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State of the Art Therapy of Advanced Hodgkin Lymphoma

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1. Introduction

Given that a clear, universal definition of advanced Hodgkin lymphoma does not exist, it comes as no surprise that the treatment of this disease is a controversial subject. Currently, the cure rate of advanced Hodgkin lymphoma is relatively high, although most physicians and patients confronting this disease recognize that the cure rate is less than ideal and the costs of treatment are substantial in terms of morbidity and mortality. The current research focus in this disease, as with any oncologic disorder, is to maximize the curative potential of treatment while minimizing patient suffering.

In this chapter, the following topics will be discussed: the definition of advanced Hodgkin lymphoma, the development of combination chemotherapy for this disease, the important clinical trials that led to ABVD (a combination chemotherapy regimen consisting of: adriamycin, bleomycin, vinblastine, and dacarbazine) becoming the gold standard, the emergence of escalated BEACOPP (a combination chemotherapy regimen consisting of: bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone), as a challenger to ABVD therapy, utilization and role of other combination chemotherapy regimens, the controversial role of radiotherapy, the roles of autologous and allogeneic hematopoietic stem cell transplantation, prognostic factors in both untreated and relapsed patients, promising therapies of the future, and case studies.

As a young physician and investigator, the two most exciting areas of research currently involve the use of fusion positron emission tomography/ computed tomography (PET/CT) imaging and the continued expansion of targeted treatment strategies, such as brentuximab vedotin and rituximab, which will hopefully allow both improved treatment tailoring and subsequent outcome for patients.

2. Definition of "advanced" Hodgkin Lymphoma

Applying the term "advanced" to a patient with Hodgkin lymphoma implies that there is a clear definition of the opposite term, or "limited" disease. Precise, universally accepted definitions do not exist for either term as applied to Hodgkin lymphoma.

Eligibility criteria for clinical trial enrollment are an important source of definitions in clinical medicine. For example, the international leaders of Hodgkin lymphoma, the German

Hodgkin Study Group (GHSG), included all patients with stage IIIB-IV disease in the HD9 trial (Diehl et al. 1998), but required that patients with stage IIB disease have one of the following: an extralymphatic site, a bulky spleen (diffuse infiltration or > 5 focal lesions), or a bulky mediastinum (more than one third of the maximum thoracic diameter). Patients with stage IIIA disease were required to have either an erythrocyte sedimentation rate >50 mm/hr or ≥ 3 affected lymph node areas. Similarly, two major Italian studies, each comparing ABVD with other regimens, enrolled patients with stage IIB along with stage III-IV disease, although one study uses the term "intermediate and advanced" (Gobbi et al. 2005) and the other "unfavorable" rather than "advanced"(Viviani et al. 2011). Studies comparing MOPP with ABVD (Canellos et al. 1992) or ABVD with hybrid regimens (Duggan et al. 2003) in North America have included only stage III and IV patients.

In order to more easily compare results of studies performed all over the globe, the Hodgkin lymphoma community should insist upon homogeneity across clinical trials. In spite of the fact that there may be prognostic rationale for including patients with "B" symptoms or bulky disease with stage III and IV patients, it is probably more important to have uniformity across clinical trials internationally. It is reasonable to reserve the term "advanced" Hodgkin lymphoma for stage III and IV patients regardless of disease bulk, B symptoms, or any other adverse prognostic factor. Patients with adverse features and stage I or II disease would fall into a category of "limited unfavorable".

3. Role of combination chemotherapy

Combination chemotherapy for advanced Hodgkin lymphoma was initially developed by Vincent DeVita at the National Cancer Institute (NCI) in response to the initial successes in childhood leukemia treatment with combinations of agents. MOMP (mechlorethamine, vincristine, methotrexate, prednisone) was the initial combination regimen developed. Once procarbazine was developed sufficiently, it replaced methotrexate and the regimen was termed MOPP (DeVita et al. 1978). In a landmark study on the results of MOPP, 81 percent of stage III/IV Hodgkin lymphoma patients achieved a complete remission, a roughly four-fold higher response rate than with single agents, and the remission duration, when compared retrospectively, was increased approximately ten-fold over single agents alone (Devita, Serpick, and Carbone 1970). Ultimately, MOPP was shown in a prospective fashion to be superior to single agent nitrogen mustard in a small, randomized trial conducted by the Southeastern Cancer Group. One hundred eight patients with stage III or IV Hodgkin lymphoma were randomized between MOPP and mechlorethamine given biweekly, and patients receiving MOPP were found to have superior complete remission rates and overall survival (Huguley et al. 1975). From that time on, combination chemotherapy for advanced Hodgkin lymphoma became standard, and comparisons between various combination regimens ensued.

The Cancer and Leukemia Group B (CALGB) performed a randomized comparison amongst four different combination chemotherapy regimens: the four-drug combinations were BOPP (mechlorethamine substituted with BCNU) and MOPP, and the three-drug combinations were BOP (procarbazine eliminated) and OPP (BCNU or mechlorethamine eliminated). This study demonstrated superiority of four-drug over three-drug combinations, it highlighted the importance of the alkylating agents mechlorethamine and procarbazine, and it further solidified the role of four-drug combinations for treating Hodgkin lymphoma (Nissen et al.

1979). Interestingly, MOPP and BOPP were equivalent regimens, which demonstrated that BCNU and mechlorethamine may have equivalent efficacy. Similarly, a comparison of LOPP (lomustine replaces mechlorethamine) with MOPP demonstrated equal efficacy as well, further demonstrating that nitrosureas could substitute for alkylating agents in treatment of this disease (Hancock 1986).

In summary, combination chemotherapy became standard on the basis a landmark study of MOPP therapy developed at the NCI, with formal confirmation of superiority over single agents in one randomized trial. Combination chemotherapy with four drugs was superior to three drugs. MOPP, with an alkylating agent meclorethamine, although equivalent in efficacy to nitrosurea-containing combinations, was likely favored by most experts in the field due to the short and long-term side effects associated with nitrosureas.

4. ABVD as gold standard

MOPP combination chemotherapy for advanced Hodgkin lymphoma resulted in twenty to thirty percent of patients failing to achieve a complete remission and only fifty percent of patients being cured with risks of both sterility and secondary malignancies such as acute leukemia (Bonadonna, Valagussa, and Santoro 1986; Longo et al. 1991). Bonadonna Gianni developed the ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) regimen in order to salvage MOPP failures (Bonadonna et al. 1975). In an initial Italian study comparing three cycles of ABVD or MOPP with receipt of radiotherapy in both arms, ABVD was superior with a seven-year overall survival of 77.4 percent versus 67.9 percent for MOPP (Santoro et al. 1987). ABVD therapy became solidified as the gold standard after a landmark three-arm CALGB study, which compared ABVD with MOPP and an alternating regimen, MOPP/ABVD. The study demonstrated five-year failure-free survival rates of 61 percent for ABVD, 50 percent with MOPP, and 65 percent for alternating MOPP/ABVD (Canellos et al. 1992). The toxicity profile of ABVD was more favorable than either the alternating regimen or MOPP, and therefore ABVD became the standard combination chemotherapy regimen for advanced Hodgkin lymphoma.

Interest in the Goldie and Coldman hypothesis (Goldie and Coldman 1979), which hypothesized that early introduction of all active agents for a disease would prevent the development of resistant clones, led to three major studies comparing hybrid and alternating regimens of MOPP and ABVD. No advantage in overall survival was found with the hybrid regimens (Connors et al. 1997; Sieber et al. 2002; Viviani et al. 1996). An important US Intergroup trial dampened further interest in hybrid regimens by demonstrating equivalent efficacy ABVD over a MOPP/ABV hybrid, with a similar failure-free survival and overall survival at five years but a better toxicity profile of the ABVD regimen (Duggan et al. 2003). The solidification of ABVD as the true gold standard would take place in the 1990 and 2000's, in which ABVD became the comparator arm for most randomized clinical trials.

