Principles of Chemotherapy in Hodgkin Lymphoma

10

David Straus and Mark Hertzberg

Contents

10.1 **Historical Introduction** 199

10.2 **Chemotherapy Applied to Advanced-Stage Hodgkin Lymphoma: Theories and Practice** 200
10.2.1 Classes of Active Classical Agents in HL 200
10.2.2 Polychemotherapy: Models and Comparative Clinical Studies 201
10.2.2.1 MOPP and Derivatives 201
10.2.2.2 ABVD and Derivatives 205
10.2.2.3 The Dose/Response Relationship: Norton and Simon Model 206
10.2.2.4 Sustained/Weekly Regimens 207
10.2.2.5 Escalated-Dose Regimens 208
10.2.2.6 High-Dose Treatment and Autologous Stem Cell Transplantation as Part of Initial Therapy 209
10.2.2.7 Risk-Adapted Regimens Based on PET 210
10.2.2.8 Incorporation of Antibody-Drug Conjugate in Primary Treatment of Advanced-Stage cHL 213

10.3 **Chemotherapy Treatment for Recurrent and Refractory Hodgkin Lymphoma** 213
10.3.1 New Systemic Treatments 213

10.4 **Conclusions** 214

References 214

10.1 Historical Introduction

Hodgkin lymphoma (HL) was the malignant disease for which the possibility of cure with combination chemotherapy in the majority of patients was first realized. As such it has provided a model upon which studies in many other types of malignancy have been based, and it is interesting to follow the trajectory of knowledge from early single-agent work through combinations,

D. Straus (✉)
Division of Hematologic Malignancies, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: strausd@mskcc.org

M. Hertzberg
Department of Haematology, Prince of Wales Hospital, Randwick, NSW, Australia
e-mail: mark.hertzberg@sesiahs.health.nsw.gov.au

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combined modalities, increasing complexity, and, most recently, selective de-escalation. Patients with advanced disease represent a minority of those affected by HL. However, these patients represent the group in which the development and effects of chemotherapy are most readily appreciated, because the role of radiation therapy is markedly less than in patients with localized disease.

As early as 1942, four patients with HL were treated with nitrogen mustard by Wilkinson and Fletcher at Manchester Royal Infirmary, although a military embargo prevented the dissemination of this information [1]. Similar considerations are applied to the bombing of the ship "USS Liberty" on December 3, 1943, in Bari, and the hematological consequences of a nitrogen mustard gas leak among the survivors. Cornelius Rhoads, an American cancer researcher, was involved in their care and understood from his observations of the effects on the bone marrow and lymphoid tissue that nitrogen mustard derivatives might be effective against lymphoid and hematological malignancies [2, 3]. In 1958, another alkylating agent, cyclophosphamide, proved effective in non-Hodgkin lymphoma (NHL) [4]. Shortly after this, vinblastine was first shown to be an effective drug in HL, as was vincristine. Although encouraging, the early results of chemotherapy were modest, with most responses short-lived after corticosteroids and alkylating and spindle cell agents [5–7]. There was a prevalent view that only extensive irradiation could yield complete cures [8, 9].

One of the first modern randomized studies was the EORTC H1 trial, which investigated whether "adjuvant" chemotherapy (weekly vinblastine for 2 years) could improve the results over radiotherapy alone [10]. A durable advantage was seen in the chemotherapy arm for relapse-free survival (RFS: at 15 years 60% vs. 38%; $P < 0.001$) although more than 50% of patients with mixed-cellularity histology developed recurrences [11]. To reduce the relapse rate, irradiation was extended to infradiaphragmatic nodal and spleen areas. Single-agent or doublet chemotherapy was added after radiotherapy, but no immediate attempt was made to use polychemotherapy, based upon the idea that the cure rate would depend upon the adequacy of irradiation [12, 13]. Two factors gradually undermined the dominance of strict pathological delineation and extensive irradiation as the basis of curative therapy in HL: the advent of accurate cross-sectional imaging by computed tomographic (CT) scanning and the recognition that relapses after irradiation alone had minimal impact on survival owing to the efficacy of salvage chemotherapy [14]. With the development of four-drug combination therapy, which for the first time resulted in cures for advanced HL without the need for irradiation, the transition to systemic therapy began in earnest.

10.2 Chemotherapy Applied to Advanced-Stage Hodgkin Lymphoma: Theories and Practice

10.2.1 Classes of Active Classical Agents in HL (Table 10.1)

Almost every class of chemotherapy drug has been shown to have some efficacy in HL, with the possible exception of the antimetabolite drugs such as 5-fluorouracil [15]. The original combination treatments were based upon evidence of single-agent activity among alkylating agents, vinca alkaloids, corticosteroids, and the hydralazine monoamine oxidase inhibitor procarbazine. All of these produced response rates of over 50% when used singly in patients not previously exposed to multiagent chemotherapy (Table 10.1). Later entrants to this field included the antibiotic drugs doxorubicin and bleomycin, the nitrosoureas and dacarbazine, and the podophyllotoxins, all of which showed appreciable single-agent activity after prior combination regimens. More recently, newer cytotoxics such as gemcitabine have been introduced, often in combination with platinum drugs, and found to produce significant response rates in recurrent disease. In 2011, brentuximab vedotin, an antibody-drug conjugate, was approved in the USA and conditionally in Europe

Table 10.1 Single-agent activity of cytotoxic drugs in Hodgkin lymphoma [15]

Drug	Overall response rate (%)	Complete response rate (%)
Single agents tested before combination chemotherapy		
Alkylating agents		
Chlorambucil	61	16
Mustine	63	13
Cyclophosphamide	54	12
Vinca alkaloids		
Vinblastine	68	30
Vincristine	60	36
Agents mainly tested after prior multiagent therapy		
Dacarbazine	56	6
Nitrosoureas		
Carmustine	44	5
Lomustine	48	12
Antibiotics		
Doxorubicin	30	5
Bleomycin	38	6
Podophyllotoxin		
Etoposide	27	6
Antimetabolite		
Gemcitabine	22	0
Antibody-drug conjugate		
Brentuximab vedotin	75	34

for treatment of relapsed or refractory HL after autologous stem cell transplantation (ASCT) or after at least two combination chemotherapy regimens in patients who are not transplant candidates. Approval was granted on the basis of an overall response (OR) rate of 75% and a complete response (CR) rate of 34% in a phase 2 trial in 102 HL patients relapsed after or refractory to ASCT, response rates approximately twice as high as those reported for other single agents [16]. This antibody-drug conjugate attaches an anti-CD30 antibody to a potent antimicrotubular agent, monomethyl auristatin (MMAE), by a protease cleavable linker. MMAE binds to tubulin and disrupts the microtubule network, inducing cell cycle arrest and apoptosis, a mechanism of action similar to those for vincristine and vinblastine [17].

