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Treatment of relapsed and refractory Hodgkin Lymphoma

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ABSTRACT

Despite the high first-line cure rates in patients with Hodgkin Lymphoma (HL) still 10%–20% of patients suffer from relapsed or refractory disease. High-dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT) is standard of care for suitable patients with relapsed or refractory HL and allows for cure in approximately 50%. Due to the poor prognosis of high-risk patients even with HDCT and ASCT, consolidation strategies have been evaluated to improve the cure rates. For patients with recurrence after HDCT and ASCT, treatment is palliative in most cases. The anti-CD30 antibody–drug conjugate brentuximab vedotin (BV) has been shown to induce high response rates in these patients; however, durable responses were reported in a small percentage of patients only. For carefully selected patients with multiple relapses, dose-reduced allogeneic transplant (RICallo) is a potentially curative option. The role of RICallo will have to be re-evaluated in the era of anti-programmed death-1 (PD1) antibodies.

1. Introduction

More than 80% of patients with Hodgkin lymphoma (HL) achieve long-term cure with current polychemotherapies and additional radiotherapy where indicated [1–4]. Even approximately 50% of patients with relapsed or refractory disease after first-line therapy can be cured with high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) followed by optional consolidation in high-risk patients [5–7]. After post-ASCT recurrence the antibody-drug conjugate (ADC) brentuximab vedotin (BV) has shown high efficacy and good tolerability [8]; however, long-term remissions ware observed in a small percentage of patients only. New combinations of BV with established drugs are currently being evaluated to further improve the outcome of patients with relapsed or refractory HL. This article summarizes the current standard of care and emerging data in the management of relapsed or refractory classical HL in patients eligible for HDCT and ASCT. The management of other subgroups and new drugs are discussed separately in this issue of *Seminars in Hematology*.

2. Standard of care in first relapsed and refractory HL

2.1. HDCT—evidence from randomized trials

Because results with conventional chemotherapy were disappointing in patients with first relapsed or refractory HL, HDCT followed by ASCT was evaluated in this setting. Two prospective, randomized trials have defined the current standard of care in the treatment of relapsed and refractory HL [9,10]. The British National Lymphoma Investigation (BNLI) [9] trial randomized 40 patients who had not responded to first-line chemotherapy to either conventional chemotherapy (mini-BEAM: 60 mg/m² carmustine, 300 mg/m² etoposide, 800 mg/m² cytarabine, 30 mg/m² melphalan every 3 weeks for up to three cycles, standard group, 20 patients) or HDCT (BEAM: 300 mg/m² carmustine, 800 mg/m² etoposide, 1.600 mg/m² cytarabine, 140 mg/m² melphalan, experimental group, 20 patients) followed by ASCT support. The joint German Hodgkin Study Group (GHSG)/ European Group for Blood and Marrow Transplantation (EBMT) HD-R1 trial [10] randomized 161 patients with relapse after polychemotherapy to either HDCT plus ASCT (88 patients) or to conventional chemotherapy (73 patients). All patients in this trial received two cycles of Dexa-BEAM consisting of 240 mg dexamethasone, 60 mg/m² carmustine, 1,000 mg/m² etoposide, 800 mg/m² cytarabine, and 20 mg/m² melphalan. Chemosensitive patients were then randomized to either BEAM plus ASCT (300 mg/m² carmustine, 1,200 mg/m² etoposide, 1,600 mg/m² cytarabine, and 140 mg/m² melphalan,

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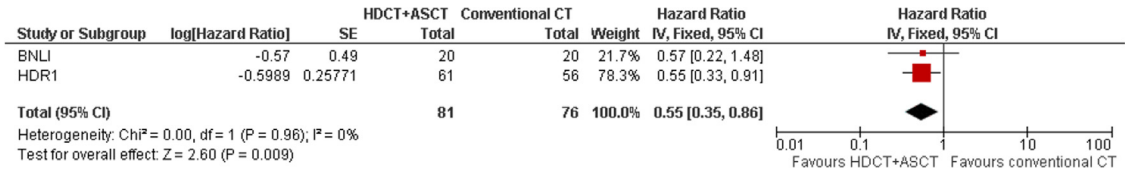

Fig. 1. Meta-analysis of trials comparing conventional chemotherapy (CT) with high-dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT) in relapsed Hodgkin lymphoma: forest plot of comparison of progression-free survival (PFS).

61 patients) or to two further cycles of Dexa-BEAM (56 patients), each after at least partial remission (PR) and hematologic recovery was shown through restaging. In both the BNLI and the HD-R1 trial patients with residual masses were allowed to receive radiotherapy, which was performed in 17 and 11 patients in the BNLI and HD-R1 trials, respectively. Both trials showed a significant superiority of HDCT in terms of event-free survival (EFS)/freedom from treatment failure (FFTF) but failed to show a significant overall survival (OS) benefit. Three-year rates were 53% versus 10% (EFS, $P = .005$) in the BNLI and 55% versus 34% (FFTF, $P = .019$) in the HD-R1 trial. Recently, a meta-analysis of the two trials using updated follow-up information was performed by the Cochrane Group for Hematological Malignancies (CHMG) [11] With a median follow-up of 34 and 83 months for BNLI and HD-R1, respectively, progression-free survival (PFS) was significantly improved in patients who were treated with HDCT plus ASCT compared to those treated with conventional chemotherapy (hazard ratio [HR] 0.55; 95% confidence interval [CI] 0.35–0.86, $P = .009$, Fig. 1). However, the available evidence from the two trials was not sufficiently powered to show a statistically significant difference between HDCT plus ASCT and conventional chemotherapy in terms of OS (HR 0.67; 95% CI 0.41–1.07, $P = .1$, Fig. 2). Nevertheless, the tendency towards an OS benefit of HDCT plus ASCT is considerable and the absence of a statistically significant OS benefit is most likely due to the small patient number in the two trials. Moreover, supportive care in patients receiving HDCT and ASCT has improved in the last years, which presumably further increases the advantage of HDCT over conventional therapy. HDCT is widely accepted as standard of care in first relapsed and refractory HL.

