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Review Article

Treatment of Newly Diagnosed and Relapsed Hodgkin Lymphoma in Children

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ABSTRACT

Hodgkin lymphoma (HL) accounts for about 10% of all childhood cancers. Five-year survival rates with modern therapies are now approaching >90-95% as a consequence of its significant sensitivity to both chemotherapy and radiation. The current challenge is to determine how much therapy is needed to improve survival and how to adapt treatment to the patient to prevent these long term toxicities. This challenge has resulted in the development of different strategies aimed at recognizing the optimal balance between preserving overall survival and avoidance of long-term treatment-related morbidity. Strategies in children could be quite different from those used for adults with HL. More defined risk stratification through imaging studies and biologic markers have been developped. Increased knowledge of the biology of HL have led to the introduction of targeted therapies in both the frontline and relapsed patients. Collaborative multicenter studies are required to develop new combination therapies for children with newly diagnosed and refractory HL.

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Introduction

Hodgkin lymphoma (HL) accounts for about 10% of all childhood cancers. Five-year survival rates with modern therapies are now approaching >90-95% as a consequence of its significant sensitivity to both chemotherapy and radiation. However, the risks of late effects associated with radiation and chemotherapy including infertility, second cancers and cardiac deaths have become more widely recognized. Treatment decisions are increasingly based on minimizing late effects and long-term treatment related mortality.[1] The current challenge is to determine how much therapy is needed to ensure survival and how to tailor treatment to the individual to prevent these long term toxicities.

Newly diagnosed Hodgkin Lymphoma

The use of systemic combined chemotherapy in children allowed physicians to successfully reduce the radiation fields from total nodal irradiation (used in the 70s) to involved fields (involved and adjacent nodes) and since the last decade to involved nodes only. Simultaneously, doses were progressively reduced from 40 Gy to 20 and even 15 Gy without sacrificing clinical outcomes.[2,3]

Classical Approach

Until recently, the treatment plan (type and duration of chemotherapy, doses and fields of radiation) was determined by initial stage of the disease with some modifications only if a complete response had not been achieved by the end of the treatment regimen. To minimize exposure of all children to high cumulative doses of anthracyclines and exposure of boys to high dose of alkylating agents, a variety of combination chemotherapy protocols with efficacy equivalent to that of the original MOPP regimen were invented with increased number of agents and limiting cumulative dose of individual agents (table 1). Combination regimens include ABVD, ABVD alternating with MOPP[2], COPP/ABV[4], VAMP[3], VBVP[5], ABVE-PC[6], OPPA or OEPA plus COPP[7]. Protocols in Europe and America using these chemotherapy regimens

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Table 1: Combination chemotherapy regimens Acronym Agents
ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine
AV-PC: Doxorubicin, vincristine, prednisone, cyclophosphamide
COPP/ABV: Cyclophosphamide, vincristine, procarbazine, and prednisone, alternating with doxorubicin, bleomycin, and vinblastine in a single course
MOPP: Nitrogen mustard, vincristine, procarbazine, prednisone
OEPA: Vincristine, etoposide, prednisone, doxorubicin OPPA Vincristine, procarbazine, prednisone, doxorubicin VAMP Vinblastine, doxorubicin, methotrexate, prednisone VBVP Vinblastine, bleomycin, etoposide, prednisone VEEP Vincristine, etoposide, epirubicin, prednisone
ABVE-PC: Adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide

in combination with IFRT have demonstrated event-free survival (EFS) rates greater than 90%.

Response-Based Approaches

Response based approaches have now become the standard approach in pediatric HL and decisions are taken according to the response to chemotherapy.

Decisions Regarding Radiation Therapy

The First HL trials in pediatrics relied on complete response (CR) to determine the need for radiation in addition to chemotherapy. The Children's Cancer Group (CCG)[4] and the German Pediatric Hodgkin's Disease Study Group (GPOH-HD)[7] both used CR assessment at the end of therapy to either randomly assign patients to radiation versus no radiation (CCG) or to eliminate radiation (GPOH).

