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Treatment of patients with Hodgkin lymphoma after disease relapse or progression – chemosensitivity, transplantation and targeted therapy

Léčba pacientů s Hodgkinovým lymfomem po relapsu nebo progresi onemocnění – chemosenzitivita, transplantace a cílená léčba

Novosad O., Rudiuk T.

Oncohaematology Department, National Cancer Institute, Kyiv, Ukraine

SUMMARY: Today, Hodgkin lymphoma (HL) is considered a curable disease, since up to 90% of patients with early stage and 70–80% with advanced stage disease achieve long-term remission after first line treatment. Approximately 15–25% of patients with HL have primary refractory disease or relapse after responding to first line therapy. About half of these patients are diagnosed with chemosensitivity and/or relapse after transplantation. High-dose chemotherapy with autologous stem cell transplantation is highly effective in patients with refractory disease or relapse; contributing to long-term survival in a significant number of patients. Patients with high-risk disease, who were treated on time and did not achieve a sufficient response to standard first-line therapy, or patients with chemo-sensitive relapse, have a good prognosis. However, high-dose chemotherapy followed by autologous stem cell transplantation is not a well-established option in patients with primary refractory disease or with chemo-resistant relapse. Allogeneic hematopoietic cell transplant and/or targeted immunotherapy represent the options for this group of patients.

KEY WORDS: Hodgkin lymphoma – relapse – chemosensitivity – transplantation – targeted therapy

SOUHRN: Dnes se Hodgkinův lymfom (HL) považuje za vyléčitelnou nemoc, protože až 90 % pacientů v časném stadiu a 70–80 % v pokročilých stadiích onemocnění dosáhne po léčbě první linie dlouhodobé remise. Přibližně 15–25 % pacientů s HL má primárně refrakterní nemoc nebo zrelabuje poté, co dosáhne odpověď po léčbě první linie. Přibližně polovina těchto nemocných je chemozenzitivních a/nebo zrelabuje po transplantaci. Vysocedávkovaná chemoterapie s autologní transplantací kmenových buněk má u pacientů s refrakterním onemocněním nebo relapsem vysokou účinnost a přispívá k dlouhodobému přežívání u významného počtu nemocných. Pacienti s vysoce rizikovým onemocněním, kteří byli léčeni načas a nedosáhli dostatečnou odpověď po standardní léčbě první linie nebo pacienti s chemozenzitivním relapsem mají dobrou prognózu. Na druhé straně, vysocedávkovaná chemoterapie následovaná autologní transplantací kmenových buněk není optimální možností u pacientů s primárně refrakterním onemocněním nebo s chemorezistentním relapsem. Alogenní transplantace krvetvorných buněk a/nebo cílená imunoterapie reprezentují léčebné možnosti pro tuto skupinu nemocných.

KLÍČOVÁ SLOVA: Hodgkinův lymfom – relaps – chemosensitivita – transplantace – cílená léčba

INTRODUCTION

Today, Hodgkin lymphoma (HL) is considered a curable disease, since up to 90% of patients with early stage and 70–80% with advanced stage disease achieve a long-term remission after first line treatment [1–4]. The incidence of HL worldwide is about 2.2 cases per 100,000 people, and the mortality of patients with disease lasting less than one year is about 9%.

About 15–25% of patients with HL relapse after responding to first line therapy, and approximately half of these are diagnosed with chemosensitivity and/or relapse after transplantation (rrHL).

The National Cancer Registry of Ukraine reports the incidence of HL in Ukraine as approximately 2.4 cases per 100,000 people; the mortality of patients with disease lasting less than one year is approximately

16.3% [5]. Unfortunately, Ukraine has no reliable data on the total number of patients with HL relapse. However, two centres report that in 2021, disease progression was recorded in about 222 patients (52% – late or early relapse, 48% – primary refractory cases). The National Cancer Institute's local database reports a trend toward the reduction of the number of new cases of rrHL; in particular: 53 cases in 2015 compared to the 14 cases in 2021.

Over the past few years, significant progress in treatment methods has contributed to the long-term survival of patients with relapsed or primary refractory HL.

ROLE OF AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH RELAPSED OR REFRACTORY HL

The results of two randomized trials have shown that second-line chemotherapy (salvage therapy) followed by high-dose chemotherapy (HDCT) and ASCT for patients with rrHL remains the standard treatment which improves the level of progression-free survival (PFS) [6,7]. Various combined "salvage" regimens have now been developed, including ifosfamide, carboplatin, and etoposide (ICE); dexamethasone, cytarabine and cisplatin (DHAP); etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP); gemcitabine, dexamethasone and cisplatin; gemcitabine, vinorelbine and liposomal doxorubicin (GVD). These regimens are standard for second-line treatment; however, none is superior to the other.

