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Therapy for Relapsed and Refractory Pediatric Hodgkin Lymphoma

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1. Introduction

The treatment of Hodgkin lymphoma (HL) has improved dramatically over the past two decades. The reported five-year event free survival ranges between 80 – 90% with combined modality chemotherapy and radiotherapy. However, 10 - 15% of patients with localized disease and 25% of patients with advanced classical Hodgkin Lymphoma (cHL) have recurrent disease after first line treatment. (Lohri, Barnett et al. 1991; Longo, Duffey et al. 1992; Ferme, Mounier et al. 2002). Refractory patients are also problematic occurring in 2 - 5% of patient with low stage (I/II) and 5 – 10% of high stage (III/IV) cHL (Diehl, Franklin et al. 2003). Retrieval of patients with relapsed and refractory Hodgkin Lymphoma (RR-HL) can be achieved with the use of salvage chemotherapy that includes front-line chemotherapy agents and high dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) (Andre, Henry-Amar et al. 1999; Lazarus, Rowlings et al. 1999). This chapter will discuss the various second line therapeutic approaches for retrieval of patients with RR-HL.

2. Prognostic factors and risk stratification at the time of relapse

Several adverse risk factors have been identified to have prognostic significance in patients with RR-HL. In adults as in the pediatric population, time to initial treatment failure is a strong predictor of survival for patients receiving salvage therapy regardless of high dose chemotherapy and ASCT. (Josting, Rueffer et al. 2000; Schellong, Dorffel et al. 2005). Chemosensitivity to induction or salvage therapy prior to HDT and ASCT is also a strong predictor of outcome (Chopra, McMillan et al. 1993), and in fact helps to define subsequent treatment plan. Patients with induction failure at the time of relapse have the worse outcome (Moskowitz, Kewalramani et al. 2004).

Over the past 15 years, two retrospective studies demonstrated that time to relapse, site of relapse, clinical stage at relapse, and the presence of anemia at the time of relapse were significant predictors of outcome (Brice, Bouabdallah et al. 1997; Josting, Engert et al. 2002).

The scoring system developed by Justing et al, demonstrated that time to relapse (<12months vs. > 12 months), clinical stage at relapse (Stage III/IV) and the presence of anemia (< 10.5 g/dL in females, < 12 g/L in males) at the time of relapse were independent

predictors of outcome with a freedom from second failure of 45%, 32% and 18% for patients with 0, 1, 2, or 3 of the above mentioned risk factors, respectively (Josting, Engert et al. 2002).

Another prospective study by Moskowitz et al, indentified the presence of B symptoms, extranodal disease, and less than 12 months to relapse as adverse prognostic factors. They estimated a EFS of 83% for patients with 0-1 adverse prognostic factors, 27% for patients with 2 factors and 10% for patients with 3 factors (Moskowitz, Nimer et al. 2001).

In the pediatric population significant predictors of poor OS and EFS are extranodal disease, mediastinal mass at relapse, stage IV at relapse and primary refractory disease (Lieskovsky, Donaldson et al. 2004; Schellong, Dorffel et al. 2005). In adolescents the presence of B symptoms at the time of relapse confers an 11-year OS of 27% after HDT and ASCT (Akhtar, El Weshi et al. 2010).

The recognition of adverse risk factors at the time of relapse in cHL defines risk group and allows assignment of treatment according to risk stratification. For instance, using time to relapse (> 12 months) and extranodal disease as predictors of outcome, Brice proposes that adult patients with no adverse prognostic factors (favorable risk), should not be exposed to HDT and ASCT to prevent long term toxicity, but instead be treated with conventional chemotherapy such as BEACOPP or MOPP/ABV. Patients with one risk factor (intermediate risk), may benefit from HDT and ASCT +/- Radiation depending on the site of relapse. Finally, patients with two risk factors (high risk for relapse), or those with induction failure or refractory disease, stage IIIB or with anemia required salvage therapy prior to HDT and ASCT (Brice 2008).

In Pediatrics, the identification of prognostic factors is used by individual groups to select therapy, however, there is no agreement across the international groups among a model for risk stratification and treatment assignment according to the prognostic parameters. The EuroNet-PHL-C1 protocol is using this concept and is stratifying patients, depending on time of relapse. Late relapse (< 12 months after primary therapy) is considered low risk, primary progression is high risk and intermediate risk are all other relapses (Daw, Wynn et al. 2011).

Patients with RR-HL regardless of their prognostic factors at the time of relapse/recurrence have several therapeutic options. The role of salvage chemotherapy, high dose therapy followed by ASCT, allogeneic stem cell transplantation (Allo SCT), and other alternatives are discussed below.

