

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 chemozitivních 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 chemozitivním 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 – chemosenzitivita – 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 HEMATOPOIETIC 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 to 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 chemo-refractory 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

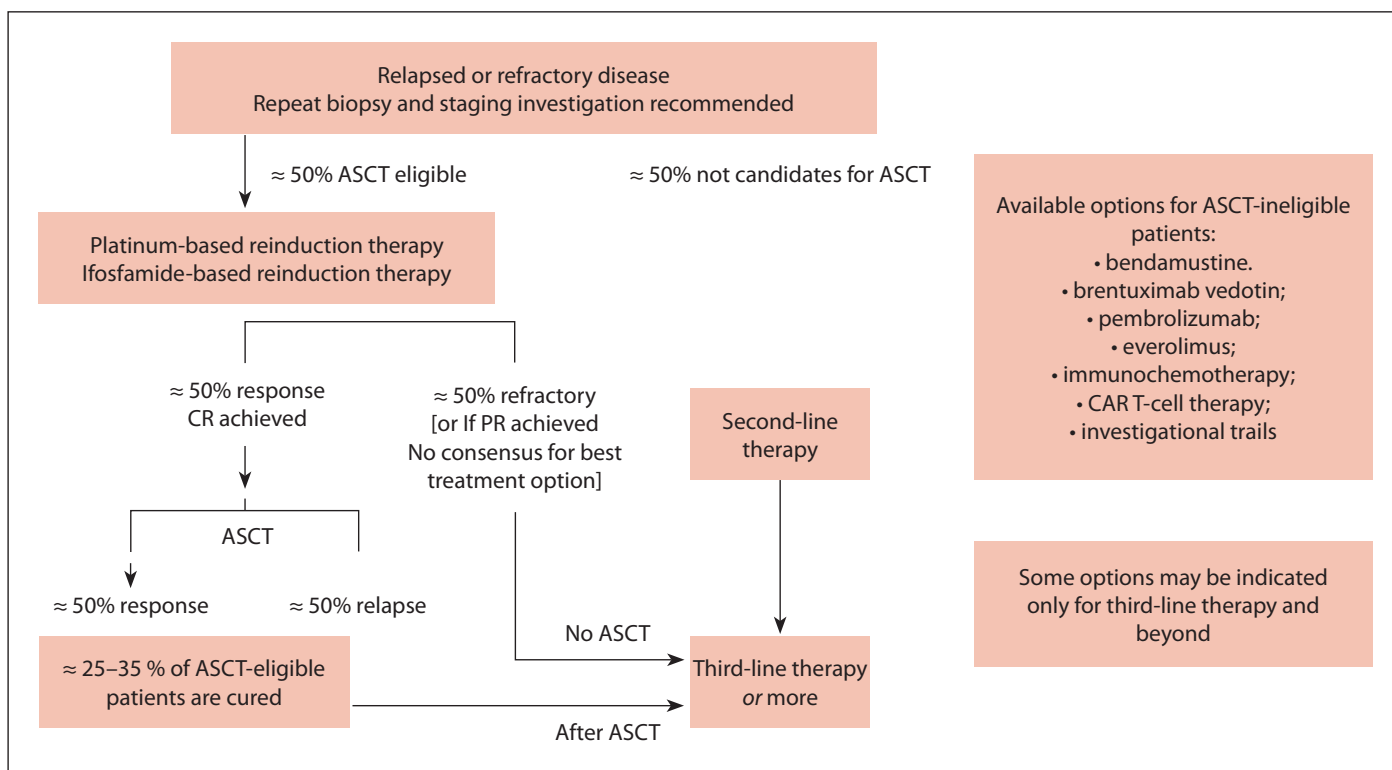


Fig. 1. Treatment options for patients who are not candidates for autologous haematopoietic stem cell transplantation.