Patients who achieve a complete response to salvage therapy prior to ASCT, have a better clinical outcome compared to patients who achieve partial remission, or in the case of relapse, those who progress to a refractory form. Thus, C. H. Moskowitz and co-authors in the analysis of 75 patients found substantially higher PFS and the overall survival (OS) rates in patients who responded to second-line treatment with standard doses after relapse, compared to those who had a poor response (66 vs. 17% and 62 vs. 23%; P < 0.001, respectively) [8].

B. Sirohi, D. Cunningham, and others found in a prospective analysis that OS was significantly higher in patients with complete response (CR) after salvage therapy, compared to the group of patients with partial response (PR) and with rrHL at the time of ASCT (5-year OS was 79 vs. 59 vs. 17%; P < 0.0001). The respective 5-year rates of PFS were 69 vs. 44 vs. 14%; P < 0.0001 [9].

In a phase II study, C. H. Moskowitz and others evaluated salvage therapy based on the ICE regimen prior to ASCT and the possibility of achieving PR in association with the following risk factors at the relapse: B-symptoms, extranodal lesions, or relapse within 1 year after the start of treatment. It was found that patients with two or more risk factors had a substantially lower chance of achieving CR according to the ICE diagram [10]. In a subsequent study, it was found that the non-favourable prognosis related to these factors could be improved by using the aICE regimen (brentuximab vedotin – BV, ifosfamide, carboplatin, and etoposide) [11].

Very recently, new targeted drugs have been incorporated into treatment regimens in order to achieve a better response to ASCT, given the importance of obtaining a negative positron emission tomography (PET) result on the Deauville five-point scale. Back in 2012 in their phase II study, C. H. Moskowitz, M. J. Matasar and others demonstrated that if a patient achieved PET-negative status prior to ASCT, the PFS rate was 80% compared to 29% in PET-positive patients [12]. Other studies confirmed that a PET-negative status prior to ASCT is one of the most important predictors of a positive result after ASCT [13,14].

NEW APPLICATION FOR BV TO ACHIEVE BETTER RESPONSE PRIOR TO ASCT

Given its superior results vis a vis treatment response, the United States Food and Drug Administration (FDA) approved BV as maintenance therapy after ASCT in patients with early progression risk factors.

Risk factors of early relapse after ASCT include: duration of first remission < 1 year or primary refractory disease, the presence of extranodal lesions or the abnormal site of recurrence at relapse, the absence of chemosensitivity to second-line treatment, and the presence of residual activity of fluorodeoxyglucose on PET imaging [15]. Currently, the 2 combinations of BV and platinum regimens are considered be promising: BV + DHAP and BV + ESHAP (BRESHAP). The rapid achievement of metabolic CR in 79% of cases with BV + DHAP implies the need to further study this regimen and the long-term results of this treatment [16].

Moreover, the study by the Spanish group GELTAMO further demonstrated the potential of combining BV with chemotherapy prior to ASCT. After approximately 27 months of follow-up, 74% of patients reached a PFS rate of 71%, and the OS rate constituted 91% [17].

The combination of BV and bendamustine showed to be a similarly highly active salvage-therapy for patients with rrHL according to the results of a phase I/ II study, where the overall response rate was 93% due to the achievement of CR (in 74% of cases) after 2 cycles of treatment [18].

Additionally, the work of A. F. Herrera, A. J. Moskowitz and co-authors, presented positive interim results of a phase I/II study using 4 cycles of BV in combination with nivolumab as the initial salvage-therapy for patients with rrHL. The overall response rate of treated patients (N = 61) was 82% due to the CR in 61% of the patients [19].

ROLE OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT (ALLO-SCT) AND TARGETED THERAPY IN RRHL PATIENT TREATMENT

Chemo-refractory (chemo-sensitive) relapse is defined as progression or stabilization of the disease after two courses of

aggressive 2nd line treatment. The question of whether the HDCT with ASCT is reasonable in patients with first or subsequent relapse or primary refractory disease is complex, due to the lack of uniform criteria for determining chemorefractory disease in various clinical studies. The Board of the International Consensus Conference on High-Dose Therapy with Hematopoietic Stem Cell Transplant in Aggressive NHL, held in April 1998, agreed that HDCT with ASCT is not recommended during the first or subsequent relapse [20]. On the other hand, a small group of patients with primary refractory disease may benefit from HDCT with ASCT [21–24]. That is, some patients with insufficient response after induction therapy can still achieve long-term progression-free survival without HDCT with ASCT.