3. Salvage chemotherapy regimens (Re-induction chemotherapy)

There is no consensus on the gold-standard second-line chemotherapy for retrieval of RR-HL. Several regimens have been used over the past decades, as summarized in Table 1. This regimes could be classified into:

3.1 Intensive conventional regimens

Mini BEAM (carmustine, etoposide, cytarabine and melphalan); **Dexa - BEAM** (dexamethasone, carmustine, etoposide, cytarabine and melphalan).

3.2 Platinum based regimens

ESHAP (etoposide, methylprednisolone, high dose cytarabine and cisplatin); **DHAP** (dexamethasone, high-dose cytarabine, cisplatin); **APE** (cytarabine, cisplatin, etoposide)

3.3 Ifosfamide-Etoposide based regimens

ICE (ifosfamide, carboplatin, etoposide); **MINE** (mitoxantrone, ifosfamide, vinorelbine and etoposide); **EPIC** (etoposide, prednisolone, ifosfamide, and cisplatin); **OIE** (oxaliplatin, ifosfamide, etoposide); **IEP-ABVD** (ifosfamide, etoposide, prednisolone, adriamycin, bleomycin, vinblastine and dacarbazine).

3.4 Other novel combinations

IGEV (ifosfamide, gemcitabine and vinorelbine), with reported response rates of 65- 85%in RR-HL. **GV** (gemcitabine, vinorelbine).

Selection of the salvage regimen should take into consideration the primary therapy. The ideal regimen would include non-cross-resistant chemotherapy, produce high response rate with acceptable toxicity and allow peripheral stem cell mobilization (Kuruvilla, Keating et al. 2011). The number of chemotherapy cycles prior to ASCT is not known, however most authors advocate for two to four cycles. The goal of salvage chemotherapy is to assess cytoreduction and chemo sensitivity, as those factors are predictors of outcome and define the need of subsequent HDT followed by ASCT. Therefore, salvage chemotherapy should facilitate stem cell harvesting and enable patients to proceed to ASCT.

Disease status before HDT and ASCT is the most important prognostic factor for success as reported by multiple authors (Bierman, Bagin et al. 1993; Andre, Henry-Amar et al. 1999; Popat, Hosing et al. 2004) and discussed previously in this chapter. Response to salvage therapy or response to re-induction chemotherapy prior to high dose chemotherapy is a significant predictor of overall survival (OS) (Yuen, Rosenberg et al. 1997). Sirohi et al reported that patients with complete response prior to transplant, had a 5-year progression-free survival (PFS) rate of 79% compared to 59% for those with partial response and 17% for those with resistant disease (Sirohi, Cunningham et al. 2008).

In the pediatric population several strategies of combined chemotherapeutic regimens have been used in RR-HL. These include the use of ifosfamide, carboplatin and etoposide (ICE) pioneered by Memorial Sloan Kettering Cancer Center (MSKCC), reporting an 88% response rate in a combined trial with adult and pediatric patients with RR-HL. (Moskowitz, Nimer et al. 2001). In Europe the current standard approach for pediatric RR-HL retrieval is alternating IEP-ABVD. Furthermore, this regimen is using response to therapy by using functional imaging with FDG-PET prior to the use of HDT (Daw, Wynn et al. 2011).

In the United States, ICE is the most widely used re-induction treatment option in children and adolescents. Although, the use of ICE can put patients in second remission, it is not optimal, since it is associated to an increased risk of treatment-related secondary malignant neoplasm associated with the use of alkylating agents and epipodophyllotoxins. For this reason the Children's Oncology Group (COG) considering this risk of treatment-related second malignant neoplasms explored other retrieval regimens, such as the combination of ifosfamide with vinorelbine (IV) on their AHOD00P1 protocol. On AHOD00P1, each chemotherapy cycle consisted of Ifosfamide 3000 mg/m2/day during 4 consecutive days

and vinorelbine 25 mg/m2 dose on days 1 and 5. Sixty one of 66 patients (92%) had a response after 2 cycles, and 44 (72%) achieved at least a partial response. More than 90% of the patients completed induction without disease progression. This study showed Ifosfamide/Vinorelbine (IV) regimen to be a safe and effective for reinduction therapy. The toxicity profile was acceptable, with primarily hematologic toxicity (Trippet 2004).

Regimen	Drugs Involved	Response	Reference
Dexa-BEAM	Dexamethasone BCNU Etoposide Cytarabine Melphalan	CR 27% PR 54% ORR 81%	(Schmitz, Pfistner et al. 2002)
Mini-BEAM	BCNU Etoposide Cytarabine Melphalan	CR 49% PR 33% ORR 82%	(Martin, Fernandez-Jimenez et al. 2001)
ICE	Ifosfamide Carboplatin Etoposide	CR 26% PR 59% ORR 85%	(Moskowitz, Nimer et al. 2001)
DHAP Q2 weeks	Dexamethasone High-dose Cytarabine Cisplatin	CR 21% PR 68% ORR 89%	(Josting, Rudolph et al. 2005)
GVD	Gemcitabine Vinorelbine Doxil	CR 19% PR 51% ORR 70%	(Bartlett, Niedzwiecki et al. 2007)
GV	Gemcitabine Vinorelbine	ORR 76%	(Cole, Schwartz et al. 2009)
IEP-ABVD	Ifosfamide Etoposide Prednisolone Adriamycin Bleomycin Vinblastine Dacarbazine	ORR 85%	(Schellong, Dorffel et al. 2005)
IV	Ifosfamide Vinorelbine	ORR 83%	(Bonfante, Santoro et al. 1997)
MINE	Mitoguazone Ifosfamide Vinorelbine Etoposide	ORR 75%	(Ferme, Mounier et al. 2002)