5. The emergence of escalated BEACOPP

The group with a lead role in the advancement of Hodgkin therapy, the GHSG, developed the escalated BEACOPP regimen initially through mathematical modeling of tumor growth and chemotherapy effects, (Hasenclever, Loeffler, and Diehl 1996) which led to a pilot

clinical trial in which doses of cytotoxic agents were increased in a stepwise fashion (Tesch et al. 1998). Escalated BEACOPP, the new dose dense regimen relative to COPP/ABVD and dose intense regimen relative to standard BEACOPP, was tested against these two regimens in the HD9 clinical trial. Ten year follow-up of that study, in which seventy percent of patients received additional radiotherapy, demonstrated statistically and clinically significant superiority of escalated BEACOPP over COPP/ABVD and standard BEACOPP in terms of freedom from treatment failure rate (82, 70, and 64 percent, respectively) and overall survival rate (86, 80, and 75 percent, respectively) (Engert et al. 2009).

BEACOPP, given in different schedules than the German standard of eight escalated cycles, has also been compared with other regimens in two prospective, randomized, Italian studies. The HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial was initially designed as a toxicity trial to compare rates of leucopenia between three arms: a BEACOPP regimen (consisting of four escalated cycles and two standard cycles), a CEC regimen, and ABVD (Federico et al. 2009). Once the study centers became comfortable with BEACOPP administration, which requires the greatest attention and familiarity in the initial cycles, the trial was changed to a primary endpoint of failure-free survival. With a median follow-up of forty-one months and a suggestion of lower median dose intensity of BEACOPP delivered and resulting lower rates of grade III/IV hematologic toxicity compared with the escalated BEACOPP arm of the HD9 trial, the five-year estimated rates of failure-free survival were 78 and 65 percent in the arms of interest, BEACOPP and ABVD, respectively, which reached both clinical and statistical significance. The five-year estimated overall survival demonstrated numerical superiority of BEACOPP over ABVD with rates of 92 versus 84 percent, although this failed to meet statistical significance. In a second recently published Italian study, conducted in a similar time period as the HD2000 study, four cycles of escalated BEACOPP plus four cycles of standard BEACOPP were compared with ABVD with a primary endpoint of freedom from first progression (Viviani et al. 2011). With a median follow-up of sixty-one months, the estimated seven-year rate of freedom from first progression was 85 percent in the BEACOPP group versus 73 percent in the ABVD group. The primary endpoint importantly achieved both statistical and clinical significance. Counter to this, the secondary endpoints, which did not have statistical power, were overall survival and rate of freedom from second progression. These endpoints were 84 and 82 percent in the ABVD arm, respectively, versus 89 and 88 percent in the BEACOPP arm, and they did not reach statistical significance. Details of exact dose intensity were not provided, and one could certainly debate, in spite of the author's conclusions, the relevance of a five percent difference in overall survival, which numerically favored the BEACOPP program. The final analysis of the HD12 trial (Diehl et al. 2008), a comparison of eight cycles of escalated BEACOPP with four escalated cycles followed by four standard cycles of BEACOPP, demonstrates statistical equivalence at five year follow-up between the arms, with the eight escalated cycles being numerically superior and still the gold standard comparator arm for the HD15 study. The HD15 trial (Kobe et al. 2008) compares eight escalated cycles of BEACOPP with six escalated cycles of BEACOPP or eight cycles of fourteen day compressed BEACOPP. The results of this study, as well as the results of a global study comparing four cycles of escalated BEACOPP followed by four cycles of baseline BEACOPP with eight cycles of ABVD (European Organization for Research and Treatment of Cancer 2002), are eagerly anticipated.

6. Other chemotherapy regimens

Stanford V is a regimen incorporating twelve total weeks of alternating weekly cycles of myelotoxic and nonmyelotoxic polychemotherapy followed by liberal irradiation of 36 Gy to sites > 5 cm or macroscopic splenic disease (Bartlett et al. 1995). It was originally designed at Stanford although the chemotherapy backbone was likely drawn from the VACOPB regimen designed in Vancouver for non-Hodgkin lymphoma (O'Reilly et al. 1991). Stanford V was initially compared with ABVD and a regimen called MOPPEBVCAD by the Intergruppo Italiano Linfomi. Focusing on the Stanford V and ABVD arms, the primary endpoint of failure-free survival at five years was 76 perecent with Stanford V versus 89 percent with ABVD, with overall survival of 82 percent versus 90 percent, respectively (Gobbi et al. 2005). The trial has been criticized for utilizing radiotherapy differently than the original Stanford V report, as 66 versus 89 percent of patients, respectively, received radiotherapy. Sites > 6 cm rather than >5 cm were irradiated, and radiotherapy occurred 4-6 weeks rather than 2-4 weeks post-chemotherapy (so called optional versus adjuvant radiotherapy). More recently, a large Intergroup study was reported which compared Stanford V with six to eight cycles of ABVD. Somewhat unrealistically, the trial was designed to detect a 33 percent reduction in the failure-free survival hazard rate with Stanford V versus ABVD, and the failure-free survival at five years with Stanford V was 71 versus 73 percent with ABVD with 87 and 88 percent overall survival rates, respectively (Gordon et al. 2010). This trial further solidifies ABVD as the standard polychemotherapy regimen in advanced Hodgkin lymphoma, and is still the comparator arm for further investigational work.

Other polychemotherapy regimens which have been the subject of prospective, randomized investigation in advanced Hodgkin lymphoma which have not gained widespread appeal include: MEC, CHLVPP/EVA, and VAPEC-B. MEC, or MOPPEBVCAD (a regimen consisting of: mechlorethamine, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin), was compared with Stanford V and ABVD in an Italian study, with all arms receiving optional radiotherapy. MEC provided similar disease control as ABVD with similar rates of freedom from first progression, although the grade III-IV toxicity rates, particularly hematologic toxicity, were higher with MEC than ABVD (Gobbi et al. 2005). Therefore, given the better balance of efficacy and toxicity afforded by ABVD, MEC fell out of favor. A United Kingdom/Italian study compared the hybrid regimen CHLVPP/EVA to VAPEC-B (Radford et al. 1997), an abbreviated 11 week polychemotherapy regimen similar to VACOP-B or Stanford V. CHLVPP/EVA resulted in a superior three year disease-free and overall survival, with rates of 82 and 89 percent versus 62 and 79 percent, respectively for VAPEC-B. When British investigators compared ABVD with CHLVPP/EVA or a similar regimen, CHLVPP/PABLOE, the three year event-free survival and overall survival were similar, and ABVD was better tolerated (Johnson et al. 2005). Since that study, these hybrid polychemotherapy regimens have not been utilized.

In summary of chapters five and six, there is still controversy regarding the optimal chemotherapy approach in untreated Hodgkin lymphoma patients. In spite of the two "negative" Italian studies, and considering the difference in patient numbers between those studies and HD9, it is reasonable to treat patients with advanced Hodgkin lymphoma with either escalated BEACOPP or ABVD. Stanford V can be considered in selected patients,

recognizing that it has never shown superiority over ABVD or a similar regimen. Further refinement of chemotherapy for advanced Hodgkin lymphoma, utilizing both PET/CT guidance and monoclonal antibodies, is likely to occur in the future.

7. Role of radiotherapy

Radiotherapy is a treatment modality that is believed to be non-crossresistant with standard combination chemotherapy (DeVita 2008). Its use can be considered in several contexts in advanced Hodgkin lymphoma: as an adjuvant therapy after complete remission is obtained with chemotherapy, integrated as combined modality therapy, or utilized as a definitive modality when response to chemotherapy is unsatisfactory.