The chemotherapy protocol included four to six cycles of COPP/ABV with intensified cytarabine and etoposide for stage IV disease on the CCG study. The CCG study was halted because of increased risk of relapse in non-radiated patients versus radiated patients (3-year event-free survival 87% versus 92%; P<0.057). However, these results suggested that disease control may be achieved without radiation in 85%-90% of HL patients and the overall survival was similar for both radiated and non-radiated children.[4]

The GPOH-HD 95 multicenter trial used two to six cycles of OPPA (adriamycin, vincristine, procarbazine, and prednisone)/COPP for girls and OEPA (adriamycin, vincristine, etoposide, and prednisone)/COPP for boys, with radiation dose determined by end-of-chemotherapy response. Overall, the results were excellent, but EFS was higher among intermediate (TG2) and high-risk (TG3) patients treated with involved field radiation therapy (IFRT) versus those who did not receive IFRT.[7]

Decisions Regarding the Intensity of Chemotherapy

The French Society of Pediatric Oncology study (MDH90) addressed the question of intensification of chemotherapy in early slow responder patients and dose of radiation therapy in late slow responder patients. In that study, 202 children with stage I or II HL were treated with four cycles of vinblastine, bleomycin, etoposide, prednisone (VBVP). Good responders (85% of the patients) received only four cycles of VBVP and 20 Gy IFRT alone. They did not receive anthracyclines or alkylating agents and so had a low risk of long-term gonadal toxicity. Poor responders were given an additional one to two cycles of OPPA and then either 20 Gy IFRT (good responders at second evaluation) or 40 Gy IFRT (poor responders). The 5-year OS and EFS were 97.5% and 91.1%, respectively.[5]

The COG study P9425 was based on early response to limit cumulative chemotherapy in advanced-stage HL patients and to enhance early response through a dose-dense chemotherapy regimen (adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC). Early response, defined by gallium scan and computed tomography (CT; 50% 2-dimensional reduction), was evaluated after three cycles (9 weeks) of chemotherapy. Rapid early response (RER) was documented in 63% of patients who proceeded to 21 Gy IFRT. Slow early responders (SER) received two additional courses of ABVE-PC, followed by 21 Gy IFRT. Five-year EFS and OS were 84% and 95%, respectively. No difference in outcome was distinguishable for "rapid early response" group versus "slow early response" group (86% vs. 83%; P<0.85), thus achieving the goal of delivering optimal therapy titrated to the need of an individual within the context of a clinical trial.[6]

Implementation of the Early Response to FDG-PET Scan for Therapeutic Decision

The 18F-fluorodeoxyglucose positron emission tomography with computerized tomography (FDG-PET/CT) is a functional imaging modality that has become a standard tool complementing contrast enhanced CT (CECT) scans in the diagnosis and management of HL. Evaluation of the disease with FDG-PET scan before chemotherapy identifies the correct pretreatment stage in HL more accurately compared with CECT. One study of patients with early-stage HL showed that 36% of lymph nodes detected by PET were radiographically occult on CT scan.[8] However, FDG-PET/CT is reported to upstage the disease from early to advanced stage in only 10–15% of patients in whom treatment is ultimately modified.[9,10]

FDG-PET scan has showed the prognostic value of early response in treatment of HL. In a prospective study of 88 patients with early-stage non bulky HL uniformly treated with a chemotherapy regimen of AVG (doxorubicin, vinblastine, gemcitabine), 2-year PFS rates were 88% and 54% for negative and positive FDG-PET groups, respectively (P=0.0009).[11]

The European pediatric (EuroNet-PHL-C1, figure 1) has tried a procarbazine-free protocol and tailored treatment

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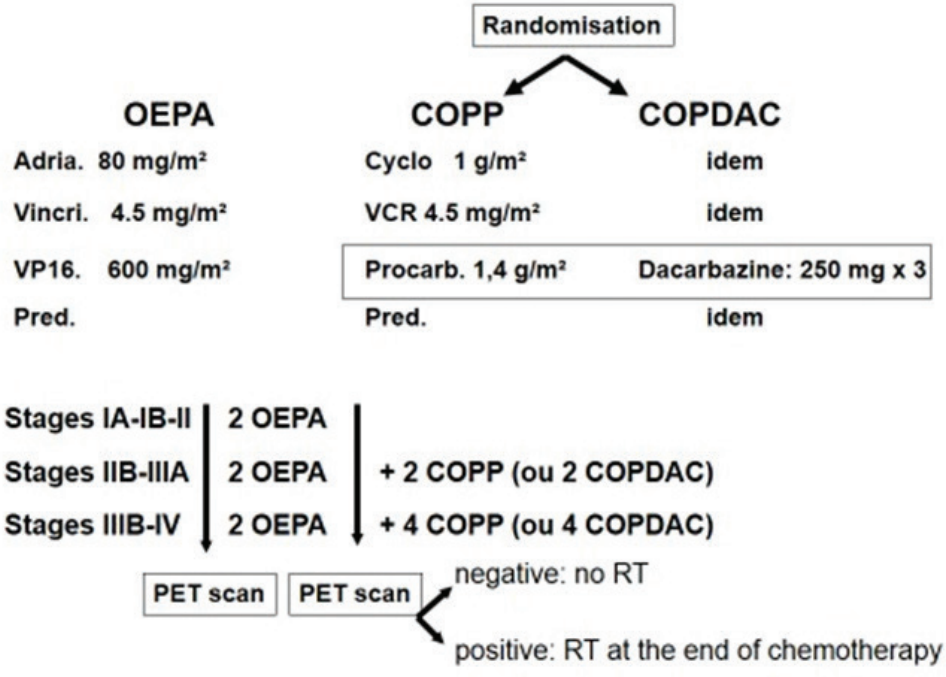