RR-HL: recurrent / relapsed Hodgkin Lymphoma; BCNU: Carmustine; CR: complete remission; PR: partial response; ORR: overall response rate

Table 1. Salvage Chemotherapy Regimens for Patients with RR – HL.

Another alternative regimen tested by the COG as a salvage regimen in pediatric patients with RR-HL is Gemcitabine in combination with Vinorelbine (**GV**). This combination was used by the Memorial Sloan-Kettering Cancer Center (MSKCC) in 13 adults with second relapse after HDT and ASCT. The doses used by MSKCC were Gemcitabine 1275 mg/m2

and 30 mg/m2 of vinorelbine every 21 days. The overall response rate was 62% (6 PR and 2 CR) (Hamlin PA 2002). Ozkaynak also reported a small limited experience in a pediatric series (Ozkaynak and Jayabose 2004). The Children's Oncology Group in the AHOD0321 protocol evaluated the Children's Oncology Group in the AHOD0321 protocol, that looked at the efficacy and toxicity of the combination of gemcitabine/vinorelbine in pediatric cHL patients in in second or greater recurrence. The doses used in the COG study were Gemcitabine 1000 mg/m2/dose on day 1 – 8 and Vinorelbine 25 mg/m2 on day 1 and 8. The study accrued 26 evaluable patients. Of those, 19 were responders (CR or PR). The 2-year EFS and OS were 60% and 87% respectively. The regimen proved to be effective and well tolerated (Cole, Trippett et al. 2007; Cole, Schwartz et al. 2009).

Both of these regimens substantiated the use of these novel approaches as acceptable salvage or re-induction regimen for pediatric patients with RR-HL. These regimens, VI or GV, were very well tolerated with a very acceptable toxicity profile and have the advantage of eliminating the use of etoposide and reducing the increased incidence of treatment-related secondary myelodysplasia and acute myelocytic leukemia associated with this medication.

More recently, COG completed another phase II pilot study (AHOD0521) for RR-HL pediatric patients. The study evaluated the addition of bortezomib, a proteasome inhibitor, to ifosfamide / vinorelbine (IV). The study was designed to test the efficacy and safety of bortezomib as a chemo-sensitizing agent in primary RR-HL in first relapse by comparing the results to the historical data of AHOD00P1 with IV regimen alone. The study accrued 23 evaluable patients with RR-HL in first relapse; 48% (11/23patients) had negative FGD-PET scans after 2 cycles. The overall response after 4 cycles of chemotherapy was 89%. Fourteen patients (74%) achieved complete response, and 3 (16%) had a partial response. Four patients had progressive disease and went off protocol. The 2-year EFS and overall survival were 69 and 87%, respectively, demonstrated better results than with ifosfamide/vinorelbine alone (Horton 2010).

Another single-institution pediatric trial has used a combination of Methotrexate, Ifosfamide, etoposide and dexamethasone for children with RR-HL, with an overall response of 84% (Sandlund, Pui et al. 2011).

Table 2. demonstrates the most recent salvage chemotherapy regimens introduced by COG, and provides detail of their schema, chemotherapy doses and timing of administration.

Although all of the salvage regimens produce remission rates in the range of 50 – 65% for RR-HL, they are not curative and the disease free survival (DFS) remains low for this group of patients. Addition of more intensive chemotherapy regimens followed by stem cell rescue has shown to improve DFS compared to salvage chemotherapy alone (Linch, Winfield et al. 1993; Schmitz, Pfistner et al. 2002).

4. High Dose Therapy (HDT) as conditioning regime for ASCT

The current standard therapy for RR-HL, after re-induction or salvage chemotherapy, is high dose therapy (HDT) followed by autologous stem cell transplantation (ASCT). The two landmark studies that proved that high dose chemotherapy followed by ASCT improved survival were conducted by the British National Lymphoma Investigation Group lead by Linch in 1993. This small randomized clinical trial for patients with RR-HL compared BEAM (carmustine, etoposide, cytarabine and melphalan) followed by ASCT vs. mini-BEAM alone.

The 3-year event free survival (EFS) was 53% in the first group and 10% in the second group. (Linch, Winfield et al. 1993).