The first use, as an adjuvant after complete response with polychemotherapy, was assessed in four randomized studies. Two studies compared radiotherapy with observation, and two studies compared radiotherapy with two additional cycles of chemotherapy. The Southwest Oncology Group randomized three hundred and twenty two patients with stage III or IV Hodgkin lymphoma who achieved a complete remission by computed tomographic assessment after six cycles of MOP-BAP between observation or low-dose (2000 cGy to lymph nodes, 1000-1500 cGy to other organs) involved field radiotherapy (IFRT). With a median follow-up of eight years, there were no statistically significant differences in relapse-free or overall survival (Fabian et al. 1994). The GHSG randomized patients with stage III or IV disease in complete remission by computed tomographic assessment after six cycles of COPP/ABVD to two more cycles of chemotherapy or low-dose (20 Gy) IFRT, and this study demonstrated no difference in relapse rate between the two arms (Diehl et al. 1995). A GELA study assessed the role of more extensive radiotherapy (subtotal nodal or total) versus two more cycles of chemotherapy in stage III/IV patients having achieved a complete or very good partial remission (≥ 75% size reduction) with six cycles of either MOPP/ABV or ABVPP. With a median follow-up of forty-eight months, the five year disease-free survival was 79 percent for the radiotherapy versus 74 percent for continued chemotherapy (Ferme et al. 2000). In the largest trial to determine the role of IFRT in stage III/IV Hodgkin lymphoma, four hundred twenty-one patients with computed tomogram complete remission after MOPP/ABV polychemotherapy were randomly assigned to observation versus IFRT. With a median follow-up of seventy-nine months, the five year event-free and overall survival rates were 84 percent and 91 percent in the observation group, respectively versus 79 percent and 85 percent in the IFRT group, which demonstrated that there is no role for IFRT in advanced Hodgkin lymphoma patients who achieve a complete remission with polychemotherapy (Aleman et al. 2003).

The second use, as an integrated therapy with chemotherapy, implies that radiotherapy is a pre-planned treatment regardless of response. The most common example of this is the administration of 36 Gy radiotherapy to patients receiving the Stanford V regimen who have sites of disease > 5cm or macroscopic splenic involvement. Unfortunately, radiotherapy administered in this context is completely of unproven value, and the harms are certain. For example, with intense polychemotherapy such as escalated BEACOPP, the GHSG has been able to reduce the percentage of patients on their studies receiving pre-planned radiotherapy from nearly 70 percent to approximately 10 percent without loss of efficacy and with a clear-cut reduction in the rate of secondary leukemia, from 1.7 to 0.6 percent

comparing HD9 data with HD12 data (Diehl et al. 1998; Diehl et al. 2008). Unfortunately, many recently completed clinical trials still include pre-planned radiotherapy, such as the ECOG 2496 Intergroup study comparing ABVD with Stanford V, which provided radiotherapy to all patients on the ABVD arm with bulky mediastinal disease (Gordon et al. 2010). Fortunately, most of the new generation of clinical trials, such as SWOG 0816 and CALGB 50604, which utilize PET/CT to risk stratify patients for subsequent therapeutic strategy, only include radiotherapy to patients categorized as high risk with a positive PET/CT after a certain number of chemotherapy cycles (Southwest Oncology Group 2011; Cancer and Leukemia Group B 2011).

The third use, with utilization based on an unsatisfactory response to chemotherapy, certainly has theoretical appeal in order to improve outcomes of those patients with partial response to combination chemotherapy. Many studies include involved field radiotherapy for those patients with "residual tumor", which again has various definitions. Indirect justification for this approach is made by analysis of the Aleman study. The cohort of patients who were irradiated after achievement of a partial response with chemotherapy had five year event-free and overall survivals of 79 and 87 percent, respectively, which compared favorably with those patients having achieved a complete response with chemotherapy alone, with event-free and overall survivals of 84 and 91 percent, respectively (Aleman et al. 2003). An important question is whether a subset of the patients in partial response can be spared the additional toxicity of radiotherapy. In a recent analysis of the HD15 trial, in which eight cycles of escalated BEACOPP was compared with six cycles of escalated BEACOPP or 14 day compressed BEACOPP, thirty-eight percent of patients had residual tumor > 2.5 cm at the completion of chemotherapy. Of this patient group, twenty-one percent had a positive post-therapy PET/CT and seventy-nine percent had a negative PET/CT. The patients with a negative PET/CT were observed, and patients with a positive PET/CT received IFRT. The 18 month progression-free survival was 95 percent for patients who achieved a CR with chemotherapy, 96 percent for patients with > 2.5 cm residual tumor with PET/CT negativity who were observed, and 85 percent for PET/CT positive patients who received additional IFRT (Kobe et al. 2008). The authors recommend additional study, but in the meantime, a reasonable clinical practice would be to omit radiotherapy in those patients in complete metabolic remission post-therapy regardless of the initial disease features.

In summary, there is no role for adjuvant radiotherapy in patients who achieve a computed tomography defined complete remission based on several randomized studies. There is no clear role of a pre-planned chemotherapy plus radiotherapy approach in advanced Hodgkin lymphoma, and although preliminary, it appears reasonable to defer decisions about radiotherapy until the post-therapy PET/CT is completed. It appears that patients with non-FDG avid residual tumors can be safely observed, and based on indirect evidence, radiotherapy may benefit those with remaining FDG avidity in tumor masses.

8. Role of autologous hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplant has been studied in four separate prospective, randomized controlled clinical trials in Hodgkin lymphoma, in two instances in upfront consolidation and in two instances in the relapsed setting.

First, two studies utilizing transplant as consolidation of upfront polychemotherapy of Hodgkin lymphoma will be discussed. In a Scottish and Newcastle Lymphoma Group Study, sixty-five patients with "poor risk" disease were administered three cycles of PVACE-BOP chemotherapy with or without XRT. Those patients with a good partial or complete response were randomized to a melphalan/etoposide-conditioned autologous hematopoietic stem cell transplant versus 2 additional cycles of PVACE-BOP chemotherapy (Proctor et al. 2002). With a median follow-up of six years, the arms had a similar time to treatment failure, 79 percent in the transplant arm versus 85 percent in the non-transplant arm. The major conclusion of this study is that for a subset of patients with "poor risk" features derived by calculation of a Scottish Newcastle Lymphoma Group prognostic index, autologous hematopoietic stem cell transplantation offers no benefit over standard chemotherapy if a very good response on computed tomography is obtained after three cycles of polychemotherapy. In a second European Intergroup study, the HD 01 trial, one hundred sixty-three patients with "poor risk" disease at baseline were randomized after four cycles of ABVD or ABVD-like therapy in complete or partial response to a BEAM or CVB-conditioned autologous transplant or four additional cycles of chemotherapy (Federico et al. 2003). With a median follow-up of 48 months, the five year failure-free survival was 75 percent in the transplant arm versus 82 percent in the chemotherapy arm. Rates of overall survival were 88 percent in each arm. Although the transplant conditioning regimens utilized were different, both trials have similar features, such as attempting to identify a poor-risk subset of patients in spite of different criteria used. Additionally, an abbreviated course of chemotherapy was utilized prior to the randomization of continued chemotherapy versus transplant. Both trials only randomized patients with a response to chemotherapy, were small in number, and obtained similar results. Based on these data, there appears to be no role for performing autologous transplantation in previously untreated Hodgkin lymphoma patients with poor risk features who achieve a response on computed tomography imaging.