2.2. Salvage chemotherapy

Conventional re-induction chemotherapy, often referred to as salvage therapy, is standard of care before administration of HDCT. It allows for a tumor reduction before ASCT and several reports have shown that the response to salvage therapy before ASCT is predictive for the final outcome [12,13]. From a straight evidence-based point of view, Dexa-BEAM should be the standard salvage regimen because it was used in the randomized HD-R1 trial that established HDCT as standard of care in relapse or refractory HL [10]. However, Dexa-BEAM is hardly used today because it has a relatively high treatment-related mortality (TRM) as compared to newer salvage combinations and is stem cell toxic leading to an inadequate stem cell harvest in many cases [14,15]. Owing to the lack of prospective, randomized trials comparing different salvage regimens the optimal choice of a salvage regimen is unclear. The ICE (5 g/m² ifosfamide, area under the curve [AUC] 5 carboplatin, 300 mg/m² etoposide) chemotherapy regimen, which is regularly administered as an inpatient treatment for two cycles, has become the standard salvage used in the United States [16]. In prospective clinical trials, the complete response (CR) rate was approximately 50% and the overall response rate (ORR) was approximately 80%. For patients with unfavorable risk factors an augmented dosing has been evaluated (10 g/m² ifosfamide, AUC 5 carboplatin, 600 mg/m² etoposide) [16]. Cytarabine-based regimens such as DHAP (160 mg dexamethasone, 4,000 mg/m² high dose ara-C [cytarabine], 100 mg/m² cisplatin) and ESHAP (160 mg/m² etoposide, 2,000 mg methylprednisolone, 2,000 mg/m² high dose ara-C [cytarabine], 100 mg/m² cisplatin) have demonstrated similar response rates as compared to ICE[17,18]. The GHSG and other European cooperative groups regard DHAP as standard salvage regimen. The optimal cycle length of platin-based salvage chemotherapies has not been analyzed in prospective trials; however, a recent retrospective analysis of the GHSG showed that dose density of DHAP induction therapy is an independent prognostic factor for PFS and OS in relapsed HL [19]. Therefore, salvage chemotherapy should be administered in a dose dense way, where possible.

In the large randomized HD-R2 trial with 241 patients with relapsed HL, sequential high-dose chemotherapy (SHDCT) after DHAP before BEAM was compared to conventional DHAP plus BEAM [20]. However, FFTF and OS were not different in the two groups whereas patients treated with SHDCT had longer treatment duration and experienced more toxicity. Therefore, SHDCT before HDCT and ASCT is not a suitable strategy in patients with relapsed HL.

Gemcitabine-based chemotherapy regimens have been evaluated as alternative salvage regimens. The advantages of gemcitabine-based regimens are good tolerability and easier outpatient administration. GVD (2,000 mg/m² gemcitabine, 40 mg/m² vinorelbine, and 30 mg/m² pegylated liposomal doxorubicin in transplant-naïve patients) was evaluated in 91 patients with relapsed or refractory HL and ORR was 70%, albeit with a modest 19% CR rate based on computed tomography (CT) imaging [21]. Another program, IGEV (8000 mg/m² ifosfamide, 400mg prednisolone, 1600 mg/m² gemcitabine, and 20 mg/m² vinorelbine) was administered to 91 patients of which 49 (54%) achieved a CR and 25 patients (27.5%) had a PR for an ORR of 81.3%, based upon positron emission tomography (PET) imaging [22]. Lastly, Kuruvilla et al retrospectively compared GDP (2,000 mg/m² gemcitabine, 40 mg dexamethasone, and 75 mg/m² cisplatin) with mini-BEAM; response rates were similar but GDP was far less toxic [23].

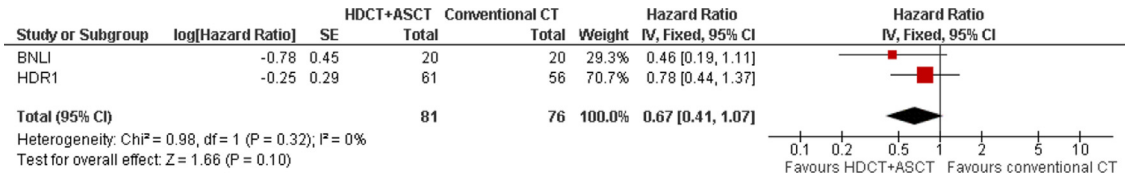

Fig. 2. Meta-analysis of trials comparing conventional chemotherapy (CT) with high-dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT) in relapsed Hodgkin lymphoma: forest plot of comparison of overall survival (OS).