ASCT – autologous haematopoietic stem cell transplantation; CAR – chimeric antigen receptor; CR – complete response

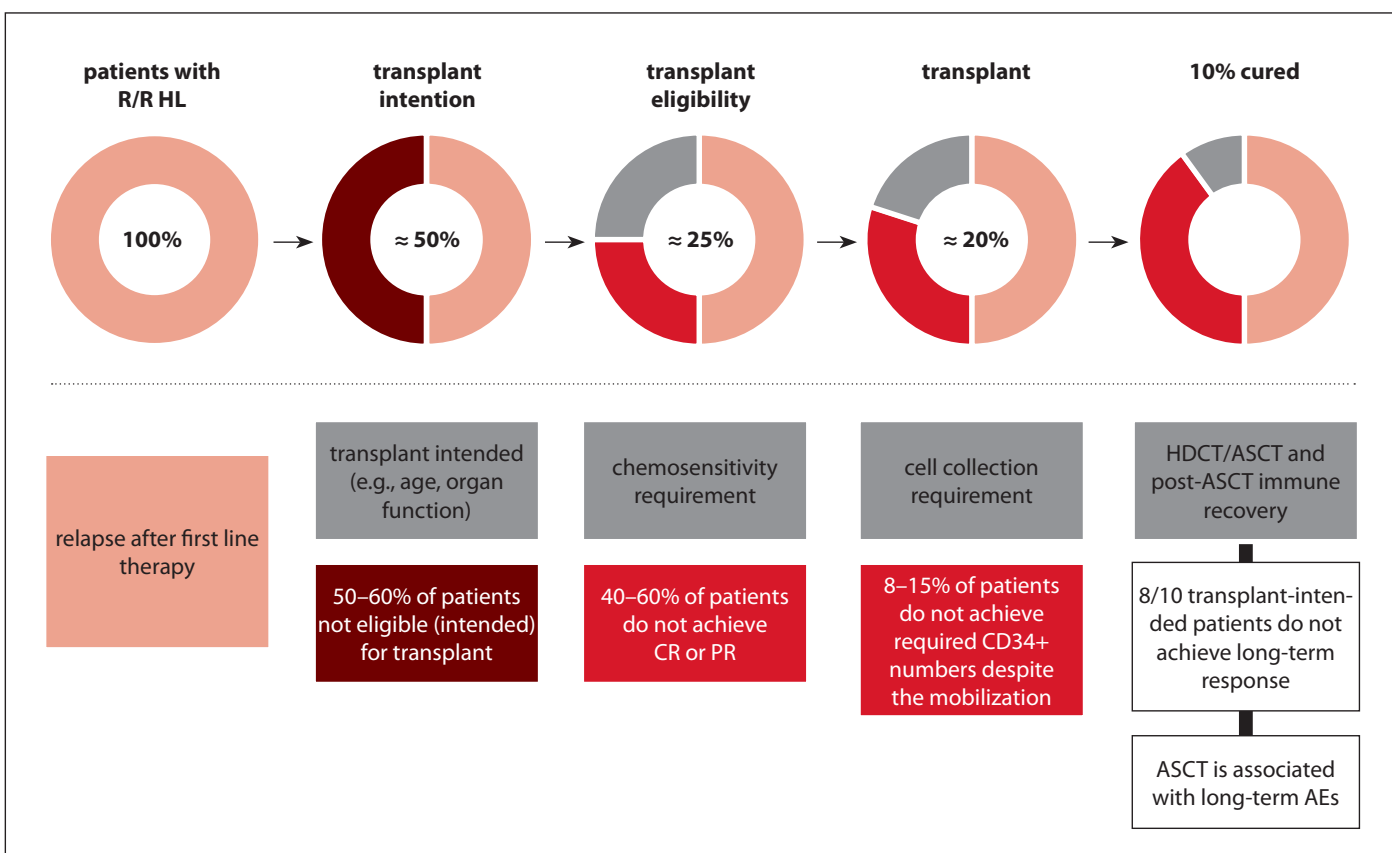


Fig. 2. Factors that may lead to a decrease in the number of patients recommended for transplantation.