Allo-SCT remains the therapeutic method with the highest cure rate for patients with multiple rrHL, when the donor immune system is used to prevent relapse. Data results on bone marrow allogeneic transplantation have been already discussed in detail in various scientific articles [25]. An important factor for allogeneic bone marrow transplant is donor availability. Over the past years, several studies have evaluated or considered the use of haploidentical donors, and obtained some encouraging results [26–29]. Practically all patients will have a donor, provided haploidentical sources and sources of umbilical blood are available, which is no longer a limiting factor for allo-SCT [26,27,30–32]. Recently, the European Society for Blood and Bone Marrow Transplant conducted a registry study of 709 patients (haploidentical, N = 98; match-related donors, N = 338; and corresponding unrelated donor, N = 273), where no significant differences were found in PFS or OS between the individual donor types [27]. As these results expand the possibilities of donor selection, the priority of patient selection and transplant-related toxicity come into the fore for achieving positive results. Prior to the development of new treatment methods, the median survival of patients with HL relapse after ASCT was 25 months [33].

In recent years, 2 classes of drugs have dramatically changed the landscape of patients with rrHL. Today, many new drugs are being investigated precisely for the treatment of patients with relapse after ASCT, with approval of BV and checkpoint inhibitors – CPIs of nivolumab and pembrolizumab [34–36].

The multicentre phase II study (Checkmate 205) included only patients with HL relapse after ASCT and BV, and showed a total response rate of 68% (13% CR, 55% PR) with nivolumab at 3 mg/kg every 2 weeks [37]. With a minimum follow-up of 23 months, the median PFS was 14.8 months with 1-year PFS of 54.6%, and 1-year OS of 94.9% [38]. The median time to response was 2.1 months, and the median duration of response was 16 months. Patient quality of life improved during the course of treatment with nivolumab, and adverse events were rare, mostly in the form of grade 1 and 2 reactions at the infusion site in 20% of patients. Serious adverse events included pneumonitis and autoimmune hepatitis, which were reported in 1 patient.

The Keynote-013 (Ib phase) study included patients with classical HL who progressed after BV and who received 10 mg/kg of pembrolizumab every 2 weeks until disease progression [39]. Important adverse events were observed in some patients, including grade 1–2 hypothyroidism in 16%, thyroiditis in 6%, and pneumonitis in 10% of patients. In the Keynote-087 clinical trial, pembrolizumab was administered to patients at a fixed dose of 200 mg once every 3 weeks for 24 months [40]. The overall response for all patients was 69% (22% CR and 47% PR).

The OS rate was 73.9% in patients with progression after ASCT + BV (N = 69), 64.2% in those who did not qualify for ASCT due to chemo-resistant disease after 2nd line treatment and BV (N = 81), and 70% in patients with progression after ASCT, who did not receive BV as remission consolidation (N = 60; 41% of patients received radiation treatment prior to ASCT). After 6 months, the PFS rate was 72.4% and the OS was 99.5%, though the mean duration of response, and OS was not reached in all the cohorts. Similar to nivolumab, there was a substantial improvement in patient quality of life. Low-grade hypothyroidism was the most frequent immune adverse event (13.8%).

Similarly, monoclonal antibodies including humanized IgG1, atezolizumab and fully human IgG1, avelumab, and durvalumab have been developed against the PD-L1 ligand. However, the treatment results and efficiency are still being studied.

In the phase I study, avelumab (NCT02603419) was evaluated in patients with HL who are not eligible for transplant or have relapsed after ASCT or allo-SCT [41]. The OS for all patients who were unable to undergo transplant was 54.8% (6.5% CR and 48.4% PR), including 8 patients after allo-SCT. Histone deacetylase inhibitors, including mocetinostat, panobinostat, and vorinostat, showed OS levels of 4–59%, although with a low incidence of complete remissions and limiting toxicity [42–45].

Therefore, considerations regarding the timing, efficacy and toxicity of new drugs remain the priority. In 2022, a patient is unlikely to undergo a transplant without prior administration of BV and/or CPIs.

G. Shah and C. Moskowitz suggested the following recommendations for rrHL post-ASCT patients [46]: for patients who did not receive BV in the previous line of treatment, it remains a highly active choice in the event of first relapse post-ASCT, as CR frequency with BV is higher than CR frequency with CPI. The authors believe that those patients should be referred for an allo-SCT consultation during the initiation of CPI treatment.