Figure 1: First European study EuroNet-PHL-C1
17-AAG=Geldanamycin; AKT=AKT kinase; ERK=Extracellular signal regulated kinase; HDACs=Histone deacetylases; HRS=Hodgkin and Reed-Sternberg cell; JAK=Janus kinases; MMAE=Monomethylauristatin E; mTOR=Mammalian target of rapamycin; NF-KB=Nuclear factor kappa B; STAT=Signal transducer and activator of transcription

according to the early metabolic response (depicted by FDG-PET scan after two courses of chemotherapy) attempting to minimize the proportion of children receiving radiation therapy. Patients with an adequate response after 2 OEPA courses (roughly: CR or PR but PET-negative) were not irradiated, whatever the treatment groups. Patients with higher stages than IIA were randomly assigned to receive either the standard COPP protocol or COPDAC in which dacarbazine replaces Procarbazine. By October 2012, 2033 patients had been registered into the trial of whom 1593 were eligible for the third interim analysis. COPP and COPDAC appeared similarly efficacious and COPDAC was considered as a new standard consolidation treatment in HL. Half of the patients did not receive RT and there was no difference in outcome of patients treated with or without radiation therapy. Table 2 gives an overview of the Euronet protocol and the adult protocols (EORTC/LYSA/ FIL[13] and GHSG German groups) which tailored treatment according to the metabolic response (FDG-PET) after two courses of chemotherapy. Adult protocols were designed not only to reduce the indications of RT but also to select poor responding patients who might benefit from a shift to a more intensive approach.

Due to an unexpected excess of relapses occurring on the no-RT arms of EORTC/LYSA/FIL Intergroup H10 trial, the authors decided to stop enrollment in the early PET-negative part of the study and to maintain combined modality treatment as standard for early PET-negative scans.[13] These results means that RT after initial chemotherapy marginally improves the progression free survival over chemotherapy alone but at the expense of irradiating all "PET 'negative" patients; most of whom are already cured. The recently published UK study showed that in patients with stage IA-IIA HL, and PET negative after 3 cycles of ABVD, the addition of radiotherapy slightly improves their PFS rate but has no impact on their overall survival.[14] The German HD16 and HD17 are still open to accrual.

Patients with Relapsed Hodgkin Lymphoma

Patients with relapsed HL should be identified according to their prognostic factors at relapse: end-of-treatment to first progression interval <12 months versus >12 months, extranodal disease, stage and treatment given at first diagnosis (duration and intensity of chemotherapy, relapse in or outside the previously irradiated site). Presence of B-symptoms and anemia at the time of relapse proposed by the GHSG may be more accurate but represents rare events. This enables relapsing patients to be categorized in different prognostic groups.

All relapsed HL should receive second-line chemotherapy which the response could be crucial for determining the outcome. No existing randomized trial has compared the effectiveness of salvage regimens as second-line treatment for HL. These regimens have varied according to the initial chemotherapy the patient has received; for instance the given cumulative dose of anthracyclines has already reached or not. Most groups have used platinum-based regimens, such as ASHAP (doxorubicin, methylprednisolone, high-dose cytarabine, cisplatin)[15] and/or DHAP (dexamethasone, high-dose cytarabine,

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Table 2: Salvage chemotherapy for Hodgkin lymphoma

Reference	Regimen	No. patients	Overall response rate
Rodriguez et al[15]	ASHAP	56	66%
Josting et al[16]	DHAP	57	80%
Brice et al[17]	IVA	43	60%
Ferme et al[18]	MINE	83	74%
Moskowitz et al[19]	ICE	65	88%
Santoro et al[20]	IGEV	91	81%
Schellong et al[21]	IEP-ABVD	176 children	85%
Linch et al[22]	Mini-BEAM	55	82%
Schmitz et al[23]	dexaBEAM	161	80%