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 modalities (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.

References

- Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *New Engl J Med*. 2011;365(3):203–212. doi: 10.1056/NEJMoa1100340.
- Novosad O, Skrypets T, Pastushenko I, et al. A Ukrainian multicenter prospective study of the value of PET/CT prognostic role in primary patients with Hodgkin's lymphoma in a real-life cohort. *Klin Onkol*. 2020;33(6):450–457.
- Johnson P, Federico M, Kirkwood A, et al. (2016). Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *New Engl J Med*. 2016;374(25):2419–2429. doi: 10.1056/NEJMoa1510093.
- Novosad OI, Kriachok IA, Grabovyy OM, Antonuk SA. Prognostic risk factors for newly diagnosed patients with advanced stages classical Hodgkin's lymphoma. *Lik Sprava*. 2014;(9-10):88–94. doi: 10.1056/NEJMoa1408648.
- Федоренко ЗП, Гулак ЛО, Михайлович ЮЙ, Горюх ЄЛ, Рижов АЮ, Сумкіна ОВ, Куценко ЛБ. Рак в Україні, 2020–2021. Захворюваність, смертність, показники діяльності онкологічної служби. Бюлетень Національного Канцер-реєстру України. 2022;22:101.
- Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359(9323):2065–2071. doi: 10.1016/S0140-6736(02)08938-9.
- Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341(8852):1051–1054. doi: 10.1016/0140-6736(93)92411-1.
- Moskowitz CH, Kewalramani T, Nimer SD, Gonzalez M, Zelenetz AD, Yahalom J. Effectiveness of high dose chemoradiotherapy and autologous stem cell transplantation for patients with biopsy-proven primary refractory Hodgkin's disease. *Br J Haematol*. 2004;124:645–652. doi: 10.1111/j.1365-2141.2003.04828.x.
- Sirohi B, Cunningham D, Powles R, Murphy F, Arkenau T, Norman A. Long-term outcome of autologous stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma. *Ann Oncol*. 2008;19:1312–1319. doi: 10.1093/annonc/mdn052.
- Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. *Blood*. 2001;97:616–623. doi: 10.1182/blood.v97.3.616.
- Moskowitz AJ, Schöder H, Gavane S, et al. Baseline metabolic tumor volume is an independent prognostic factor for relapsed and refractory Hodgkin lymphoma patients receiving PET-adapted salvage therapy with brentuximab vedotin and augmented ICE. *Hematol Oncol*. 2017;35(suppl 2):36–37. doi: 10.1182/blood-2017-06-788877.
- Moskowitz CH, Matasar MJ, Zelenetz AD, et al. (2012). Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood*. 2012;119:1665–1670. doi: 10.1182/blood-2011-10-388058.
- Gentzler RD, Evens AM, Rademaker AW, et al. F-18 FDG-PET predicts outcomes for patients receiving total lymphoid irradiation and autologous blood stem-cell transplantation for relapsed and refractory Hodgkin lymphoma. *Br J Haematol*. 2014;165:793–800. doi: 10.1111/bjh.12824.
- Akhtar S, Al-Sugair AS, Abouziad M, et al. Pre-transplant FDG-PET-based survival model in relapsed and refractory Hodgkin's lymphoma: outcome after high-dose chemotherapy and auto-SCT. *Bone Marrow Transplant*. 2013;48:1530–1536. doi: 10.1038/bmt.2013.88.
- Martínez C, Canals C, Sarina B, et al. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. *Ann Oncol*. 2013;24(9):2430–2434. doi: 10.1093/annonc/mdt206.
- Hagenbeek A, Zijlstra JM, Plattel WJ, et al. Combining brentuximab vedotin with DHAP as salvage treatment in relapsed/refractory Hodgkin lymphoma: the phase II HOVON/LLPC transplant BRaVE study. *Blood*. 2021;106(4):1129–1137. doi: 10.3324/haematol.2019.243238.
- García-Sanz R, Sureda A, De La Cruz F, et al. Brentuximab vedotin and ESHAP is highly effective as second-line therapy for Hodgkin lymphoma patients (long-term results of a trial by the Spanish GELTAMO group). *Ann Oncol*. 2019;30:612–620. doi: 10.1093/annonc/mdz009.
- Lacasce AS, Bociek R G, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;132:40–48. doi: 10.1182/blood-2017-11-815183.
- Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131:1183–1194. doi: 10.1182/blood-2017-10-811224.
- Takeda Pharmaceuticals. (Adcetris) summary of product characteristics. (2018). Retrieved from https://www.ema.europa.eu/en/documents/product-information/adcetris-epar-product-information_en.pdf. Accessed 1 Jan 2020.
- Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30:2183–2189. doi: 10.1200/JCO.2011.38.0410.
- Chen R, Gopal AK, Smith SE, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2016;28:1562–1566. doi: 10.1182/blood-2016-02-699850.
- Walewski J, Hellmann A, Siritanaratkul N, et al. Prospective study of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma patients who are not suitable for stem cell transplant or multi-agent chemotherapy. *Br J Haematol*. 2018;183:400–410. doi: 10.1111/bjh.15539.
- Chen R, Palmer JM, Martin P, et al. Results of a multicenter phase II trial of brentuximab vedotin as second-line therapy before autologous transplantation in relapsed/refractory Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2015;21:2136–2140. doi: 10.1016/j.bbmt.2015.07.018.
- Perales M-A, Ceberio I, Armand P, et al. Role of cytotoxic therapy with hematopoietic cell