Later in 2002, the German Hodgkin Lymphoma Study Group performed a larger randomized study that included 161 patients. All patients received Dexa-BEAM (dexamethasone, carmustine, etoposide, cytarabine and melphalan) for 2 cycles. Patients with complete or partial response where randomized to receive two additional cycles of Dexa-BEAM vs. high dose BEAM followed by ASCT. The 3-year failure free survival (FFS) was 55% in the transplant group compared to 34% in the Dexa-BEAM group (Schmitz, Pfistner et al. 2002).

Josting et al compared intensification of the pre ASCT conditioning regimen, by using two cycles of DHAP (dexamethasone, high-dose cytarabine, cisplatin) followed by ASCT vs. DHAP plus cyclophosphamide, high dose MTX, vincristine and etoposide. The 30 months freedom from treatment failure (FFTF) was 69% with no difference in the two arms (Josting, Rudolph et al. 2005).

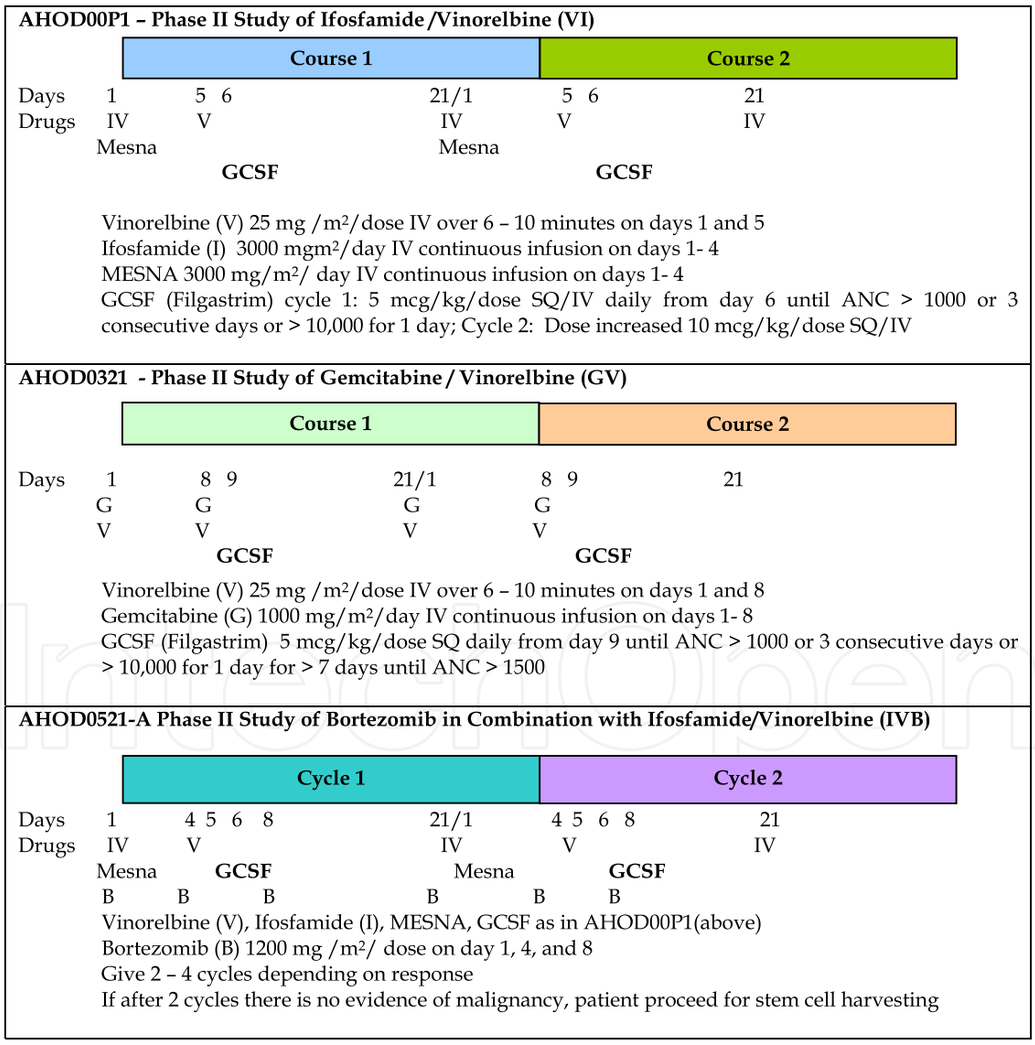


Table 2. Pediatric Salvage Chemotherapy Regimen for Relapsed / Recurrent Hodgkin Lymphoma.

Although the outcome with HDT followed by ASCT has proven superior to salvage chemotherapy alone, nospecific regimen has shown to be superior. Comparing toxicity and efficacy of the various conditioning regimen using HDT prior to ASCT is somewhat difficult, because the doses used in each of the trials are different. For comparison, Table 3 contrasts the specific chemotherapy doses.