It is clear that HL is broadly sensitive to phase-specific, cycle-specific, and non-cycle-specific agents, although it is less clear whether this is a feature of the malignant cells themselves or their associated inflammatory infiltrate, which may be critical to sustaining them. The development of combination therapies has been based mainly upon the use of agents with non-overlapping toxicity as far as possible, and as cure rates have risen, the emphasis has fallen increasingly upon avoiding long-term side effects. The most important among these are infertility and myelodysplasia, mainly caused by the alkylating agents; pulmonary fibrosis caused by bleomycin and nitrosoureas; and cardiomyopathy related to anthracyclines, a risk increased by the concomitant use of mediastinal radiotherapy.

10.2.2 Polychemotherapy: Models and Comparative Clinical Studies (Tables 10.2 and 10.3)

10.2.2.1 MOPP and Derivatives

Combination chemotherapy was first attempted clinically in childhood acute lymphoblastic leukemia by Jean Bernard [18], who designed two doublets of cortisone-methotrexate and prednisone-vincristine, at the same time as pursuing work on chemotherapy for HL. Lacher and Durant were the first to use doublet combination chemotherapy in HL with vinblastine and chlorambucil [19]. At the NCI, Freireich, Frei, and Katon added 6-mercaptopurine into the more effective VAMP (vincristine, amethopterin, mercaptopurine, and prednisone) regimen [7]. This led on to MOMP (cyclophosphamide, vincristine, methotrexate, and prednisone) and MOPP (mechlorethamine, vincristine, procarbazine, prednisone), developed by DeVita and Carbone, also at the NCI [20, 21]. Some of the critical features of success were prolonged treatment (6 months, more than any other regimen at the time); the use of each drug at "optimal" dose and schedule with a sliding scale for dose adjustment according to marrow suppression; an interval of 2 weeks for recovery of normal tissue (marrow, GI epithelium), ideally before HL recovery; and treatment with curative intent rather than palliation. MOPP provided an 80% response rate and long-term disease-free (DFS) and overall survival

Table 10.2 Chemotherapy regimens designed for advanced Hodgkin lymphoma

Drugs	Dose, mg/m^2	Route	Schedule
Four-drug regimens			
MOPP			q. 28 days
Mechlorethamine	6	Iv	d1 and 8
Vincristine	1.4 (cap 2 mg)	Iv	d1 and 8
Procarbazine	100	Po	d1–14
Prednisolone	40	Po	d1–14
MVPP			q. 42 days
Mechlorethamine	6	Iv	d1 and 8
Vinblastine	6 (cap 10 mg)	Iv	d1 and 8
Procarbazine	100	Po	d1–14
Prednisolone	40	Po	d1–14
ChlVPP			q. 28 days
Chlorambucil	6 (cap 10 mg)	Po	d1–14
Vinblastine	6 (cap 10 mg)	Iv	d1 and 8
Procarbazine	100	Po	d1–14
Prednisolone	40	Po	d1–14
COPP			q. 28 days
Cyclophosphamide	650	Iv	d1 and 8
Vinblastine	6	Iv	d1 and 8
Procarbazine	100	Po	d1–14
Prednisolone	40	Po	d1–14
ABVD			q. 28 days
Doxorubicin	25	Iv	d1 and 15
Bleomycin	10 iu/m^2	Iv	d1 and 15
Vinblastine	6	Iv	d1 and 15
Dacarbazine	375	Iv	d1 and 15
Hybrid regimens			
MOPP/ABV			q. 28 days
Mechlorethamine	6	Iv	d1
Vincristine	1.4	Iv	d1
Procarbazine	100	Po	d1–7
Prednisolone	40	Po	d1–14
Doxorubicin	35	Iv	d8
Bleomycin	10 iu/m^2	Iv	d8
Vinblastine	6	Iv	d8
ChlVPP/EVA			q. 28 days
Chlorambucil	6 (cap 10 mg)	Po	d1–7
Vincristine	1.4 (cap 2 mg)	Iv	d1
Procarbazine	90	Po	d1–7
Etoposide	75	Po	d1–5
Prednisolone	50	Po	d1–7
Doxorubicin	50	Iv	d8
Vinblastine	6 (cap 10 mg)	Iv	d8
BEACOPP baseline			q. 21 days
Bleomycin	10 iu/m^2	Iv	d8
Etoposide	100	Iv	d1–3
Doxorubicin	25	Iv	d1
Cyclophosphamide	650	Iv	d1
Vincristine	1.4 (cap 2 mg)	Iv	d8

Table 10.2 (continued)

Drugs	Dose, mg/m^2	Route	Schedule
Procarbazine	100	Po	d1–7
Prednisolone	40	Po	d1–14
Escalated regimens			
Escalated BEACOPP			q. 28 days
Bleomycin	10 iu/m^2	Iv	d8
Etoposide	200	Iv	d1–3
Doxorubicin	35	Iv	d1
Cyclophosphamide	1250	Iv	d1
Vincristine	1.4 (cap 2 mg)	Iv	d8
Procarbazine	100	Po	d1–7
Prednisolone	40	Po	d1–14
G-CSF		Sc	d8–14
BEACOPP-14			q. 14 days
Bleomycin	10 iu/m^2	Iv	d8
Etoposide	100	Iv	d1–3
Doxorubicin	25	Iv	d1
Cyclophosphamide	650	Iv	d1
Vincristine	1.4 (cap 2 mg)	Iv	d8
Procarbazine	100	Po	d1–7
Prednisolone	80	Po	d1–7
G-CSF		Sc	d8–13
Weekly regimens			
Stanford V			4-week cycle
Doxorubicin	25	Iv	d1 and 15
Vinblastine	6	Iv	d1 and 15
Mechlorethamine	6	Iv	d1
Vincristine	1.4 (cap 2 mg)	Iv	d8 and 22
Bleomycin	5 i.u./m^2	Iv	d8 and 22
Etoposide	60	Iv	d15 and 16
Prednisolone	40	Po	Daily to week 10 then taper
VAPEC-B			4-week cycle
Doxorubicin	35	Iv	d1 and 15
Cyclophosphamide	350	Iv	d1
Etoposide	75–100	Iv	d15–20
Vincristine	1.4 (cap 2 mg)	Iv	d8 and 22
Bleomycin	10	Iv	d8 and 22
Prednisolone	50	Po	Daily to week 6 then taper
BV/AVD			
Brentuximab vedotin	1.2 mg/kg	Iv	d1 and 15
Doxorubicin	25	Iv	d1 and 15
Vinblastine	6	Iv	d1 and 15
Dacarbazine	375	Iv	d1 and 15