transplantation in the treatment of Hodgkin lymphoma: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2015;21(6):971–983. doi: 10.1016/j.bbmt.2015.02.022.

26. Ghosh N, Karmali R, Rocha V, et al. Reduced-intensity transplantation for lymphomas using haploidentical related donors versus HLA-matched sibling donors: a Center for International Blood and Marrow Transplant research analysis. *J Clin Oncol.* 2016;34(26):3141–3149. doi: 10.1200/JCO.2015.66.3476.

27. Martínez C, Gayoso J, Canals C, et al. Post-transplantation cyclophosphamide-based haploidentical transplantation as alternative to matched sibling or unrelated donor transplantation for Hodgkin lymphoma: a registry study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *J Clin Oncol.* 2017;35(30):3425–3432. doi: 10.1200/JCO.2017.72.6869.

28. Castagna L, Bramanti S, Devillier R, et al. Haploidentical transplantation with post-infusion cyclophosphamide in advanced Hodgkin lymphoma. *Bone Marrow Transplant.* 2017;52(5):683–688. doi: 10.1038/bmt.2016.348.

29. Messer M, Steinzen A, Vervölgyi E, et al. Unrelated and alternative donor allogeneic stem cell transplant in patients with relapsed or refractory Hodgkin lymphoma: a systematic review. *Leuk Lymphoma.* 2014;55(2):296–306. doi: 10.3109/10428194.2013.802780.

30. Majhail NS, Weisdorf DJ, Wagner JE, et al. Comparable results of umbilical cord blood and HLA-matched sibling donor hematopoietic stem cell transplantation after reduced-intensity pre-parative regimen for advanced Hodgkin lymphoma. *Blood.* 2006;107(9):3804–3807. doi: 10.1182/blood-2005-09-3827.

31. Karantanos T, Politikos I, Boussiotis VA. Advances in the pathophysiology and treatment of relapsed/refractory Hodgkin's lymphoma with an emphasis on targeted therapies and transplantation strategies. *Blood Lymphatic Cancer.* 2017;7:37–52. doi: 10.2147/BLCTT.S105458.