Group	Regimen Name	Regimen Drugs +and Doses	Outcome	Reference
British National Lymphoma Investigation Group1993	BEAM + ASCT	Carmustine: 300 mg/m² x1 Etoposide: 800 mg/m² x1 Cytarabine: 1600 mg/m² x1 Melphalan: 140 mg/m² x1	3-year-EFS 53%	(Linch, Winfield et al. 1993)
	Mini-BEAM	BCNU /Carmustine:60 mg/m² Etoposide: 300 mg/m² Cytarabine: 800 mg/m² Melphalan: 30 mg/m2	3-year-EFS 10%	
German Hodgkin Lymphoma Study Group 2002	Dexa-BEAM	Dexamethasone 24 mg x 10 Carmustine 60 mg/m² x Etoposide 250 mg/m² x 4 Cytarabine 200 mg/m² IV x 4 Melphalan 20 mg/m² x 1	3-year –FF2F 34%	(Schmitz, Pfistner et al. 2002)
	BEAM + ASCT	Carmustine 300 mg/m² x 1 Etoposide 300 mg/m² x 4 Cytarabine 400 mg/m² x 4 Melphalan 140 mg/m² x1	3-year-FF2F 54%	
German Hodgkin Lymphoma Study Group 2005	DHAP + ASCT	Dexamethasone 40 mg/m² x 4 HD-Cytarabine 4000mg/m² x 2 Cisplatin 100 mg/m² x 1	Median Follow up 30 months FFTF 59% OS 78%	(Josting, Rudolph et al. 2005)
	DHAP x 2 + CPM, HD-MTX, VCR ETO	Dexamethasone 40 mg/m² x 4 HD-Cytarabine 4000mg/m² x 2 Cisplatin 100 mg/m² x 1 Cyclophosphamide 4 g/m² High dose MTX 8 g/m² Vincristine 1.4 g/m² Etoposide 2500 mg/m²		
	BEAM + ASCT	Bendamustine 200 mg /m² Etoposide 800 mg/m² Cytarabine 1600 mg/m² Melphalan 140 mg/m²	Median DFS 19 months	(Visani, Malerba et al. 2011)

EFS: event free survival; FF2F: freedom from second failure; FFTF: freedom from treatment failure; DFS: disease free survival ; ASCT autologous stem cell transplantation

Table 3. High Dose Therapy as Conditioning Regimen Prior to ASCT Comparative Doses.

It is important to recognized that although carmustine (BCNU)-containing regimens are the most widely used as conditioning regimen for the treatment of RR-HL, there are some major pitfalls such as a high incidence of interstitial pneumonitis or idiopathic pneumonia (2- 23%), a

still high incidence of relapse, and the risk of non-relapse related death (Seiden, Elias et al. 1992; Reece, Nevill et al. 1999; Alessandrino, Bernasconi et al. 2000). In addition, the increase of secondary malignancies after treatment with alkylating agents and epidophylotoxins is of great concern, particularly in children and adolescents and young adults (AYA). For these reasons the search for new and optimal conditioning regimens continues.

In search for this optimal conditional regimen, Visai et al. recently presented the results of a phase I / II trial using BeEAM (bendamustine, etoposide, cytarabine and melphalan) as a conditioning regimen for ASCT in patients with lymphomas. The phase I study used escalating doses of bendamustine (160 mg/m^2, 180 mg/m^2 and 200 mg/m^2). This study included 15 HL patients out of the 43. None of the 43 patients had dose limiting toxicities. The regimen was well tolerated with minimal treatment related mortality. Although the regimen seemed to have worked better for non-Hodgkin lymphoma (NHL) patients, the median DFS for HL patients was 19 months after ASCT. The major limitations of this study is the small number of patients with HL, and therefore this regimen warrants further studies to confirm the efficacy of this novel regimen in the treatment of RR-HL (Visani, Malerba et al. 2011).

Even with the use of HDT and ASCT approximately 50% of patients continue to have refractory disease or recur after ASCT (Chopra, McMillan et al. 1993) so that more effective therapy is still needed.

In Pediatrics, the use of HDT and ASCT is reserved for patients with high risk for relapse or those with primary progressive disease. There is very little evidence to support the use of this approach in first relapse for children and adolescents. The implementation of this approach in the pediatric population has been adapted from the adult experience described above.

5. Tandem autologous transplantation

The use of tandem autologous transplants seem to have a role for a subset of patients with RR-HL and certain risk factors at the time of initial salvage therapy.