(OS) of almost 50% and 40%, respectively [22]. The results have held up, and the 20-year analysis confirmed among 198 patients a CR rate of 81%, a 19% rate of induction failures, a 36% relapse rate, and a 54% mortality. Of the 106 deaths, 30 occurred in patients free of disease; among the 92 patients who survived (46%), only two had persistent HL [23]. These results have been reconfirmed in subsequent trials (Table 10.3) [24–27]. Although the rise in cures from HL can be

Table 10.3 Summary results of combination chemotherapy regimens used in first-line therapy of advanced Hodgkin lymphoma

Regimen	CR (%)	5 year EFS (%)	5 year OS (%)	≥7 year OS (%)
MOPP [22–25, 101]	67–81	40–60	65–73	51–70
MVPP [38, 102, 103]	72–76	60	65–75	
ChlVPP [39, 104]	57–74	55–60	66	65
ABVD [24, 47, 68, 69, 77, 78, 105]	68–92	61–80	73–90	77
MOPP/ABVD alternating [24, 106, 107]	83–92	65–70	75–84	74
COPP/ABVD alternating [62, 108]	85	69	83	75
MOPP/ABV hybrid [47, 107, 109, 110]	80–88	66–75	76–83	72
Stanford V [66–69]	72–91	54–94	82–96	
VAPEC-B [71]	47	62	79	
ChlVPP/EVA [71, 105]	67	82–84	89	
BEACOPP baseline [62]	88	76	88	80
Escalated BEACOPP [62]	81–96	87	91	86
BV/AVD [95]	73	82[a,b]	97[a]	

[a]2 Years
[b]Modified PFS (time to disease progression, death, or modified progression)

ascribed to multiple advances and not just the introduction of effective chemotherapy, the 1970 report convinced almost all groups treating HL to accept the inclusion of polychemotherapy (MOPP or MOPP derivatives) in the treatment strategy for localized as well as advanced disease. In almost all instances where a combined treatment was compared to irradiation alone, whether patients were staged or not with laparotomy, advantages in terms of response and disease- and relapse-free survival were observed when MOPP or a MOPP-derived chemotherapy was used [28].

Analysis of the results with MOPP has proven a fruitful source of information to design and interpret future studies. Thus, complete response was seen to be a prerequisite for sustained remission, and a high percentage of complete responses was correlated with higher survival rates. Capping the vincristine dose at 2 mg may have been detrimental to the results. Patient and initial disease characteristics were good predictors of outcome, with confirmation of the adverse prognostic significance of systemic "B" symptoms. Maintenance treatment with intermittent MOPP or carmustine did not appear beneficial [29]. In patients treated previously by irradiation and chemotherapy, MOPP was less well-tolerated and less effective [30]. Conversely, retreatment in relapsed patients whose initial remission lasted over a year proved efficient on the second occasion [31]. MOPP therapy carries consequences in terms of carcinogenicity, in particular with secondary acute myeloid leukemia (AML) [32, 33]. It is also responsible for impaired fertility in both men and women [34]. Immunosuppression related to the treatment, or to the underlying disease, brings risks of different types, in particular of opportunistic infection [35].

There were many attempts to improve upon these results. The three best-known MOPP-derived regimens have been MVPP, with vinblastine instead of vincristine; ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisolone); and COPP, with an additional substitution of mechlorethamine, replaced by chlorambucil or cyclophosphamide (Tables 10.2 and 10.3). These alternatives have never undergone direct comparison, and historical controls are difficult to interpret. In addition, the proportion of patients who have also had radiotherapy varies considerably between series. For example, in the NCI series, 32/198 patients had been irradiated prior to MOPP, and 28/198 patients received total nodal irradiation (TNI) "to prevent recurrent disease in previously involved nodes" as consolidation after chemotherapy. MVPP, devised in the UK, proved easier to handle than MOPP (with less constipation and neurological toxicity), but was slightly more myelotoxic [36–38]. ChlVPP appeared more patient-friendly, inducing minimal nausea/vomiting, constipation or neurologic toxicity, and limited hematotoxicity, and the number of cycles could be adapted to the

response: a maximum of five beyond CR. The 66% OS rate in advanced HL was comparable to mustine-containing regimens, at lower toxic cost, for all of these acute toxicities, except myelosuppression [39, 40]. COPP is less myelotoxic than MOPP and is often used in children [41].

10.2.2.2 ABVD and Derivatives

The ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) was devised just 10 years after MOPP, in 1973, for intravenous-only administration at fixed 2-week intervals. Like MOPP, ABVD was a combination of hematotoxic and neurotoxic drugs. Both doxorubicin and vinblastine had been shown highly effective in HL. The results with dacarbazine were numerous but possibly less convincing, and bleomycin was also felt to have considerable potential [10, 42–45]. By comparison to MOPP, hematotoxicity after ABVD was predictable, noncumulative, and milder as a result of the intravenous dosing and short intervals. Further, ABVD was far less neurotoxic. Bonadonna developed ABVD at the Milan NCI with the intention: "to compare the efficacy of ABVD with MOPP, and to demonstrate absence of cross-resistance between the two regimens" [46]. The results of MOPP were well established and the potential of ABVD in terms of "alternative to MOPP to be used either in MOPP failures or in sequential combination with MOPP" was clearly in the mind of the authors, based on these very early results achieved in 45 patients. No significant cardiac toxicity was seen in this first series, probably because of the relatively small cumulative dose of doxorubicin (6 cycles = 300 mg/m^2), the short follow-up, and the small numbers of patients. Conversely, bleomycin pulmonary toxicity was apparent from the outset, while the effects upon fertility were initially overestimated through short observation which did not take into account the reversal of temporary amenorrhea in some women.