Two prospective randomized trials of autologous transplant have been conducted in patients with relapsed Hodgkin lymphoma. In the first trial, British investigators randomized forty patients with both relapsed and refractory "high risk" disease to either a chemotherapy regimen, mini-BEAM, or a BEAM-conditioned autologous transplant without details of exact number of chemotherapy courses given. The event-free survival at three years was 53 percent in the BEAM group versus 10 percent in the mini-BEAM group (Linch et al. 1993). The three year overall survival rate favored the BEAM group but did not achieve statistical significance. In the second study, German investigators randomized one hundred sixty-one patients with relapsed Hodgkin lymphoma to four cycles of Dexa-BEAM versus 2 cycles of Dexa-BEAM followed by a BEAM-conditioned autologous transplant (Schmitz et al. 2002). The three year estimated freedom from treatment failure was significantly better at 55 percent in the transplant arm versus 34 percent in the chemotherapy alone arm, while the overall survival did not reach statistical significance, with a rate of 71 percent in the transplant arm versus 65 percent in the chemotherapy alone arm. In spite of the lack of overall survival improvement, the disease-free survival improvement demonstrated in the above studies has lead to international acceptance that relapsed Hodgkin lymphoma is a definite indication for autologous hematopoietic stem cell transplantation.

A small number of refractory patients were included in the British transplant trial, and based on their inclusion in that study plus retrospective datasets indicating possible benefit of autologous transplant, (Lazarus et al. 1999; Andre et al. 1999; Josting et al. 2000) patients with refractory Hodgkin lymphoma who achieve a response or even disease stabilization with a salvage chemotherapy regimen can be considered for autologous transplantation.

Various conditioning regimens for autologous transplantation exist, and the BEAM (BCNU, etoposide,cytarabine, melphalan) regimen has been utilized in both randomized trials for relapsed/refractory disease. Other reported high-dose chemotherapy regimens include: CBV (cyclophosphamide, BCNU, VP-16), CBVP (CBV + cisplatin), Etoposide/Melphalan, high dose Melphalan, CCV (cyclophosphamide, CCNU, VP-16), and TLI (total lymphoid irradiation)+VP-16/cyclophosphamide). No prospective comparative trials of these regimens exist, and due to heterogeneity in parameters reported, even indirect comparison is challenging. In a retrospective comparison of two different condidtioning regimens, one radiation based with TBI/ cyclophosphamide/etoposide versus a chemotherapy regimen of busulfan/melphalan/ thiotepa (Bu/Mel/T), investigators at Fred Hutchinson Cancer Center found no difference in efficacy or toxicity of either preparative regimen. Patients who had a history of dose-limiting irradiation were treated with the Bu/Mel/T regimen preferentially (Gutierrez-Delgado et al. 2003). The BEAM regimen, given its use in the randomized trials, is a reasonable choice in the absence of comparative data, and the primary clinical issues with use of this regimen are melphalan-related gastrointestinal toxicity and BCNU-related pulmonary toxicity, the latter of which requires corticosteroid initiation at recognition.

Further intensification of a single autologous transplant for relapsed/refractory patients has been studied, both by utilizing higher doses of standard chemotherapy pre-transplant and by the addition of a planned second, or tandem transplant. In the HD-R2 trial, a European multicenter (GHSG, EORTC, EBMT, and GEL/TAMO) study for relapsed Hodgkin lymphoma, investigators randomized two hundred forty one patients without progressive disease after two cycles of DHAP to either a BEAM conditioned autologous transplant or sequential high dose chemotherapy with cyclophosphamide 4gm/m^2, methotrexate 8gm/m^2, and etoposide 500mg/m^2, followed by a BEAM conditioned autologous transplant, with IFRT to residual masses > 1.5cm in both arms. With a median follow-up of 42 months, the three year OS was 87 percent in the standard arm versus 83 percent in the high dose sequential arm, with corresponding rates of freedom from treatment failure of 71 percent and 65 percent, respectively (Josting et al. 2010). The conclusions of the authors, based on the largest randomized trial in relapsed Hodgkin lymphoma to date, is that sequential high dose chemotherapy has no role and that patient outcomes were quite good with two cycles of DHAP followed by a BEAM conditioned transplant. In the prospective, multicenter H96 trial conducted by the GELA/SFGM group, investigators studied the role of tandem autologous transplant for relapsed/refractory Hodgkin lymphoma patients with poor risk disease, defined as primary refractoriness to initial chemotherapy or ≥ 2 risk factors of the following: relapse < 12 months from primary therapy, stage III/IV disease at relapse, and relapse within a previously irradiated site with combined modality therapy. These poor-risk patients received two cycles of chemotherapy followed by a CBV plus mitoxantrone or BEAM-conditioned first transplant, with a second transplant with TAM (total-body irradiation, cytarabine, melphalan) or BAM (busulfan, cytarabine, melphalan)

45-90 days later. On an intent-to-treat basis, with a median follow-up of fifty one months, the five year freedom treatment failure and overall survival rates were 46 percent and 57 percent, respectively (Morschhauser et al. 2008). Seventy percent of poor risk patients received a second transplant with a transplant-related mortality of four percent. The authors concluded that tandem transplant was an advance in the treatment of poor risk patients with partial response to salvage chemotherapy and in those with primary refractory disease, given the superior results to historical data of single transplant in those populations.

In summary, autologous hematopoietic stem cell transplant has no role in the upfront treatment of patients with Hodgkin lymphoma. For patients with relapsed disease, it is considered the standard of care if chemotherapy sensitivity can be demonstrated. For patients with primary refractory disease, autologous transplantation is controversial but a small amount of retrospective data indicates a possible benefit. Chemotherapy intensification over traditional salvage regimens for relapsed/refractory patients appears to have no role, and there is possible benefit in tandem transplant for patients who are at high risk for poor outcome with a single autologous transplant.

9. Salvage therapy for relapsed/refractory disease

For patients who experience relapse after achievement of a complete response or who do not achieve a complete response and have biopsy proven residual Hodgkin lymphoma, conventional treatment consists of several cycles of non-crossresistant chemotherapy followed by autologous hematopoietic stem cell transplantation. In this chapter, the roles of radiotherapy and chemotherapy specifically for relapsed disease will be discussed.

The use of radiotherapy alone or in combination with salvage chemotherapy in relapsed/refractory Hodgkin lymphoma is controversial. Several retrospective reports exist on utilizing isolated radiotherapy for patients with relapsed/refractory disease after failure of combination chemotherapy. In the largest study, the GHSG found that of the one hundred patients in their database treated with radiotherapy alone after failure of anthracycline-based chemotherapy, the five-year freedom from treatment failure was 28 percent with an overall survival of 51 percent (Josting et al. 2005). The authors conclude that salvage radiotherapy is a treatment option for a subset of patients without B symptoms but with good performance status, limited stage, and late relapses, which effectively excludes the majority of Hodgkin lymphoma patients with relapsed disease and all patients with refractory disease.

No reports have compared outcomes of patients who do and do not receive radiotherapy as a component of salvage chemotherapy with autologous transplantation, and therefore the balance of efficacy and toxicity in this scenario is uncertain. Radiotherapy to "residual lesions" after the BEAM-conditioned autologous transplant was recommended in the German transplant study in relapsed disease, although too few patients received radiotherapy to allow comparison of outcomes to those without radiotherapy. Given that the opportunity for cure is greatly diminished in relapsed/refractory Hodgkin lymphoma, in spite of an absence of evidence of a definite benefit of radiotherapy, it is reasonable to include radiotherapy as part of a treatment regimen that includes salvage chemotherapy and autologous transplantation, particularly if the relapse is localized on imaging. Based on retrospective information regarding high rates of toxicity when radiotherapy is utilized pre-

transplant (Tsang et al. 1999), it may be most reasonable to use this modality post-transplant.

Salvage chemotherapy is administered to the majority of patients with relapsed/refractory Hodgkin lymphoma with the goal of disease reduction or eradication prior to autologous transplantation. In fact, in the era of computed tomography, multiple reports document that the response to salvage chemotherapy is a major determinant of the outcome of autologous transplant (Sureda et al. 2001; Gutierrez-Delgado et al. 2003; Martin et al. 2001) and that the degree of response is associated with the progression-free survival at five years (Sirohi et al. 2008).