Brice et al used two different conditioning regimen CBV (cyclophosphamide, carmustine, etoposide) vs. CBV (cyclophosphamide, carmustine, etoposide) plus mitoxantrone (30 mg/m^2) for the first ASCT and a second conditioning regimen with total body irradiation (TBI) of 12 Gy or busulfan (12 mg/kg) followed by high dose cytarabine (6 g/m^2) and melphalan (140 mg/m^2). The two-year survival rate from the date of progression were respectively at 65% and at 74%.(Brice, Divine et al. 1999)

A US group lead by Fung used a preparative regimen of melphalan (150 mg/m^2) and a second preparative regimen with fractionated TBI (1200cGy) or carmustine (450 mg/m^2) plus etoposide (60mg/kg) and cyclophosphamide (100mg/kg). This US group reported a 5-year FF2F of 55% and a OS of 54% suggesting that in patients with primary progressive or poor risk recurrent HL, tandem ASCT is well tolerated and compares favorably with the conventional single transplant. (Fung, Stiff et al. 2007).

Castagna et al investigated the feasibility and toxicity of ifosfamide, gemcitabine and vinorelbine (IGEV) as salvage therapy followed by two tandem ASCT using melphalan

(200mg/m^2) alone as the first conditioning regimen and BEAM as the second conditioning regimen. The response rate increased with each step, from 47% after salvage chemotherapy, to 65% after first ASCT to 75% after second transplant. The 3-year FFP was 63% and the OS was 72% (Castagna, Magagnoli et al. 2007).

The Group d'Etude des Lymphomes de L'adulte (GELA) tested the feasibility of tandem ASCT vs. single ASCT in patients with primary refractory disease or high risk for relapse as defined by the presence of at least two of the following three adverse risk factors: 1) relapse in a previous radiation field, 2) stage III/IV at the time of relapse or 3) time to relapse < 12 months; or intermediate-risk patients those with one risk factor. Intermediate risk patients received single ASCT showing a FF2F and OS of 73% and 85%, respectively. High risk patients received tandem ASCT with a FF2F and OS of 46% and 57% respectively, which was comparable to previous reports. The results of this study suggest that single ASCT is appropriate for intermediate-risk patients, and that high risk patients with RR-HL may benefit of tandem ASCT (Morschhauser, Brice et al. 2008). In spite of these encouraging results the use of tandem ASCT for RR-HL is still considered experimental.

6. Second autologous transplants

For patients who relapse after a previous ASCT a second auto graft is a viable option, although very limited data exist to support this strategy (Smith, van Besien et al. 2008). This option can be considered as a treatment alternative in patient with a time to relapse > 1 year after the initial transplant. Allografting after ASCT in general is not recommended (Kuruvilla, Keating et al. 2011). Nonetheless, it can still be used in certain circumstances as described below.

7. Allogeneic stem cell transplantation

In the past, allogeneic stem cell transplant (Allo-SCT) offered a chance for a better disease free survival (DFS) but the procedure associated mortality has negated this advantage yielding a worse event free survival. ASCT substituted allo-SCT due to this high treatment-related mortality and the non-infrequent incidence of relapse. However, the introduction of reduced-intensity chemotherapy (RIC) as the preparative regimen for allogeneic transplantation has improved the safety of the procedure. RIC allo-SCT is now being considered an effective approach for selected patients, including those who have failed HDT with ASCT, or for patients with bone marrow involvement at relapse or insufficient stem-cell collection for a second HDT (Brice 2008; Salit, Bishop et al. 2010). Although, the feasibility of RIC allo-SCT has improved, there is still a lack of durable response (Peggs, Sureda et al. 2007; Devetten, Hari et al. 2009). The use of a RIC allo-SCT strategy is best used within the context of prospective clinical trials, as its use remain highly controversial.

8. Standard-dose chemotherapy

A non-ASCT-based strategy has a role in some patients with late relapse (>1 year after completion of induction chemotherapy) and chemo sensitive disease. The Italian group lead by Bonfante found an 8-year freedom from second progression (FF2P) and OS of 53% and 62% respectively in patients treated with mechlorethamine, vincristine, procarbazine,

prednisone (MOPP) and Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) (Bonfante, Santoro et al. 1997). The German group demonstrated good results for patient with the above mentioned characteristics treated with IEP-ABVD regimen followed by radiation therapy to nodal regions involved at the time of relapse and original regions had they not been irradiate. A 10-year DFS and OS was 57% and 75% respectively was reported (Schellong, Dorffel et al. 2005).

9. Role of radiotherapy for RR-HL

Radiotherapy alone can achieve long-term remission, but only in a small proportion of patients. Radiotherapy (RT) is used less as a first line therapy in RR-HL due to its limited efficacy in patients with advanced disease. In some ongoing pediatric clinical trials the use of RT has been omitted from the upfront therapy for patients with good response to initial chemotherapy. Therefore, some patients may be radiation naïve at the time of relapse or have received only limited RT. This fact, makes the use of RT at the time of relapse an attractive alternative for certain relapsed patients, particularly the ones with limited stage disease and relapse at the site of original disease only.