It took a surprisingly long time for ABVD to be accepted as a standard of care, and it was initially considered only as a salvage treatment in MOPP failures. However, the Milan group undertook a larger trial, comparing MOPP and ABVD directly in patients with stage IIB, IIIA, and IIIB HL. In 232 patients, a combined modality approach of three cycles before and after extensive irradiation yielded a CR rate of 80.7% after MOPP/radiotherapy and 92.4% after ABVD/radiotherapy ($P < 0.02$). At 7 years follow-up, ABVD surpassed MOPP for freedom from progression (FFP) (80.8% vs. 62.8%; $P < 0.002$), RFS (87.7% vs. 77.2%; $P = 0.06$), and OS (77.4% vs. 67.9%; $P = 0.03$). With longer follow-up, the disadvantages of MOPP in terms of fertility damage and second myelodysplasia (MDS) and leukemia were also more apparent. The final establishment of ABVD as the favored regimen, at least in North America, was based on two randomized trials for advanced HL. In the first, MOPP vs. ABVD vs. MOPP alternating with ABVD were associated with 5-year failure-free survival rates of 50%, 61%, and 65%, respectively. There was less toxicity with ABVD than with MOPP or MOPP alternating with ABVD and no significant difference in survival among the three regimens [24]. A second trial compared ABVD with a hybrid regimen, MOPP/ABV; 5-year failure-free survival rates were 63% and 66%, respectively. There was a greater incidence of acute toxicity, myelodysplastic syndrome, and leukemia for MOPP/ABV compared with ABVD. Again, there was no significant difference in survival [47].

Currently, ABVD is considered by most investigators as the standard chemotherapy for most patients with HL, with the possible exception of high-risk patients with advanced disease and poor prognostic features. Reasons to avoid ABVD relate to previous lung impairment and decreased left ventricular ejection fraction. Hematological toxicity is usually moderate, and ABVD may be delivered safely at full dose and on schedule to a non-selected average population of adult patients without the need to modify doses in the presence of neutropenia [48]. The most frequent serious toxicity with ABVD is pulmonary fibrosis, which may be fatal [49]. The discontinuation of bleomycin for toxicity during ABVD treatment does not appear to have an adverse effect on outcome, which calls into question the importance of bleomycin in the ABVD regimen [47, 49–51]. This possibility has recently been

tested prospectively in a randomized study of patients showing a good early response to ABVD, where patients either continued all drugs, or AVD only [17, 52]. The results confirmed the excess toxicity associated with bleomycin, particularly reduced lung function and more instances of venous thromboembolism. There was no decrease in efficacy by omission of bleomycin from the last four cycles of treatment.

10.2.2.3 The Dose/Response Relationship: Norton and Simon Model

Much of the thinking about how to maximize the cure rate in lymphoma has centered upon the relationship between dose and response to cytotoxic therapy. Theories of tumor cell ecology have suggested that as the mass of disease is reduced, the growth fraction may rise. This, together with the assumed selection of resistant subclones, underlies the idea that tumor eradication is dependent upon the delivery of treatment at adequate dose intensity early in a course of treatment. If doses are too small or too infrequent, the fractional cell kill might be expected to decline and allow the emergence of resistance [53].

Three prospective clinical trials have directly addressed the question of dose versus response using the same chemotherapy drugs in both arms. In the first-line treatment of advanced disease, a critical study, HD9, was performed by the German Hodgkin Study Group (GHSG), as detailed later, in which patients were randomized between the baseline BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen and an escalated regimen, with the doses of doxorubicin, cyclophosphamide, and etoposide increased to 140%, 185%, and 200%, respectively. This resulted in an increase in freedom from treatment failure (FFTF) at 5 years from 76% to 87% ($P < 0.01$), which was translated into a small but significant improvement in survival on longer follow-up (80% vs. 86% at 10 years; $P = 0.0053$). This was at the cost of an increased risk of MDS and AML in the escalated arm, but at a frequency too low to reverse the gain in survival from better control of the lymphoma [54].

There are two randomized studies for recurrent disease which have yielded similar data on the dose-response relationship. The UK group compared the myeloablative BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen to mini-BEAM, which uses the same drugs at nonmyeloablative doses. The high-dose treatment yielded superior PFS ($P = 0.005$), although the trial was closed with only 44 patients recruited and had insufficient power to demonstrate a survival advantage [55]. A study of similar design was conducted by the GHSG, and this too demonstrated superior FFTF at 3 years (55% for BEAM, 34% for nonmyeloablative dexa-BEAM, $P = 0.019$), although once again no survival difference could be demonstrated [56].

While there is good evidence for an overall dose-response relationship, there are several areas of continuing uncertainty. For example, it is not clear whether the dose of treatment over a whole course is the critical determinant of outcome, or whether initial dose intensity during the first weeks of treatment is more important. From retrospective analyses comparing outcomes to doses administered, it appears that the most influential factor is the total dose of treatment given, with some scope for compensating suboptimal early treatment by later escalation, a finding that may distinguish HL from many other malignancies [57–59].

Dose/Response Relationships and Treatment Tolerance: An Individual Characteristic?

A dose response for both malignant and normal tissue toxicity is well-recognized, raising the question of whether the efficacy of tumor control can be related to toxic side effects, effectively using each subject as his or her own pharmacodynamic control. The GHSG explored hematotoxicity as a surrogate for pharmacological and metabolic heterogeneity, in relation to reduced systemic dose and disease control. Patients treated with various regimens in the HD6 trial (validated on two other cohorts) were retrospectively classified as showing WHO

grade leukocytopenia of 0–2 and >2, respectively. Patients with a high hematological toxicity had a 5-year FFTF rate of 68% versus 47% for those with low toxicity, independent of the actual drug doses received [60]. No pretreatment pharmacokinetic parameters could be found to explain these observations; however, recent work from the French Study Group of the Adult Lymphoma (GELA) has explored polymorphisms in a population of HL patients that might determine anticancer agent metabolism. The UGT1A1 polymorphism has been identified as a possible candidate for influencing the metabolism of several anticancer drugs and patient outcomes [61]. Unfortunately, similar dose-response relationships are also seen for long-term toxicities, for example, infertility and secondary leukemias [62–64].