An ideal salvage regimen has an excellent response rate, non-overlapping organ toxicities with the primary regimen, and preserves the ability to mobilize and collect hematopoietic stem cells. Because initial treatment of Hodgkin lymphoma nearly always consists of anthracycline and bleomycin therapy, and because autologous transplant is the usual goal, which is a stress on the cardiopulmonary system, salvage therapy choices are typically made to limit cardiopulmonary toxicity.

Many different salvage polychemotherapy regimens have been utilized in the past, and all studies have been phase II investigations with heterogeneous patient populations with relapsed/refractory disease. See Table 1. Because only DEXA-BEAM and mini-BEAM regimens have been used pre-transplant in randomized clinical trials, the purist would utilize these regimens at the exclusion of other choices in spite of a toxic death rate between two to five percent. In one-hundred forty four patients, the DEXA-BEAM regimen resulted in a complete response rate of 27 percent, a partial response rate of 54 percent, and a toxic death rate of 5 percent (Schmitz, 2002). In fifty-five patients, the mini-BEAM regimen produced a complete response rate of 49 percent, a partial response rate of 33 percent, a toxic death rate of 2 percent, and in another cohort of patients, 82 percent collected $\geq 2 \times 10^6$ CD34 cells/kg (Martin et al. 2001; Kuruvilla et al. 2006).

The platinum-based salvage regimens include ESHAP (etoposide, solumedrol, high-dose cytarabine, and cisplatin), ASHAP (doxorubicin, solumedrol, high-dose cytarabine, and cisplatin), DHAP (dexamethasone, cytarabine, and cisplatin), and GDP (gemcitabine, dexamethasone, and cisplatin). ASHAP as a salvage regimen has limited applicability given that most patients will have anthracycline exposure during initial treatment. In twenty-three patients, the GDP regimen was reported to have a complete response rate of 17 percent, partial response rate of 52 percent, no toxic deaths, and 97 percent of patients collected $\geq 2 \times 10^6$ CD34 cells/kg. (Baetz et al. 2003; Kuruvilla et al. 2006). In twenty-two patients given the ESHAP regimen, the complete response rate was 41 percent, partial response rate 32 percent, toxic death rate 4 percent, with no stem cell collection data provided (Aparicio et al. 1999). In a report on one hundred two patients administered DHAP on an every two week schedule, the complete response rate was 21 percent, partial response rate 68 percent, and toxic death rate zero without collection data provided (Josting, Rudolph, et al. 2002).

Of the ifosfamide-based salvage regimens, two of the regimens are worth mention, ICE (ifosfamide, carboplatin, etoposide) and IGEV (ifosfamide, gemcitabine, vinorelbine, prednisolone). The ICE regimen, developed at Memorial Sloan-Kettering in an effort to reduce the nonhematologic toxicity of cisplatin-based regimens, resulted in a complete response rate of 26 percent, partial response rate of 59 percent, a toxic death rate of zero, and 86 percent of the sixty-five patients studied achieved a collection of $\geq 2 \times 10^6$ CD34 cells/kg (Moskowitz et

al. 2001). In a report of ninety-one patients given the IGEV regimen, the complete response rate was 54 percent, partial response rate 37 percent, a toxic death rate of zero, and 98.7 percent achieved a stem cell collection of ≥ 3 x 10^6 CD34 cells/kg (Santoro, 2007).

In spite of the lack of comparative data, the ICE, IGEV, and GDP regimens appear to have the most favorable balance of the three key factors of response, low toxic death rate, and stem cell preservation. The ICE regimen is typically administered in the inpatient setting with the other two regimens given in an outpatient setting. Individual patient factors, such as pre-existing neuropathy or renal dysfunction, do play an important role in the final choice of a salvage combination chemotherapy regimen.

In summary, the role of radiotherapy, particularly isolated radiotherapy, in the management of relapsed Hodgkin lymphoma remains uncertain, and the standard of care is salvage combination chemotherapy for an arbitrary number of cycles followed by high dose preparative chemotherapy with autologous hematopoietic stem cell transplantation. Given the poorer results in salvage than upfront treatment, and the belief that disease is ultimately the greater problem than therapy toxicity in this younger patient population, erring on the side of consolidative radiotherapy post-transplant in those with limited stage relapse is reasonable.

Regimen	Composition	CR, ORR%	Toxic Death Rate	Stem Cell Colllection
DEXA-BEAM	Dexamethasone, BCNU, Etoposide, Ara-C, Melphalan	27, 81	5	NR
Mini-BEAM	BCNU, Etoposide, Ara-C, Melphalan	49, 82	2	82 percent ≥ 2 x 10^6 CD34+ cells/kg
GDP	Gemcitabine, Dexamethasone, Cisplatin	17, 69	0	97 percent ≥ 2 x 10^6 CD34+ cells/kg
ESHAP	Etoposide, SoluMedrol, Ara-C, Cisplatin	41, 73	4	NR
DHAP	Dexamethasone, Ara-C, Cisplatin	21, 89	0	NR
ICE	Ifosfamide, Carboplatin, Etoposide	26, 85	0	86 percent ≥ 2 x 10^6 CD34+ cells/kg
IGEV	Ifosfamide, Gemcitabine, Vinorelbine, Prednisone	54, 91	0	98 percent ≥ 3 x 10^6 CD34+ cells/kg

Table 1. Comparison of salvage chemotherapy regimens for relapsed/refractory Hodgkin lymphoma.

10. Role of allogeneic hematopoietic stem cell transplantation

Patients with Hodgkin lymphoma who relapse after autologous hematopoietic stem cell transplantation have a very poor long term outlook, with several series documenting a low rate of long term survivors (Crump 2008; Constans et al. 2004). In a retrospective Spanish analysis of patients who relapsed after autologous transplant, the progression free survival and overall survival were 23 percent and 35 percent at three years, respectively. Investigators at Wayne State retrospectively studied this patient population, and found an approximate 10 percent survival rate at four years post autologous transplant, and similar results were found in a series of patients from Memorial Sloan Kettering (Varterasian et al. 1995). Two findings were interesting in the Memorial series: one, nearly all of the long term survivors received a reduced-intensity allogeneic hematopoietic stem cell transplant, and second, the reduced-intensity allogeneic transplant appeared to be of little benefit to patients who relapsed within six months of the autologous transplant (Moskowitz et al. 2009).

Allogeneic transplants are typically divided into myeloablative versus reduced-intensity or nonmyeloablative depending on the intensity of the preparative regimen. Multiple reports on the efficacy and toxicity of myeloablative transplants for Hodgkin Lymphoma exist in the literature, and all are consistent in demonstrating an unacceptably high rate of treatment-related mortality. In a retrospective assessment of one hundred patients in the International Bone Marrow Transplant Registry (IBMTR), eighty-nine percent of the patients had active disease at the time of transplant, with a resulting three year disease-free survival rate of 15 percent, overall survival of 21 percent, and probabilities of acute and chronic graft-versus-host disease of 35 and 45 percent, respectively (Gajewski et al. 1996). The authors appropriately concluded that myeloablative sibling transplants have little role in the treatment of Hodgkin lymphoma. In a similar retrospective analysis, the European Bone Marrow Transplant (EBMT) registry retrospectively analyzed the outcomes of one hundred sixty-seven allogeneic transplants in patients with Hodgkin lymphoma, and found an actuarial overall survival of 24 percent at four years, primarily related to a 52 percent procedure-related mortality at four years (Peniket et al. 2003). Again, the authors appropriately concluded that the toxicity of allogeneic procedures would have to be reduced before broader applicability would be realized. In a retrospective matched case analysis by the EBMT of forty five allogeneic and forty five autologous transplants, it was found that the four year probability of survival, progression-free survival, relapse, and non-relapse mortality were 25, 15, 61, and 48 percent after allogeneic transplant with corresponding figures of 37, 24, 81, and 27 percent after autologous transplant (Milpied et al. 1996). The authors concluded that the positive effect of a decreased relapse rate with allogeneic transplant is offset by the toxicity and transplant-related mortality. Hence, multiple retrospective series of myeloablative allogeneic transplantation in Hodgkin lymphoma reached the same conclusion, namely the toxicity outweighs the small benefit from the treatment.