Josting et al reported a 5-year freedom from treatment failure (FFTF) and OS of 29% and 51% respectively for RR-HL treated with radiotherapy alone. The presence of B symptoms, advanced stage (III/IV) at relapse, Karnofsky of < 90% were identified as poor prognostic factors for those patients (Josting, Nogova et al. 2005).

10. Role of chemotherapy plus radiation without ASCT

Combined modality therapy with multi-agent chemotherapy followed by radiotherapy is the standard treatment for limited-stage HL (Press, LeBlanc et al. 2001; Engert, Franklin et al. 2007; Ferme, Eghbali et al. 2007). This modality is particularly attractive for patients who have not received radiotherapy with prior treatment or have relapsed with disease in sites that have not previously been radiated (Press, LeBlanc et al. 2001; Kuruvilla, Keating et al. 2011). Radiotherapy can also be given to patients with RR-HL and bulky disease after standard HDT therapy and ASCT.

Kurovilla et al suggested the use of standard dose chemotherapy plus radiotherapy as a salvage therapy for patients with very late relapse (>5 years) after primary therapy who suffer localized relapse without B symptoms (Kuruvilla, Keating et al. 2011)

11. Salvage therapies following ASCT

More than 50% of patients with RR-HL will not be cured, either because their tumors are not chemotherapy sensitive to proceed with ASCT or because they do not achieve a durable response after ASCT. For those patients, single or combined conventional therapies that can provide disease control such as Gemcitabine / Vinorelbine or Vinorelbine / Ifosfamide plus bortezomib are possible re-induction regimens. As previously mentioned an allo-RIC SCT is also an alternative and should always be considered when in the context of a prospective clinical trial.

The Children's Oncology Group, in the US is performing a trial to evaluate immunomodulation after HDT and ASCT. The study had two parts. The first one is to

determine toxicity and feasibility of administering cyclosporine, interferon-γ, and interleukin-2 following BEAM chemotherapy with ASCT. The second part aims to assess whether greater levels of autologous GVHD and/or autoreactive cytolytic lymphocytes are associated with improved survival, whether expression of the target molecule of autologous GVHD is associated with improved survival, and whether immunotherapy can produce better outcomes in patients identified as having high risk disease on the basis of high serum levels of interleukin-10 or soluble interleukin-2 receptor. The results of this trial have not been reported yet.

12. New agents

The development of novel drugs for the treatment of cHL has been slow partially due to the high success rate of the treatment of the disease. However, the better understanding of the pathology, biology and immunology has allow the introduction of several therapeutic targets. This new drug development not only is aiming for better survival but also to decrease toxic effects.

12.1 Antibody/receptor therapy

One of the defining features of cHL is CD30 expression by Reed-Stenberg cells. The use of an anti-CD30 molecule has been an attractive target in the treatment for HL (Forero-Torres, Leonard et al. 2009). Several anti CD30 antibodies have been engineered: MDX-060 (Medarex) a fully humanized antibody to CD30 (SGN-30), a chimeric monoclonal anti-CD30 antibody, both have shown to inhibit cell proliferation and to induce cell death in CD30 positive lymphomas. However, when used alone they were not effective as single agents, showing response rates much lower than traditional cytotoxic chemotherapy.

Newer generation of anti-CD30 antibodies with enhanced Fc receptor-antibody activity (Medarex, MDX-1401) and with antibody-drug conjugates are currently under study (Foyil and Bartlett 2010).

The recent introduction of a conjugated anti-CD30 antibody conjugated to the antitubuline agent, Brentuximab Vedotin, (SGN-35) has shown excellent results in CD30 positive lymphomas. In a phase I, open label, multicenter dose-escalation study published in the New England Journal of Medicine, 42 evaluable patients with refractory CD30 lymphomas demonstrated tumor regression of 86%. (Younes, Bartlett et al. 2010). An additional phase II clinical trials using Brentuximab Vedotin intravenously at a dose of 1.8 mg/kg every 3 weeks was reported at ASCO in 2011. The study found a response of 75% (76 out of 102) in patient with HL, with a complete remission in 34% of them. The average duration of response was 6.7 months. The excellent results of these studies resulted in the recent FDA approval of Brentuximab Vedotin for the treatment of patients with HL whose disease has progressed after autologous stem cell transplant, or after two prior multiagent chemotherapy treatments among patients ineligible to receive a transplant. Prospective studies in the pediatric population are warranted.

The use of the anti-CD20 antibody, Rituximab, has demonstrated excellent activity against nodular lymphocyte predominant HL (NLPHL) with overall response rates of 94% (Ekstrand, Lucas et al. 2003; Rehwald, Schulz et al. 2003). Rituximab is currently being studied in cHL (Younes, Romaguera et al. 2003).