32. Thompson PA, Perera T, Marin D, et al. Double umbilical cord blood transplant is effective therapy for relapsed or refractory Hodgkin lymphoma. *Leuk Lymphoma.* 2016;57(7):1607–1615. doi: 10.3109/10428194.2015.1105370.

33. Moskowitz AJ, Perales M-A, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. *Br J Haematol.* 2009;146(2):158–163. doi: 10.1111/j.1365-2141.2009.07727.x.

34. Khan N, Moskowitz AJ. Where do the new drugs fit in for relapsed/refractory Hodgkin lymphoma? *Curr Hematol Malign Rep.* 2017;12(3):227–233. doi: 10.1007/s11899-017-0384-z.

35. Borchmann S, von Tresckow B. Novel agents in classical Hodgkin lymphoma. *Leuk Lymphoma.* 2017;58(10):2275–2286. doi: 10.1111/bjh.15695.

36. Jethava Y, Guru Murthy GS, Hamadani M. Relapse of Hodgkin lymphoma after autologous transplantation: Time to rethink treatment? *Hematol Oncol Stem Cell Ther.* 2017;10(2):47–56. doi: 10.1016/j.hemonc.2016.12.002.

37. Fanale M, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma after autologous transplant: full results after extended follow-up of the phase 2 Check-mate 205 trial. *Hematol Oncol.* 2017;35(2):135–136. doi: 10.1200/JCO.2017.76.0793.

38. Timmerman JM, Engert A, Younes A, et al. Checkmate 205 update with minimum 12-month follow up: a phase 2 study of nivolumab in patients with relapsed/refractory classical Hodgkin lymphoma. *Blood.* 2016;128(22):1110. doi.org/10.1182/blood.V128.22.1110.1110.

39. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. *J Clin Oncol.* 2016;34(31):3733–3739. doi: 10.1200/JCO.2016.67.3467.

40. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol.* 2017;35(19):2125–2132. doi: 10.1200/JCO.2016.72.1316.

41. Chen R, Gibb AL, Collins GP, et al. Blockade of the PD-1 checkpoint with anti-PD-L1 antibody avelumab is sufficient for clinical activity in relapsed/refractory classical Hodgkin lymphoma (CHL). *Hematol Oncol.* 2017;35(2):67. doi.org/10.1002/hon.2437.

42. Kirschbaum MH, Goldman BH, Zain JM, et al. A phase 2 study of vorinostat for treatment of relapsed or refractory Hodgkin lymphoma: Southwest Oncology Group Study S0517. *Leuk Lymphoma.* 2012;53(2):259–262. doi: 10.3109/10428194.2011.608448.

43. Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study. *J Clin Oncol.* 2012;30(18):2197–2203. doi: 10.1200/JCO.2011.38.1350.

44. DeAngelo DJ, Spencer A, Bhalla KN, et al. Phase Ia/II, two-arm, open-label, dose-escalation study of oral panobinostat administered via two dosing schedules in patients with advanced hematologic malignancies. *Leukemia.* 2013;27(8):1628–1636. doi: 10.1038/leu.2013.38.

45. Younes A, Oki Y, Bociek RG, et al. Mocetinostat for relapsed classical Hodgkin's lymphoma: an open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2011;12(13):1222–1228. doi: 10.1016/S1470-2045(11)70265-0.

46. Shah GL, Moskowitz CH. Transplant strategies in relapsed/refractory Hodgkin lymphoma. *Blood.* 2018;131(15):1689–1697. doi: 10.1182/blood-2017-09-772673.

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

AUTHORS DISCLOSURE

Authors declared no potential conflicts of interest; preparation of manuscript has not been supported by any company.

Submitted: November 1st, 2022.

Accepted after review and revision:

February 1st, 2023.

Olga Novosad, MD, PhD

Oncohematology Department

National Cancer Institute

Kyiv

Ukraine

e-mail: novosad.o.ua@gmail.com