The applicability of allogeneic hematopoietic stem cell transplantation in a wide spectrum of hematologic disorders has been broadened by the advent of reduced-intensity conditioning, in which lower, non or partially myeloablative doses of chemotherapy either with or without radiotherapy are administered prior to infusion of allogeneic stem cells.

A convincing graft versus Hodgkin lymphoma effect was demonstrated after reduced-intensity allogeneic transplantation (Peggs et al. 2005). Several reports of long term follow-

up of reduced-intensity allogeneic transplant demonstrate the curative potential of this procedure. In an EBMT retrospective analysis, with a median follow-up of seventy-five months for survivors, 18 percent were progression free at five years with an overall survival rate of 20 percent (Sureda et al. 2008). In another report with a median follow-up of forty-nine months, the estimated progression-free survival was 34 percent and overall survival 51 percent at five years.

In summary, myeloablative allogeneic transplantation appears to have little role in the treatment of Hodgkin lymphoma given the morbidity and mortality associated with the procedure. However, reduced-intensity allogeneic transplantation is a reasonable consideration in patients with a matched donor who have relapsed following an autologous transplant given the curative potential of the procedure in a desperate clinical situation.

11. Prognostic factors along the disease spectrum of advanced disease

Prognostic factors are measurements on individuals performed at or soon after diagnosis which gives likely outcome of the disease. Although far less useful to the clinician than predictive factors, which are directly influenced by treatment, prognostic factors can be used as guides in choosing an appropriate treatment strategy. Prognostic factors for advanced Hodgkin lymphoma are fairly well established because treatment over time has been more uniform and relapses are higher in frequency than for limited stage Hodgkin lymphoma.

The most useful information for prognosis in advanced Hodgkin lymphoma comes from a large retrospective analysis, a so-called tour de force, performed by German investigators (Hasenclever and Diehl 1998). They analyzed baseline characteristics and determined the outcomes of five thousand one hundred forty-one patients with primarily stage III/IV disease treated with ABVD or similar regimens in multiple centers. The authors found, on multivariate analysis that the prognosis of patients with advanced Hodgkin lymphoma depended on seven baseline characteristics including: age, gender, total leukocyte count, lymphocyte percentage or absolute number, albumin, hemoglobin, and stage. Because the relative risk for poorer outcome was similar between factors, the authors created the International Prognostic Score (IPS) for advanced Hodgkin lymphoma by simply adding each factor for a total score of 0-7: 1 point for age>45, male gender, total leukocyte count >15,000 cells/mcL, absolute lymphocyte count <600 cells/mcL or lymphocyte percentage <8%, albumin <4 g/dL, hemoglobin <10.5 g/dL, and stage IV. Higher scores indicate a worse prognosis, and this information was confirmed in an independent data set. Although many other reports exist describing other adverse prognostic features in advanced Hodgkin lymphoma, the significance of other factors in relation to the IPS is uncertain, and the IPS appears to be the principal prognostic tool for patients at baseline.

The risk factors in relapsed Hodgkin lymphoma are more controversial than in untreated disease, but the GHSG contributed a large retrospective study analyzing the risk factors for poor outcome in four hundred twenty-two relapsed patients. They developed a prognostic score based on three factors: time to relapse, clinical stage, and presence of anemia (Josting, Franklin, et al. 2002).

More recently, interest has grown to better refine baseline prognosis with information on disease response with therapy, which has consistently shown to be an important factor

when degree of response in untreated or relapsed patients is considered. In other words, attainment of complete response, as is the case for most hematologic malignancies, is the name of the game for Hodgkin lymphoma. Computed tomography, an extremely valuable tool for assessment of anatomic structures, has been the traditional assessment tool for response in lymphomas, with criteria for definition of complete and partial response clearly delineated (Cheson et al. 1999). Given that lymph node size may correlate less well with viable cancer than functional imaging with positron emission tomography, it is now generally accepted that either fusion PET/CT or PET and CT are superior to CT alone at baseline and post-therapy restaging. Given the superiority in re-staging, interest grew in obtaining information from PET at earlier and earlier timepoints, in order to utilize that information, the so-called interim PET, for treatment decisions. A major report in this arena was a retrospective study by an Italian group of patients with advanced Hodgkin lymphoma treated with ABVD or similar regimens, who underwent PET scanning after two cycles of treatment, and outcomes were compared between PET positive and negative patients, with a comparison with IPS to delineate the most robust prognostic factor. The results of PET essentially made results of IPS inconsequential, with a clear difference between patients with positive and negative PET, with progression-free survivals of 12.8 versus 95 percent, respectively, and only PET was significant for prognosis in multivariate analysis, which included the IPS (Gallamini et al. 2007). Based on this result and promising information from other similar yet smaller reports, most current clinical trials in Hodgkin lymphoma are determining in a prospective fashion the prognostic value of PET/CT. Additionally, many are also testing risk-adapted therapeutic strategies to improve outcomes.

Not only has PET scanning been found to be prognostic in untreated patients as a re-staging strategy, but it has been utilized prior to autologous or allogeneic transplant (Svoboda et al. 2006; Jabbour et al. 2007), with a clear improvement in transplant outcome in those patients with negative functional imaging prior to transplant.

12. Promising therapies of the future

There are many exciting therapies on the horizon for patients with advanced Hodgkin lymphoma. Although none of the treatments discussed below have made their way into the armamentarium for the newly diagnosed patient, the treatments below have been selected as they appear to be associated with the most promise and are furthest in development in relapsed/refractory Hodgkin lymphoma. The most important future therapies, in the opinion of the author, are brentuximab vedotin, rituximab, bendamustine, panobinostat, and lenalidomide. See Table 2. Each will be discussed in further detail in this section.

Brentuximab vedotin, long known as SGN-35, and now known as Adcetris after the United States Food & Drug Administration granted accelerated approval of this antibody-drug conjugate on August 19, 2011, appears to be an important new treatment option in Hodgkin lymphoma. The approval was long awaited by those who had seen multiple failures of unconjugated monoclonal antibodies to CD30, a protein expressed on the surface of Reed Sternberg cells. To specifically enhance clinical anti-tumor activity, the antitubulin agent monomethyl auristatin E was attached to the CD30-specific monoclonal antibody cAC10 by an enzyme-cleavable dipeptide linker (Hamblett et al. 2004). It is indicated for patients with

relapsed or refractory Hodgkin's lymphoma after failure of autologous stem cell transplant or at least two prior multi-agent chemotherapy regimens in patients who are not transplant candidates. The accelerated approval was based on a single-arm, multicenter clinical trial in one hundred two patients with multiply relapsed or refractory Hodgkin lymphoma to evaluate the objective response rate as a single agent. Patients were treated with 1.8 mg/kg intravenously over thirty minutes every three weeks. The primary efficacy endpoint, the overall response rate, was achieved in 73 percent of patients with a complete remission rate of 32 percent. The median duration of response was 6.7 months (Chen et al. 2010). The most common adverse events were peripheral sensory neuropathy, fatigue, nausea, neutropenia, diarrhea, and pyrexia, with most events being grade 1 or 2, and no grade 5 events occurred on treatment. The response rate associated with this agent given as monotherapy is highly encouraging, and further study of this compound is anxiously anticipated. Currently, it is being investigated in a phase I clinical trial in combination with ABVD chemotherapy (Seattle Genetics 2011), and in a phase III randomized clinical trial, AETHERA, in which its use is compared with placebo in "high risk" Hodgkin lymphoma patients post-autologous transplant (Seattle Genetics 2011). This compound appears to represent a major advance in the treatment of Hodgkin lymphoma given the unprecedented response rates in multiply relapsed and highly refractory patient populations.