10.2.2.4 Sustained/Weekly Regimens

Pursuing the idea of increased dose intensity, several groups developed novel, brief duration regimens for the treatment of advanced HL. The rationale for the development of these regimens was, firstly, increased dose intensity of chemotherapy by reduction in the total duration of treatment but an increase in the number of different agents and, secondly, reduced cumulative doses of drugs responsible for long-term toxic effects, including alkylating agents, doxorubicin, and bleomycin. The PACEBOM, VAPEC-B, and Stanford V regimens were all designed to deliver weekly treatments, alternating between myelosuppressive and nonmyelosuppressive agents. The preliminary results from single-arm studies appeared promising, with high response and survival rates [65]. Unfortunately, the results of randomized trials did not confirm the early promise of these regimens.

The Stanford V program developed from the close collaboration of radiotherapy and chemotherapy, endeavoring to minimize the use of each modality to achieve improved results with less toxicity. Initial chemotherapy was composed of the standard drugs from the MOPP/ABVD scheme (mechlorethamine, doxorubicin, bleomycin), plus etoposide, with dose intensity increased for better and earlier tumor response, while cumulative doses, thought to be responsible for late toxicity (marrow, heart, lung), were reduced. The use of alkylating agents was limited in order to avert gonadal damage. The final scheme was an abbreviated 12-week program with radiotherapy started 2–4 weeks after chemotherapy, restricted to sites at higher risk for relapse (bulky sites), and delivered at 36 Gy, in order to reduce the incidence of late cardiopulmonary effects, and "mini-mantle" instead of mantle fields, sparing the axillae to decrease the risk of secondary breast carcinoma. The results of the initial Stanford V phase 2 approach were confirmed in the Eastern Cooperative Oncology Group (ECOG) E1492 study in 45 patients, of whom 87% received radiotherapy; FFP was 85% at 5 years, and OS was 96% with one death from HL and one from an M5 AML [66]. Later analysis confirmed these excellent results and the relative preservation of fertility in both women and men; no case of secondary MDS/leukemia or NHL had been registered at a 65 months median follow-up [67].

A randomized trial (Italian Lymphoma Group: ILL) compared Stanford V to mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine (MOPPEBVCAD) and to ABVD as the standard in 355 patients with stage IIB–IV HL. In this trial, the Stanford V arm was inferior to the other two arms in terms of 5-year FFS (54% vs. 78% for ABVD and 81% for MOPPEBVCAD, respectively ($P < 0.01$) for comparison of Stanford V with the other two regimens) [68]. However, only 66% of patients in the Stanford V arm received irradiation, against 87% in the ECOG phase 2 study: this is important in a strategy that was originally designed to combine both modalities. The Stanford V program was also compared to ABVD in a large prospective trial run by the UK National Cancer Research Institute Lymphoma Group (NCRI) in 520 patients with stage IIB–IV HL. Results in the Stanford V and in the ABVD arm were similar for 5-year PFS and OS rates (76% and 90%, for ABVD; 74% and 92% for Stanford V, with radiotherapy administered in 53% and 73%, respectively) [69]. The North American Intergroup trial

led by ECOG (E2496) compared ABVD with IFRT only to bulky mediastinal sites with the combined modality Stanford V. There was no difference in response rates or in 5-year FFS or OS rates between the two arms of the trial. The relatively extensive use of radiotherapy required to achieve optimum results for weekly regimens makes them a less attractive choice for many patients: in the UK study, 73% of patients treated with Stanford V received consolidation radiotherapy, compared to 37% in the previous UK study using ABVD in a similar group of patients. In E2496, 75% of patients on the Stanford V regimen received radiation therapy, while 41% of those on ABVD had irradiation of bulky mediastinal sites [70]. The short 12-week duration of the Stanford V regimen has some appeal for patients and remains a reasonable approach for those with low-risk non-bulky disease, for whom limited or no irradiation is needed, but this is only a minority.

The only other weekly regimen to be compared with a hybrid regimen in a randomized trial featured myelosuppressive (doxorubicin, cyclophosphamide, and etoposide) and relatively non-myelosuppressive (vincristine and bleomycin) drugs given on an alternating weekly basis for 11 weeks: VAPEC-B. This regimen was compared to a hybrid ChlVPP-EVA schedule for advanced disease, was expected to still be significantly more myelosuppressive and to impair fertility, and showed inferior PFS for the weekly regimen in all but the best prognosis subgroup. Event-free survival at 5 years in newly diagnosed patients with advanced disease following the hybrid regimen was 78% versus 58% for VAPEC-B, which translated into better OS, at 89% versus 79% [71].

10.2.2.5 Escalated-Dose Regimens

In order to spare patients the acute gastrointestinal and hematologic toxicities, the original recommendation of the NCI to follow a "sliding scale" of dose adaptation for MOPP was gradually superseded by fixed doses at well-tolerated levels and intervals. Retrospective studies of MOPP and MVPP suggested that the cumulative dose, as much as frequency of administration or dose intensity, might determine the outcomes [25, 72]. These observations also appear to hold for ABVD [59], although all these studies are retrospective and need to be confirmed in a prospective study.

The GHSG has pioneered the exploration of two levels of dose increment, in the conventional dose range, by reducing the length of treatment and adding etoposide to the standard regimen, COPP/ABVD [73]. Further intensification was carried out by increasing the myelosuppressive drug doses, with growth factor support. Both intensified regimens provided higher CR and FFTF and, crucially, statistically higher OS rates as compared to standard COPP/ABVD [54]. The early effects of dose intensification were maintained in the long-term results at 10 years: FFTF was 64%, 70%, and 82% with OS rates of 75%, 80%, and 86% for patients treated with standard COPP/ABVD, BEACOPP baseline, and BEACOPP escalated, respectively ($P < 0.001$) [62]. The higher overall chemotherapy doses, as given in the escalated BEACOPP scheme, appear to provide greater disease control than any of the previous or contemporary regimens. This is supported by the very low number of deaths due to the progression of lymphoma (2.8%). The GHSG has conducted a series of studies, HD12, HD15, and HD18, all using escalated BEACOPP in advanced HL patients (under the age of 61) whose results replicate closely those of the escalated BEACOPP arm in the HD9 study [74–76].

