. Various drug regimens have been used to mobilise peripheral blood cells. At SBH, patients have received Adriamycin: 35mg/m² i.v. on day one, with Etoposide 100mg/m² orally, on days 1-5, followed by G-CSF 5µg/kg daily, cells being collected when the neutrophil count exceeds 1.0 x 10⁹/l. In the majority of patients, admission to hospital is not required and sufficient cells can be collected in one pheresis, with subsequent blood count recovery occurring within 2-3 weeks. The use of PBPC has reduced the treatment-related mortality, thus making the treatment more widely applicable.

Table 5. Results of myeloablative therapy.

No. of Patients	Progression-free Survival (time)	Median Follow-up (months)	Tr. Related Deaths	Ref
73	38.6% (4 yrs)	30	7	24
128	25% (4 yrs)	77	11	30
47	49% (3yrs)	24	8	23

155	50% (5 yrs)	36	20	27
58	64% (4 yrs)	27	3	25
85	52% (3yrs)	28	1	26

Management

As with any therapy, an explanation of the actual treatment and its side effects needs to be made. The likelihood of success or failure should be discussed, as should the potential treatment-related mortality. Most patients receiving myeloablative therapy for Hodgkin's disease will become permanently infertile; this needs to be addressed.

At SBH, cytogenetic analysis of the bone marrow is performed prior to starting treatment. In view of the experimental nature of the treatment, if a clonal abnormality is detected, the high-dose treatment is not given because of the risk of developing myelodysplasia and secondary AML. In patients who have received a lot of previous Anthracycline and/or Bleomycin, studies of cardiac and lung function should be carried out. In practice, most centres use BEAM or CBV. A recent retrospective analysis by the European Bone Marrow Transplant Registry has in fact shown BEAM to be superior in Hodgkin's disease as opposed to non-Hodgkin's lymphoma.

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