Rituximab is an intravenous chimeric monoclonal antibody directed at the CD20 antigen, which is present only on a minority of Reed Sternberg or Hodgkin cells of classic Hodgkin lymphoma (Schmid et al. 1991). In spite of this, a pilot study of rituximab was performed in patients with relapsed/refractory classic Hodgkin lymphoma regardless of CD20 status (Younes et al. 2003). In that study, five of twenty-two patients (22 percent) responded with 36 percent achieving stable disease with expected excellent tolerability. Further study by the same investigators at MD Anderson focused on the addition of rituximab to ABVD therapy. One hundred four patients with newly diagnosed advanced disease were treated with six weekly doses of rituximab during ABVD chemotherapy, and their outcomes were compared with historical patients treated with ABVD. The five year event-free survival with ABVD was 66 percent versus a projected 87 percent for R-ABVD with a median follow-up time of five years, and all IPS risk groups seemed to benefit from the addition of rituximab (Copeland et al. 2009). This study generated great excitement, and it is the springboard for two major ongoing advanced Hodgkin lymphoma studies. In the HD18 trial of the GHSG, patients with PET positivity after two cycles of escalated BEACOPP are randomly assigned to further chemotherapy with or without rituximab (University of Cologne 2011). The second trial is a phase II study randomizing patients to R-ABVD versus ABVD at a single institution (M.D. Anderson Cancer Center 2011). In summary, rituximab appears to be a promising step forward with little toxicity in the treatment of advanced classic Hodgkin lymphoma, and the results of the above studies are eagerly anticipated.

In contrast to classic Hodgkin lymphoma, the neoplastic cells, known as the lymphocyte predominant cells of nodular lymphocyte predominant Hodgkin lymphoma, express CD20 strongly. Importantly, several studies indicate that rituximab as a single agent in both previously treated and untreated patients carries a very high response rate in this subtype of Hodgkin lymphoma (Ekstrand et al. 2003; Schulz et al. 2008), and it is reasonable, given the rarity of advanced disease with nodular lymphocyte predominant Hodgkin lymphoma, to utilize rituximab in combination with chemotherapy for patients with this disease.

Bendamustine, an intravenous bifunctional alkylator and nucleoside analogue, was synthesized in East Germany in 1963 but only recently its use has become popularized in the United States with FDA approval for CLL and indolent NHL occurring in 2008. Its activity in Hodgkin lymphoma was well known to the East Germans, and recently Memorial Sloan Kettering investigators put this compound on the international map in Hodgkin lymphoma. Benadmustine was administered at a dose of 120mg/m^2 day one and two of twenty-eight day cycles with pegylated filgrastim support in a single center phase II study of relapsed Hodgkin lymphoma patients post-transplant or transplant-ineligible. Although major conclusions are limited by the small evaluable patient number of sixteen, the overall response rate of 75 percent and CR rate of 38 percent are encouraging, along with twelve of sixteen patients with response becoming eligible for a non-myeloablative allogeneic transplant. Currently, an Italian study is investigating in a phase I/II trial its efficacy and toxicity combined with another promising agent for Hodgkin lymphoma, lenalidomide (Fondazione Giovanni Pascale).

Another promising new compound in the treatment of advanced Hodgkin lymphoma is the oral histone deacetylase inhibitor, panobinostat. Preliminary evidence of activity in refractory Hodgkin lymphoma was demonstrated in a small phase I/II prospective, multicenter study of thirteen patients, and a remarkable response rate of 38 percent was found with computed tomography criteria, with 58 percent of patients responding by positron emission tomography criteria (Dickinson et al. 2009). The principal dose-limiting toxicity with panobinostat is thrombocytopenia, unfortunately, as many patients with relapsed disease have impaired bone marrow reserve. Forty percent of patients in this study developed grade 3/4 thrombocytopenia. In a large multicenter, prospective, phase II study, 40 mg of panobinostat was administered orally three times per week every week in 21 day cycles to one hundred twenty-nine relapsed/refractory patients (Sureda et al. 2010). Responses were observed in 27 percent of patients with 82 percent of patients having stable disease or better. This phase II study, with very promising response rates in a large number of heavily pre-treated patients, has led to a number of current studies in Hodgkin lymphoma, including a phase III study of panobinostat versus placebo for maintenance therapy (Novartis Pharmaceuticals 2011), and a phase I study in combination with ICE and a planned follow-on phase II study of panobinostat plus ICE versus ICE alone (M.D. Anderson Cancer Center 2011).

Lenalidomide is an oral immunomodulatory agent with an uncertain mechanism of action that appears to have activity in a broad range of hematopoietic malignancies. The use of lenalidomide was empiric, and in an initial small cohort of twelve patients with multiply relapsed Hodgkin lymphoma treated in Germany, it was found to be safe with no toxicity greater than grade two. Additionally, it was efficacious with a response rate of fifty percent with at least disease stabilization in all patients (Boll et al. 2010). In a prospective phase II Canadian study, fifteen patients with relapsed/refractory disease were enrolled and given lenalidomide 25 mg orally day 1-21 of 28 day cycles. The overall response rate was 14 percent with at least disease stabilization in 64 percent of patients. Hematologic toxicity was the predominant toxicity seen, with 29 percent of patients with grade 3/4 neutropenia and thrombocytopenia (Kuruvilla et al. 2008). In a similar study conducted by United States investigators, thirty-eight patients were enrolled on a prospective phase II study of relapsed/refractory patients with lenalidomide administered in the same fashion as the prior study (Fehniger et al. 2009). Of thirty-five evaluable patients, the overall response rate

was 17 percent with stabilization of disease for greater than six months in 34 percent. Grade 3/4 toxicity was primarily hematologic, with neutropenia being the most common at 40 percent of patients. The authors concluded that activity was seen and continuous dosing and utilization in combinations would be reasonable in the future. Currently, lenalidomide is under evaluation in phase I studies in combination with benadmustine (Fondazione Giovanni Pascale 2011), AVD (University of Cologne 2011), and as maintenance post-autologous transplant (Washington University School of Medicine).

In summary, there are a number of agents with promising activity in relapsed Hodgkin lymphoma currently in development. Further study will define their ultimate role, but the favorable toxicity profile and encouraging reports of activity of the monoclonal antibodies make these compounds of high interest for further investigation.

Compound	Mechanism	Route	CR, ORR% Median Response Duration	Current Status
Brentuximab Vedotin	Monoclonal Antibody-drug conjugate (anti-CD30)	Intravenous	32%, 78% 6.7 months	FDA approved, relapsed/ refractory Ongoing phase I, III studies
Rituximab	Chimeric monoclonal antibody (anti-CD20)	Intravenous	5%, 22% 7.8 months	Ongoing phase II, III studies
Bendamustine	Bifunctional Alkylator/ nucleoside analog	Intravenous	38%, 75% 2.6 months	Ongoing phase I/II study
Panobinostat	Histone deacetylase inhibitor	Oral	4%, 27% 6.9 months	Ongoing phase I, III studies
Lenalidomide	Immunomodulator (many mechanisms)	Oral	3%, 17% 4.5 months	Ongoing phase I/II studies

Table 2. Promising Drugs in Development for Hodgkin lymphoma.

13. Case studies

In this section, several case scenarios will be presented, and management will be discussed, which integrates material covered in prior sections.