The GHSG reported early on its concerns for the immediate toxicity, especially among patients older than 65, and, in younger patients, impaired fertility and risk of MDS or secondary AML. A review of the HD9 results concerning the cumulative incidence of all second tumors at 10 years confirmed that the rate for AML/MDS was lower after COPP/ABVD (0.4%) versus BEACOPP baseline (2.2%) and BEACOPP escalated (3.2%; log-rank test; $P = 0.03$). However, counting all secondary malignancies, there was no difference (5.3% after COPP/ABVD, 7.9% after BEACOPP baseline, and 6.5% after BEACOPP escalated) [62].

The immediate and long-term toxic effects of escalated BEACOPP and the reluctance of many specialists to consider COPP/ABVD as a standard

comparator have hindered acceptance of escalated BEACOPP as a new standard of care. Two Italian trials, HD2000 and GSM-HD, have demonstrated superior PFS with escalated BEACOPP in comparison to ABVD. In HD2000, BEACOPP resulted in an 81% (95% CI, 70–89%) 5-year PFS versus 68% (95% CI, 56–78%) for ABVD, but no significant OS difference was observed [77]. Similarly, the GSM-HD trial demonstrated a higher 3-year FFP for escalated plus baseline BEACOPP (4 + 4) versus ABVD (87 ± 3% and 71 ± 4%), respectively, but freedom from second progression (FF2P) and OS were alike [78]. ABVD was declared preferable, taking into account the lesser toxicity, including fewer toxic deaths (one vs. six).

The outstanding results of escalated BEACOPP, despite the toxicity, have made it most appealing for high-risk patients. This has been called into question by results in two recent randomized clinical trials. In a multi-institutional Italian trial comparing ABVD with BEACOPP (4 cycles escalated dose + 4 cycles standard dose) for patients with stages IIB, III, or IV HL, the superior freedom from first progression for BEACOPP was confirmed (at 7 years, 73% for ABVD vs. 85% for BEACOPP; $P = 0.004$), which was the primary endpoint of the trial. However, there was no significant difference in freedom from second relapse following ASCT or in OS between the two treatment arms. The treatment-related mortality was 4% for BEACOPP vs. 1% for ABVD [79]. This suggests that most patients can be treated initially with ABVD and only those who relapse be salvaged with ASCT and thus exposed to a treatment-related mortality similar to that with initial BEACOPP treatment. The EORTC randomized patients with high-risk stages III or IV HL (international prognostic score ≥ 3) to BEACOPP (4 cycles dose escalated + 4 cycles standard dose) or ABVD. There was no significant difference in 4-year event-free survival (EFS) or OS, which was the primary endpoint, although this trial also confirmed a superior PFS for BEACOPP [80]. Progression-free survival may not be the most clinically important treatment result, and these two trials suggest that ABVD is an acceptable initial treatment approach even for high-risk advanced-stage HL patients because of the effectiveness of salvage ASCT in the minority of patients who relapse.

As with ABVD, it was found that omission of bleomycin because of toxicity during treatment with BEACOPP did not have an adverse impact on PFS or OS. In addition, with this intensive regimen, omission of vincristine during treatment because of toxicity also had no adverse impact on these outcomes [81].

10.2.2.6 High-Dose Treatment and Autologous Stem Cell Transplantation as Part of Initial Therapy

Attempts have been made to improve results by using intensified consolidation and peripheral blood stem cell (PBSC) rescue for patients considered at high risk. Three randomized studies have explored this concept for HL. The Scotland and Newcastle Lymphoma Group HD3 study randomized 65 out of 126 high-risk patients, resulting in a nonsignificant advantage for the conventional arm (time to treatment failure 85% vs. 79%; $P = 0.35$) [82]. A European study of similar design randomized 163 high-risk patients achieving CR or partial response (PR) after four cycles of ABVD or an equivalent regimen to receive high-dose therapy plus ASCT (83 patients) or four more cycles of conventional chemotherapy (80 patients). There was no evidence of a benefit to the group receiving high-dose therapy (CR 92% vs. 89%, 5-year FFS 75% vs. 82%, and OS 88% vs. 88%, respectively) [83].

The Groupe Ouest-Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) undertook a randomized study in 158 high-risk patients, comparing conventional intensive chemotherapy with vindesine (5 mg/m^2), doxorubicin (99 mg/m^2), carmustine (140 mg/m^2), etoposide (600 mg/m^2), and methylprednisolone (600 mg/m^2) (VABEM) followed by low-dose lymph node irradiation in 82 patients versus four cycles of ABVD followed by myeloablative carmustine (300 mg/m^2), etoposide (800 mg/m^2), cytarabine (1600 mg/m^2), and melphalan (140 mg/m^2) and ASCT in 76 patients. The results were remarkably

similar for CR (89% vs. 88%), 5-year FFTF (79% vs. 75%), and OS (87% vs. 86%) [84].

In summary, there is no evidence to support the use of high-dose consolidation at first remission in HL at present.

10.2.2.7 Risk-Adapted Regimens Based on PET

Response to treatment for classical HL (cHL) is assessed by positron emission tomography–computed tomography (PET/CT) at end of treatment (EOT). Negative PET/CT is associated with a 10% or lower likelihood of relapse [85]. Interim PET/CT after one or two cycles of ABVD or similar regimens is also highly predictive of outcome [86, 87].

Three recent clinical trials have utilized PET/CT to determine if negative PET after or during treatment will identify a population of early-stage patients with non-bulky disease who can safely be treated with ABVD alone (Table 10.4). The Randomized Phase 3 Trial to Determine the Role of FDG-PET Imaging in Clinical Stages IA/IIA Hodgkin lymphoma (RAPID) found high rates of 3-year PFS among patients who were PET-negative after three cycles of ABVD, regardless of whether they received IFRT or no further treatment (90.8% vs. 94.6%; $P = 0.16$) [88]. Though the PFS rate for chemotherapy alone was excellent, non-inferiority criteria were not met when compared with addition of IFRT; OS did not differ between groups, as the 22 patients who relapsed without further IFRT were successfully treated with salvage therapy. Of note, 5 of the 22 received only radiation therapy as a salvage treatment, and only 7 of 22 received chemotherapy followed by ASCT. Negative PET was defined as a Deauville score of 1–2 (FDG uptake less than mediastinal blood pool).