If patients achieve CR with CPI, the same treatment is recommended for an additional 3 months. If CR remains, it is

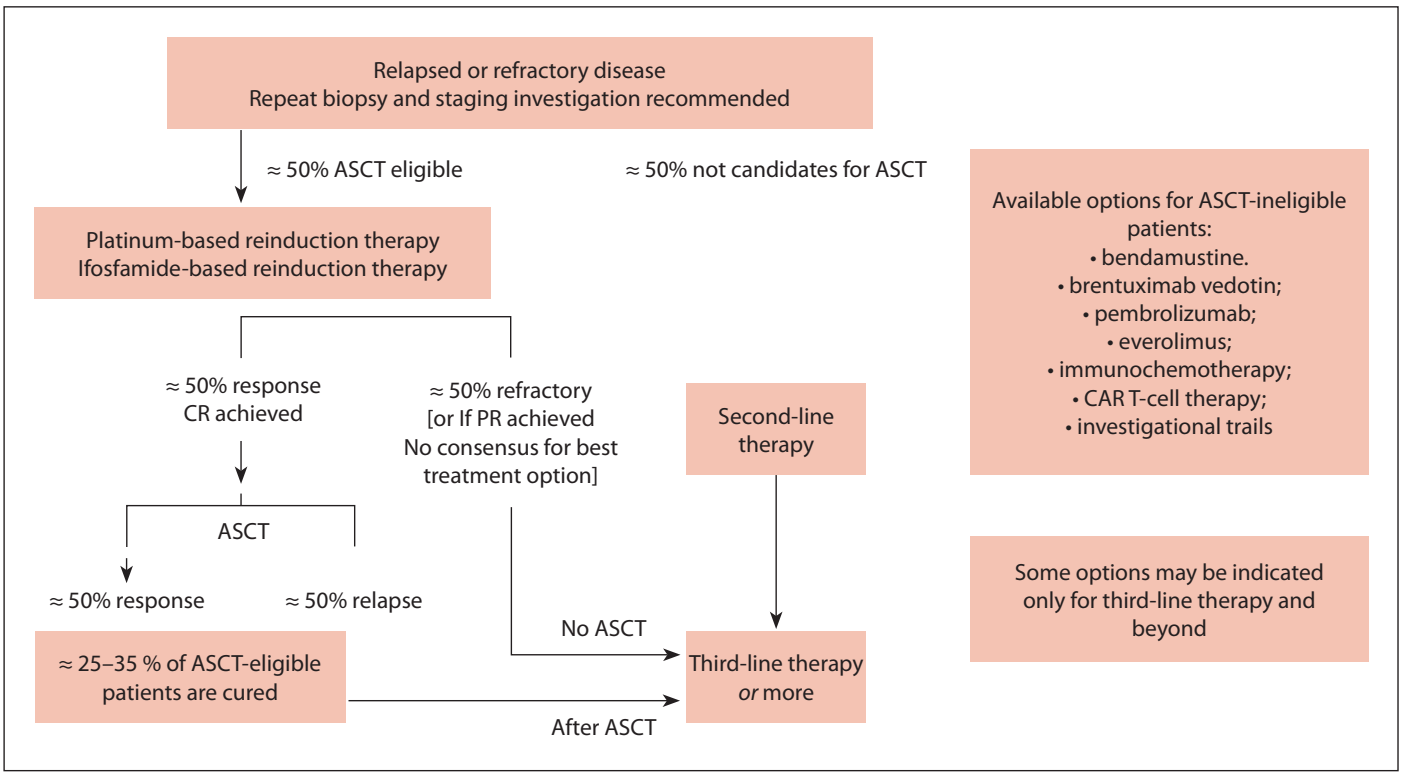

Fig. 1. Treatment options for patients who are not candidates for autologous haematopoietic stem cell transplantation.
ASCT – autologous haematopoietic stem cell transplantation; CAR – chimeric antigen receptor; CR – complete response