Case 1. A twenty-three year old otherwise healthy Caucasian female was diagnosed with stage IIIB nodular sclerosis Hodgkin lymphoma after an excisional biopsy was performed due to left neck adenopathy. The mediastinum was bulky at diagnosis. The IPS was 1 for anemia. She was treated with six cycles of ABVD at full dose and schedule and achieved a complete

metabolic remission on PET/CT. Fifteen months later, PET/CT revealed asymptomatic FDG avid mediastinal adenopathy, and thoracotomy with excisional biopsy revealed a relapse of nodular sclerosis Hodgkin lymphoma. Hemoglobin was normal. She was treated with ICE for three cycles followed by stem cell mobilization and collection and autologous hematopoietic stem cell transplantation with BEAM conditioning. She receives 36 Gy to the mediastinum two months post-transplant and is alive and well seven years post-transplant.

Case 1 Discussion. This young woman was given a standard of care for advanced Hodgkin lymphoma at diagnosis, and ABVD was favored in this instance over escalated BEACOPP for fertility preservation, as the patient expressed interest in maintaining fertility. The author's preference is to enroll patients with advanced Hodgkin lymphoma on a clinical trial if possible, and currently this would be the SWOG 0816 at the author's institution. The lack of thoracic radiotherapy was reasonable given the PET/CT defined complete remission. This patient's relapse can be classified as low risk by the Josting score as she had none of the the adverse factors which include: early relapse, advanced stage at relapse, and anemia. Therefore, she again received a standard of care including: choice of salvage regimen, decision for autologous transplant, and choice of preparative regimen. The exact value of thoracic radiotherapy administration post-transplant is uncertain but reasonable given the bulky disease of mediastinum initially and the limited stage relapse. The increased risk of solid cancers including breast and lung with thoracic radiotherapy should be discussed with the patient, and long term follow-up should include counseling on smoking cessation, breast and skin examination regularly, breast mammography, and vaccinations yearly for influenza, every five years for pneumococcus, and every ten years for tetanus/diphtheria (Connors 2005).

Case 2. A thirty-five year old otherwise healthy African American male is diagnosed with stage IVA mixed cellularity Hodgkin lymphoma after excisional biopsy is performed of a right inguinal mass. Bone marrow involvement is present at diagnosis and FDG avid lesions are seen in the liver. His International Prognostic Score is 5 with the following risk factors: low albumin, low lymphocyte count, low hemoglobin, stage IV, and male gender. There are no bulky sites of disease. He is treated with escalated BEACOPP for six cycles and achieves a complete remission by PET/CT post-therapy. His PET/CT after two cycles of escalated BEACOPP was negative as well. Five months later, he has biopsy proven relapsed Hodgkin lymphoma after left axillary lymph node enlargement prompts an excisional biopsy. His relapse stage is III, and GDP is administered for three cycles. He achieves a partial metabolic remission on PET/CT with a negative bone marrow biopsy. Organ function is preserved, and he receives a BEAM-conditioned autologous transplant. He suffers another biopsy-proven relapse with stage III disease seven months post autologous transplant. He is treated with IGEV salvage chemotherapy for three cycles, and achieves another partial metabolic response. Given that his organ function is preserved, he undergoes a reduced-intensity allogeneic hematopoietic stem cell transplant with Flu/Bu conditioning. He is alive three years post-allogeneic transplant with mild chronic graft versus host disease.

Case 2 Discussion. This young man was given an appropriate initial therapy, escalated BEACOPP, given his high risk disease. In fact, escalated BEACOPP is reasonable for any advanced Hodgkin lymphoma patient <60 years without pregnancy, HIV, or abnormal organ function regardless of IPS. He was given six cycles rather than the current standard of eight cycles established by the GHSG. Would he still have suffered a relapse if given eight cycles, is it appropriate to administer six cycles in this situation, and is it appropriate to

obtain interim PET/CT scans outside the context of clinical trials? The answer to each of these questions is obviously controversial. The author believes that it is reasonable to perform interim PET/CT scans off study, and to make certain therapeutic decisions on the basis of those scans. Because the PET/CT was negative after two cycles, the author believes that it was a reasonable clinical decision to administer six rather than eight total cycles. Although impossible at present to know, the author believes that it is unlikely that two more cycles of escalated BEACOPP would have cured the case patient. Again, it is the author's strong preference to obtain further prospective data regarding interim PET/CT and therapy adjustment, which is why the optimal treatment for current patients with Hodgkin lymphoma is a clinical trial. The choice of GDP as salvage chemotherapy is very reasonable, as is the choice to take a patient in partial remission to a BEAM conditioned autologous transplant. Given at least three adverse prognostic factors associated with this relapse, which are: early relapse, relapse after high intensity initial chemotherapy, and partial rather than complete metabolic response pre-transplant, the author believes, even though randomized data are not available, that performing a tandem transplant as in the H96 study would have been reasonable in this patient. Once relapse after autologous transplant occurs, prognosis is poor and this case example illustrates that a reduced-intensity allogeneic hematopoietic stem cell transplant can be curative in this setting. In addition to the chronic adverse health effects associated with allogeneic transplant, Hodgkin lymphoma survivors do have persistent challenges in health related quality of life, particularly in regards to chronic fatigue (Baxi and Matasar 2010). This patient would likely benefit from multidisciplinary follow-up care including input from psychiatry and social work.

14. Conclusion

There are many unanswered questions the clinician faces in the care of the individual patient with advanced Hodgkin lymphoma throughout the course of the disease. Polychemotherapy with regimens such as ABVD or escalated BEACOPP for six to eight cycles are the standard of care for newly diagnosed patients, and the role of radiotherapy is uncertain. Refinement of morbidity and mortality related to chemotherapy and radiotherapy may be possible in the future with a sincere commitment of physicians to enroll patients on the current generation of clinical trials testing PET/CT directed strategies. Several newer agents are likely to be incorporated into polychemotherapy in the future based on promising results in the relapsed setting. The goal of therapy in the short term is a PET/CT without FDG avidity, or complete remission, and in the long term a cure. For most patients with relapsed or refractory Hodgkin lymphoma, polychemotherapy for approximately three cycles followed by autologous hematopoietic stem cell transplantation is the current standard of care. Radiotherapy should be considered in the relapsed setting to optimize curative potential of treatment in spite of the potential morbidity and lack of clear evidence base. Reduced intensity allogeneic hematopoietic stem cell transplantation should be considered as the primary curative treatment modality in those patients without significant comorbidity who relapse after autolgous transplantation.

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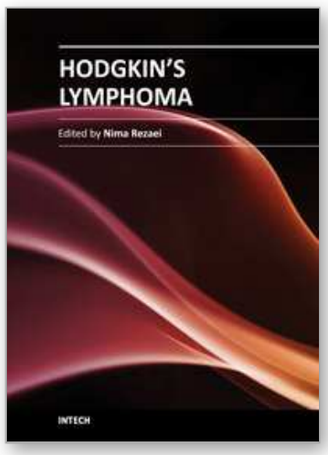

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Hodgkin's Lymphoma is the book consisting of 11 chapters: Recent insights into the biology of Hodgkin's lymphoma, including historical aspects, epidemiology, pathophysiology, genetic defects, and prognostic indicators are explained in the intro chapters. After a translational chapter from tumor microenvironment to immunotherapeutic approach, treatment of early stage, advanced, and refractory Hodgkin's lymphoma are explained in the following chapters. MALT lymphoma and adverse effects of chemotherapy and radiotherapy in the affected patients are discussed in the subsequent chapters, while the final chapter is focused on survivorship in Hodgkin's lymphoma. The book is intended to present recent advances in the pathophysiology of Hodgkin's lymphoma as well as practical approach to diagnosis and management in clinical practice, which is hoped to be welcomed by the physicians, who wish to learn more about Hodgkin's lymphoma.

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