Another phase 2 trial confirmed an excellent PFS for most patients treated with a short course of ABVD alone. CALGB 50604 treated patients with stages I/II non-bulky cHL with two cycles of ABVD. Interim PET/CT was performed and centrally reviewed. Patients whose interim PET/CT was negative, defined as Deauville scores of 1–3 (FDG uptake less than liver), received two more cycles of ABVD (total four cycles) and no irradiation (135/149; 91%). Patients whose interim PET/CT was positive received two cycles of more intensive chemotherapy with escalated BEACOPP and IFRT to a dose of 3060 cGy (13/149; 9%). Estimated PFS was 91% at 3 years for the interim PET-negative group. The estimated 3-year PFS for the interim PET-positive group was significantly lower, at 66%, than for the interim PET-negative group ($P = 0.011$), suggesting that the intensive treatment regimen did not provide benefit [89].

Table 10.4 Salvage regimens in common use for recurrent/refractory Hodgkin lymphoma drugs

	Dose, mg/m^2	Route	Schedule
Dexa-BEAM			q. 21d
Dexamethasone	24 mg daily	Po	d1–10
Carmustine	60	Iv	d2
Etoposide	250	Iv	d4–7
Cytarabine	100 bd	Iv	d4–7
Melphalan	20	Iv	d3
DHAP			q. 21d
Dexamethasone	40 mg daily	Iv	d1–4
Cytarabine	2000 bd	Iv	d2
Cisplatin	100	Ivi	d1
ESHAP			q. 21d
Etoposide	40	Iv	d1–4
Cytarabine	2000	Iv	d5
Cisplatin	25	Ivi	d1–4
Methylprednisolone	500 mg daily	Iv	d1–5

Table 10.4 (continued)

	Dose, mg/m^2	Route	Schedule
ICE			q. 21d
Ifosfamide	5000	Ivi	d2
Carboplatin	AUC 5	Iv	d2
Etoposide	100	Iv	d1–3
GDP			q. 21d
Gemcitabine	1000	Iv	d1 and 8
Dexamethasone	40 mg daily	Po	d1–4
Cisplatin	75	Iv	d1
GVD			
Gemcitabine	1000	Iv	d1 and 8
Vinorelbine	20	Iv	d1 and 8
Liposomal doxorubicin	15	Iv	d1 and 8
IGEV			
Ifosfamide	2000	Iv	d1–4
Gemcitabine	800	Iv	d1 and 4
Vinorelbine	20	Iv	d1 and 4
Prednisone	100	Po	d1–4
BeGEV			
Bendamustine	90	Iv	d2 and 3
Gemcitabine	800	Iv	d1 and 4
Vinorelbine	20	Iv	d1
Prednisone	100	Po	d1–4
BV-Benda			
Bendamustine	90	Iv	d1 and 2
Brentuximab vedotin	1.8 mg/kg	Iv	d1
BV-ESHAP			
Brentuximab vedotin	0.9–1.2–1.8 mg/kg	Iv	
Etoposide	40	Iv	d1–4
Cytarabine	2000	Iv	d5
Cisplatin	25	Iv	d1–4
Methylprednisolone	500 mg daily	Iv	d1–5
BV-DHAP			
Brentuximab vedotin	1.8 mg/kg	Iv	d1
Dexamethasone	40 mg daily	Iv	d1–4
Cytarabine	2000 bd	Iv	d2
Cisplatin	100	Iv	d1

The larger phase 3 H10 trial compared a similar interim PET-adapted approach to combined-modality therapy (CMT) for all patients [90]. Patients with early-stage cHL received two cycles of ABVD and underwent interim PET/CT. Interim PET-negative favorable patients in the PET-adapted arm received two more cycles of ABVD (total four) and no RT, while those in the CMT arm received one more cycle of ABVD (total three) and involved-node radiation therapy (INRT). Favorable patients who were interim PET-positive in the PET-adapted arm received two cycles of escalated BEACOPP and INRT, while those in the CMT arm received two more cycles of ABVD and INRT. Interim PET-negative unfavorable patients in the PET-adapted arm received four more cycles of ABVD (total six) and no RT, while those who were interim PET-negative in the CMT arm received two more cycles of ABVD (total four) and INRT. Interim PET-positive unfavorable patients in the PET-adapted arm received two cycles of escalated BEACOPP and INRT, while interim PET-positive patients in the CMT arm received two more

cycles of ABVD (total four) and INRT. Overall, in favorable and unfavorable groups together, this trial demonstrated a 5-year PFS benefit for a CMT regimen as compared with a PET-adapted regimen (91% vs. 77%; $P = 0.002$) [91]. The 5-year PFS for interim PET-negative patients in the favorable group was 87% for the PET-adapted arm versus 99% for the CMT arm. The 5-year PFS for interim PET-negative unfavorable patients was 90% for the PET-adapted arm versus 92% for the CMT arm. PFS favored CMT over PET-adapted treatment, and non-inferiority could not be demonstrated in the large number patients undergoing analysis.

In the recent HD16 randomized trial, early-stage favorable cHL patients received two cycles of ABVD + 20 Gy IFRT (control) or two cycles of ABVD plus PET, with PET-negative patients receiving no further treatment and PET-positive patients receiving 20 Gy IFRT (risk adapted). Following two cycles of ABVD only, PET-negative patients had a relapse rate of 10% at 5 year PFS, higher than those who received standard two cycle ABVD + 20 Gy IFRT [92].

These trials demonstrate a 5–10% higher relapse rate for 2–4 cycles of ABVD alone as compared with CMT for favorable early-stage cHL. Opinions differ as to whether it is more important to reduce the late risks of radiotherapy with chemotherapy only, given the excellent salvage options, or to provide a more optimal PFS with frontline treatment by adding radiotherapy to chemotherapy.

Four recent trials have employed interim PET after two cycles of chemotherapy to tailor treatment for patients with advanced-stage cHL. S0816, a phase 2 trial conducted by the US Intergroup, treated stage III and IV patients with two cycles of ABVD followed by interim PET/CT. Interim PET-negative patients received 4 more cycles of ABVD, while those who were interim PET-positive received two cycles of escalated BEACOPP. The estimated 2-year PFS was 82% for interim PET-negative patients and 64% for interim PET-positive patients. Of note, there were two treatment-related deaths (4%) among the 49 interim PET-positive patients who receive escalated BEACOPP [93].