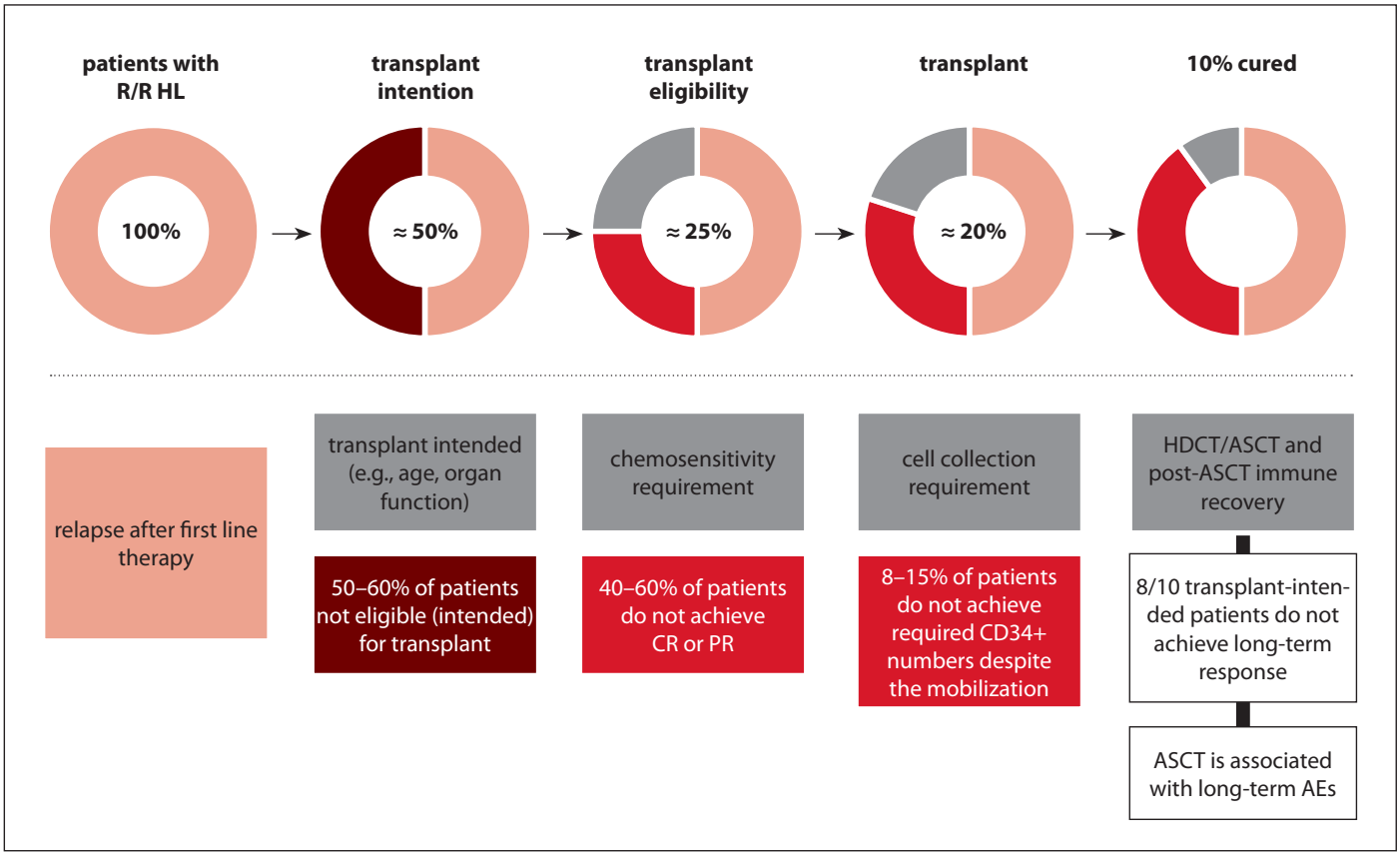

Fig. 2. Factors that may lead to a decrease in the number of patients recommended for transplantation.
ASCT – autologous haematopoietic stem cell transplantation; CR – complete response; HDCT – high-dose chemotherapy; HL – Hodgkin lymphoma; PR – partial response

recommended to stop the treatment; regular follow-up exams must ensue in order to restart treatment with these drugs in a timely manner in the event of disease progression, and to reconsider allo-SCT at that time.

In the event of PR, treatment continuation is recommended, taking into consideration the clinical situation, as the patients can still achieve CR. However, the allo-SCT plan review should be initiated prior to this.

Finally, if based on CPI treatment, patient disease is stabilized, it is recommended to continue therapy until the final progression. In the event of progression, alkylating drug-based therapy is recommended with the choice of the regimen depending on the previous treatment modalitites (Fig. 1, 2)

CONCLUSION

HDCT and ASCT are highly effective therapies in patients with rrHL, leading to a long-term survival in a substantial number of patients. Patients with high-risk disease, who were treated on time and did not achieve a sufficient response to standard first-line therapy, or patients with chemo-sensitive relapse, have a good prognosis. However, HDCT and ASCT do not benefit patients with primary chemo-resistant disease, nor patients with relapse who are not chemo-sensitive. Allo-SCT and targeted immunotherapy are options for this latter group of patients.

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THE ROLE OF THE AUTHORS

ON – prepared the manuscript
TR – participation in preparation of the abstract, prepared the part dedicated to autologous stem cell transplantation and prepared the figures

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Olga Novosad, MD, PhD
Oncohematology Department
National Cancer Institute
Kyiv
Ukraine
e-mail: novosad.o.ua@gmail.com