ASHAP: doxorubicin, methylprednisolone, high-dose cytarabine, cisplatin; DHAP: dexamethasone, high-dose cytarabine, cisplatin; IVA: ifosfamide, etoposide, doxorubicin; MINE: mitoguazone, ifosfamide, vinorelbine, etoposide; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IEP-ABVD: ifosfamide, etoposide and prednisone alternating with doxorubicin, bleomycin, vinblastine and dacarbazine; MiniBEAM: carmustine, etoposide, cytarabine, melphalan; dexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan

cisplatin)[16] or ifosfamide/etoposide-based regimens such as IVA (ifosfamide, etoposide, doxorubicin),[17] MINE (mitoguazone, ifosfamide, vinorelbine, etoposide),[18] ICE (ifosfamide, carboplatin, etoposide),[19] IGEV (ifosfamide, gemcitabine, vinorelbine)[20] or IEP-ABVD (ifosfamide, etoposide and prednisone alternating with ABVD) for children[21] to introduce other drugs.

Intensive pre-transplant regimens, such as mini-BEAM (carmustine, etoposide, cytarabine, melphalan)[22] and dexaBEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan)[23] have severe hematological toxicity and have a 2–5% rate of toxic death.

Overall response rates (ORR) [CR and partial response (PR) >50%] of some prospective pre-transplant salvage regimens are reported in table 2; ORR ranged from 60% to 88%. RT can be used in limited cases of relapse which occur outside the initial radiation field. It can also be given after ASCT to limited fields.

High-dose chemotherapy and autologous stem-cell transplantation after standard salvage therapy is indicated for high risk patients (progression during or up to six months after first line treatment). In all other patients (early relapse or late relapse of stage IIB-III or IV), chemosensitivity to salvage conventional chemotherapy is crucial and best evaluated by FDG-PET after 2 cycles. This early evaluation decides whether this salvage chemotherapy can be continued for 2 other cycles and completed with radiotherapy (adequate response) or treatment needs to be intensified with high dose chemotherapy and autologous stem cell transplantation (inadequate or unclear response). BEAM is the most widely used conditioning regimen for relapsed HL and only little available data support the use of total body irradiation in this setting.

Role of allogeneic SCT in patients with relapsed and refractory HL remains highly controversial. The results of several studies suggested that allogenic SCT might be associated with a clinically significant graft-versus-HL effect and a lower relapse rate with respect to autologous stem cell transplant (ASCT).[24] In one study, allogeneic bone marrow transplantation was compared with autologous bone marrow transplantation using the data from the European Bone Marrow Transplantation (EBMT) registry.[25] Allografted patients (n=45) were matched to patients (n=45) who underwent ASCT based on risk factors. Allogeneic transplantation did not appear to offer any advantage when compared with ASCT in terms of progression or relapse free survival and also overall survival because of a very high transplant related mortality mainly associated with acute and chronic graft-versus-host disease and concomitant infectious episodes. The recent emphasis on reduced intensity conditioning (RIC) with allogenic SCT has gained recently interest in this procedure and could be considered an effective therapeutic approach for patients who have suffered treatment failure with a previous ASCT, those with bone marrow involvement at relapse or insufficient stem-cell collection for a second high-dose chemotherapy. Other indications should be conducted only in prospective protocols mostly regarding the role of RIC after high-dose chemotherapy and ASCT for poor-prognosis relapse as proposed by the EBMT group.[26] There is no standard treatment for patients relapsing after high-dose chemotherapy and ASCT. The decision how to treat these patients has to be made individually. New drugs are being developed in recent years that may change the management of relapsed and refractory Hodgkin lymphoma patients

Monoclonal Antibodies

SGN-35 or brentuximab vedotin is an anti CD30 antibody directed to CD30-bearing lymphomas, which include HL as well as anaplastic large cell lymphoma (ALCL). CD30 membrane glycoprotein belonging to the TNF family is not usually detected in normal tissue outside the immune system except in a small fraction of B, T or eosinophils, which makes it an ideal target for treatment with monoclonal antibodies (moAb). Anti CD30 antibody is inactive in HL but the same antibody linked to an antitubulin toxin (auristatin E) appears to