12.2 Radioimmunotherapy (RIT)

Radioimmunotherapy uses the concept of targeted antibodies, typically antiferritin and anti-CD30 to deliver radiation with Yttrium-90 or iodine-131 to the tumor cells (Klimm, Schnell et al. 2005). The use of polyclonal antibodies, Ytrium 90-labelled antiferritin, In-labeled antiferritin antibody recently became available. They have been well tolerated and have shown activity in RR-HL with a response of approximately 8 months. Other attempts to increase the efficacy of antiCD30 monoclonal antibody include conjugation with Iodine-131 (Schnell, Dietlein et al. 2005).

The German group has developed an antiCD25 also known as anti IL-2 receptor (Daclizumab) and anti-CD25 linked to Ytrium-90. CD25 is found in a large proportion of Hodgkin Reed Stenberg cells and in the surrounding tumor-associated T-cell and therefore represents an attractive target therapy. Some preliminary studies using Y-90-CD25 (90Y-daclizumab) every 6 – 10 weeks yielded an overall response of 70% (O'Mahony D. Janik JE 2007).

12.3 Antiapoptotic molecules

Other novel pharmacological approaches include inhibition of NF-kB pathway. NF-kB is a transcription factor that is constitutively activated in HL, and that is thought to be responsible for cell proliferation and antiapoptosis in HL (Pajonk, Pajonk et al. 2000).

Bortezomib (Velcade) is a proteasome inhibitor that also inhibits NF-kB pathway. Bortezomib has shown some limited efficacy when used as a single agent or in combination with dexamethasone (Younes, Pro et al. 2006; Trelle, Sezer et al. 2007). However, NF-kB inhibition is postulated to sensitize malignant cells to chemotherapy, including Gemcitabine (Moskowitz, Nimer et al. 2001), TNF-related apoptosis-inducing ligand (TRAIL) (Zheng, Georgakis et al. 2004), dexamethasone and vinorelbine (Hinz, Lemke et al. 2002). Inhibition of the antiapoptotic molecule XIAP has shown some encouraging results in preclinical studies (LaCasse, Cherton-Horvat et al. 2006). As mentioned above the Children's Oncology Group recently completed a study that assess the safety of bortezomib in addition to ifosfamide / vinorelbine, the preliminary data suggest that bortezomib may have added additional efficacy to the backbone regimen of ifosfamide and vinorelbine .

12.4 Transcriptional pathways

The use of other molecules that are mediators of apoptosis, such as the histone deacetylase (HDAC) inhibitors in HL is currently under investigation. Some of these are Panobinostat, Vorinostat, Entinosat. A phase II study demonstrated 40% response in patients with RR-HL (Younes 2007; Jona and Younes 2010).

M-TOR inhibitors, particularly everolimus, have also shown some promising results with up to 42% overall response rate in patients with RR-HL (Johnston PB 2007) . The small molecule Nutlin 3A, stabilizes p53 protein via MDM2 binding, allowing to activate apoptotic pathways in Hodgkin Reed Stenberg cells (Drakos, Thomaides et al. 2007). This three novel molecules may have an interesting potential therapeutic intervention in cHL.

12.5 EBV-directed therapy

Nearly 50% of cHL patients are known to be EBV positive, making the use of EBV-targeted therapy very attractive. EBV specific cytotoxic T lymphocytes (CTL) can be generated in

vitro and then given to the patients with the intent of targeting specific EBV-infected cancer cells. Portis et al demonstrated that by using this technology 30% of treated patients achieved a complete remission (Portis and Longnecker 2004).

13. Conclusions

The treatment of RR-HL has improved over the years. The use of HDT followed by ASCT has allow 50% of patients to have durable remission. However, the management of the patient with refractory disease is a real challenge. Treatment intensification with traditional chemotherapy agents is not sufficient and new approaches are needed. As the armamentarium for the treatment of patients that have failed initial therapy continuous to expand, we are foreseeing novel treatment modalities. Some of such agents, particularly the biologically target agents, have the potential to be incorporated into front line therapy of cHL as they may have a better therapeutic profile than our current cytotoxic chemotherapy agents. The use of novel biological and targeted therapies is very attractive for the retrieval of patients with RR-HL. As we develop a better understanding of the biology of cHL, we are likely to see more effective treatment strategies that will overcome resistance, and reduced short and long term toxicity for patients with primary and refractory cHL.

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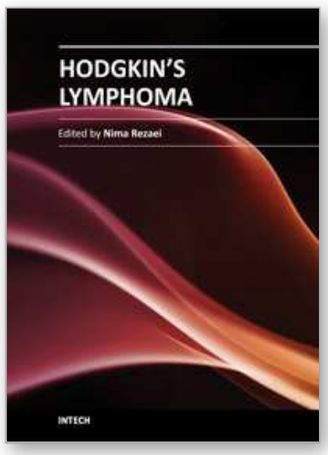
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Hodgkin's Lymphoma is the book consisting of 11 chapters: Recent insights into the biology of Hodgkin's lymphoma, including historical aspects, epidemiology, pathophysiology, genetic defects, and prognostic indicators are explained in the intro chapters. 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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