The Response-Adapted Trial in Advanced Hodgkin Lymphoma (RATHL) treated patients with stages IIB, III, and IV and high-risk stage IIA with two cycles of ABVD followed by interim PET/CT. Patients who were interim PET-negative were randomized to treatment with four cycles of ABVD or four cycles of AVD without bleomycin. Patients who were interim PET-positive were treated with escalated BEACOPP or BEACOPP-14 depending on results of further interim PET/CT studies. For post-cycle 2 interim PET-negative patients, the 3-year PFS was 85.7% for the ABVD and 84.4% for the ABVD/AVD groups, respectively. For the interim PET-positive patients treated with BEACOPP, the 3-year PFS was 67.5%. These findings justify reducing exposure to bleomycin with its attendant pulmonary toxicity for patients with advanced-stage cHL who are interim PET-negative after two cycles of ABVD [52].

The HD18 trial administered two cycles of escalated BEACOPP to patients with advanced-stage cHL followed by interim PET. Patients who were interim PET-negative just received two more cycles of escalated BEACOPP and no additional radiotherapy. PET-positive patients after two cycles of escalated BEACOPP received a total of four or six additional cycles and radiotherapy to PET-positive residual disease. For PET-negative patients, 5-year PFS was 91.2% for 8/6 escalated BEACOPP and 91.8% for four escalated BEACOPP, and there was less toxicity in the latter group [94].

The LYSA AHL2011 trial randomized advanced-stage cHL patients to standard treatment with six cycles of escalated BEACOPP plus interim PET after two and four cycles or experimental treatment. In the experimental arm, treatment was initiated with two cycles of escalated BEACOPP. Following interim PET/CT, treatment was changed to four cycles of ABVD in interim PET-negative patients, while interim PET-positive patients continued four cycles of escalated BEACOPP. There was no significant difference in 4-year PFS between the standard (86.2%) and

experimental arms (85.7%). These results suggest that treatment can be safely de-escalated to ABVD for patients with advanced-stage disease who are PET-negative after two cycles of escalated BEACOPP (Casanovas O, Presentation USHL11, Cologne, October 29, 2018).

The goal of a PET-adapted approach, by starting with either BEACOPP escalated or ABVD, is to maintain efficacy and minimize long-term toxicities. Ideally, a more effective risk-allocation strategy would use novel biomarkers such as TARC or ctDNA, with or without baseline PET parameters such as total metabolic tumor volume (TMTV). Such a strategy would allow patients with highest-risk baseline features to receive the potential benefit of more-intensive initial therapy and would identify those for whom less-intensive or de-escalation strategies can be successfully applied.

10.2.2.8 Incorporation of Antibody-Drug Conjugate in Primary Treatment of Advanced-Stage cHL

Brentuximab vedotin (BV) is an anti-CD30-drug conjugate consisting a monoclonal antibody to CD30 linked to monomethyl auristatin E, a tubulin inhibitor. As a single agent in relapsed/refractory cHL, it achieves an overall response rate of 75% and a CR rate of 34%, which is at least twice as effective as any single conventional chemotherapy agent [16]. The ECHELON-1 trial was an open-label, multicenter randomized phase 3 trial of six cycles of standard ABVD versus six cycles of BV + AVD in newly diagnosed patients with stages III and IV cHL. The 2-year modified PFS was 77.2% for ABVD and 82.1% for BV + AVD ($P = 0.03$). This result led to approval of BV + AVD for this indication by the US Food and Drug Administration. Some subgroups seemed to particularly benefit from BV + AVD, and further analyses are being performed to better define these groups. Given cost and toxicity considerations, it is unclear, at least in the USA, whether BV + AVD will be adopted as a standard treatment for all patients with stages III and IV cHL or in particular subgroups [95].

10.3 Chemotherapy Treatment for Recurrent and Refractory Hodgkin Lymphoma

10.3.1 New Systemic Treatments

There have been relatively few new conventional cytotoxic agents developed recently for HL, but both monoclonal antibodies, immune therapies, and small molecule therapeutics targeting specific abnormal pathways in HL have shown some promising results.

Antibody therapies have been directed at relatively specific molecules, such as CD30 on the surface of Reed-Sternberg cells, but the results with an unconjugated anti-CD30 were discouraging, probably because it targets only a small proportion of the cells within a mass of lymphoma [96]. On the other hand, antibody-drug conjugates (ADC) have shown very promising results, with a response rate of 75% reported using brentuximab vedotin for patients with recurrent and refractory disease, as described in Sect. 10.2.1 [16].

Anti-CD20, given with the intention of targeting the infiltrating B cells and interrupting autocrine growth factor loops, has shown some promise in an early pilot study [97], but awaits confirmatory data from a prospective trial. This approach may find more application in the treatment of nodular lymphocyte predominant disease, in which CD20 is present on the surface of the malignant cells [98].

Among the small molecule therapies being tested, proteosome inhibitors have been disappointing in HL [99], whereas inhibitors of histone deacetylase (HDACi) have resulted in significant responses in early-phase studies, despite significant marrow toxicity [100]. It is not clear whether the principal target of HDACis is the malignant cell itself or the surrounding inflammatory infiltrate, but further studies using

a range of more- or less-specific agents targeting different members of the HDAC family may yield further information.

10.4 Conclusions

A variety of pharmacologic hypotheses have been tested in the course of the last 50 years, and none has been found entirely satisfactory for predicting the outcomes of treatment. The superiority of ABVD over MOPP is established. Similarly, the more effective multiagent BEACOPP regimen is being used in more and more countries and groups. There appears to be a potential trade-off between the intensity of chemotherapy and the value of consolidation radiotherapy in advanced disease: it is not clear whether any chemotherapy is intensive enough for radiation to be dropped altogether, but functional imaging holds promise for lowering the proportion of patients irradiated very significantly.

As treatment has evolved, the balance between toxicity and efficacy has been established, and new approaches using response-adapted therapy hold the promise of identifying the minority of patients for whom early intensification is a necessity, while allowing de-escalation of treatment in those destined to do well. The addition of brentuximab vedotin, the antibody-drug conjugate, has slightly improved efficacy in the treatment of stages III and IV HL. Finally, there are a small number of novel agents currently undergoing testing against recurrent and refractory disease which appear to hold some promise.

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