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be a very active agent, the most active salvage agent ever tested in relapsed and/or refractory HL with a response rate of 75%, 34% complete remission in this population.[27] (The previously introduced new active agent for HL was gemcitabine, introduced in 2000 with less single-drug activity than brentuximab vedotin. In the initial two trials, there was a 37% response rate with 8.5% complete remissions.) Despite its exciting antitumor activity for HL, the cost of brentuximab vedotin will add considerably to the current expense of systemic therapy and the question remains that how these agents could best be combined with known active chemotherapeutic agents to improve initial response rate and durability of remission, especially in patients with advanced-stage disease. Ultimately, the question is that if this added agent results in a significant improved overall survival. The convincing evidence can only be derived from prospective randomized clinical trials that analyze precisely the additive value of the new agent. These will be essential because we seem to be entering a new era of anticancer drug based on cost and effectiveness. Safety and effectiveness of brentuximab vedotin in patients below the age of 18 has not been established.

Approximately 25% of Reed-Sternberg cells express CD20 on their cell surface. It is also postulated that the surrounding B lymphocytes which express CD20 may contribute to the survival of the Reed-Sternberg cells. Therefore, rituximab may have a role in treatment of HL by removing the supporting B cells. A pilot study of rituximab in patients with recurrent, classic HL, regardless of whether Reed-Sternberg cells expressed CD20, was conducted.[28] In total, 22 patients with nodular sclerosis histology were evaluable for treatment response. Five patients (22%) achieved remission (one CR and four PR). A phase 2 trial of the German Hodgkin Lymphoma Study Group evaluated the safety and efficacy of rituximab in patients with relapsed lymphocyte-predominant Hodgkin lymphoma or other CD20 (+) subtypes of Hodgkin disease (HD). The overall response in 14 assessable patients was 86%, with 8 complete remissions and 4 partial remissions, and 2 patients with progressive disease.[29]

Yttrium-90 radiolabeled humanized monoclonal antibody to CD25 (^{90}Y-labeled daclizumab) has been evaluated in 46 patients with relapsed and refractory HL. There were 9 CR and 14 PRs. Interestingly, many of the responses were seen in patients with CD25-negative malignant cells but with surrounding CD25-positive T cells within the tumor microenvironment.[30]

Other Novel Agents

HRS cells aberrantly express a variety of pro-survival proteins, such as nuclear factor- kappaB (NF-kappaB), Jak/STATs, Akt/mTOR, Notch-1 and extracellular signal-regulated kinase (ERK), that can be targeted by small molecules. These proteins can be targeted either by selective small-molecule inhibitors such as Jak-2, mTOR and B-cell lymphoma (Bcl)-2 family inhibitors or by broad inhibitors that modulate several unrelated molecules, such as histone deacetylase (HDAC), proteasome inhibitors and heat shock protein 90 (HSP90) inhibitors.

Several of the agents belonging to the histone deacetylase inhibitors are being employed in early clinical trials in relapsing HL. They have an antiproliferative effect on Hodgkin cells and possibly an immune-mediated effect. Panobinostat, is one of those. In contrast to brentuximab vendotin, panobinostat is an oral drug that is administered three times a week in 21-day cycles. In a phase II study, there was notable activity with a response rate of 21.7%; however, there was some reduction in tumor size in 74% of patients. Nevertheless, its high myelotoxicity would certainly limit the ability to combine panobinostat with other myelotoxic drugs.[31]

Lenalidomide, a derivate of thalidomide is thought to be an immunomodulating agent. Its mechanism of action is to interact with the microenvironment of the tumor; it has anti-angiogenic and immunomodulating properties and induces directly the death of malignant B cells. The microenvironment definitely plays variable beneficial roles in HL survival with production of cytokines, interleukins and TGFβ and existence of regulatory T-lymphocytes. Lenalidomide has been evaluated in patients with relapsed and refractory HL. In the first study, 15 patients were treated of whom12 patients were evaluated; there were one CR and three PRs.[32] In another study; among 14 evaluable patients, two PR were observed with no CR.[33]

Conclusion

Despite the high curability rate of HL, there is still a huge space for improving the treatment of refractory or relapsed patients. There are a list of drugs in clinical trials demonstrating benefit against HL, but it is certainly too soon to know whether all these drugs will contribute to improving survival more than the customary treatments we use for these patients. We also need to go deeper into the understanding and handling of toxicity and interactions with other drugs and, finally, how to rationalize their use and make this sustainable in the current economic situation.

Conflict of Interest: None declared.

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