PRESENT AND FUTURE IN TREATMENT OF HODGKIN LYMPHOMA

Andrei Turbatu[1,2], Andrei Coliță[1,2], Marilena Stoian[3], Ana-Maria Bordea[1], Mădălina Oprea[1], Cecilia Ghimici[1], Ionel Gelatu[1], Loredana Alina Ghimfus[1], Andra Georgiana Stoica[1], Cristina Elena Banu[1], Anca-Roxana Lupu[1,2]

[1]Clinic of Hematology – Colțea Clinical Hospital, Bucharest, Romania

[2]Department of Hematology – "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania

[3]Clinic of Internal Medicine – "Dr. I. Cantacuzino" Clinical Hospital, Bucharest, Romania

Abstract

Hodgkin lymphoma, formerly known as Hodgkin disease, has gone from an incurable disease to one with a cure rate of almost 75%. The disease is defined in terms of its microscopic appearance (histology) and the expression of cell surface markers (immunophenotype), but its biologic behavior and clinical characteristics are also important.

Treatment of Hodgkin lymphoma is tailored to disease type, disease stage, and an assessment of the risk of resistant disease. General treatment modalities include radiation therapy, induction chemotherapy, salvage chemotherapy, and hematopoietic stem cell transplantation.

Key words: *Hodgkin lymphoma, histology, immunophenotype, Hodgkin-Reed-Sternberg cell, chemotherapy.*

Rezumat

Limfomul Hodgkin, cunoscut anterior ca boală Hodgkin, a trecut de la o afecțiune incurabilă la una cu o rată de vindecare de aproape 75%. Afecțiunea este definită prin aspectul microscopic (histologie) și expresia markerilor de suprafață celulară (imunofenotipare), dar comportamentul biologic și caracteristicile clinice sunt, de asemenea, importante.

Tratamentul limfomului Hodgkin este adaptat tipului de boală, stadiului bolii și unei evaluări a riscului de rezistență la tratament. Modalitățile generale de tratament includ radioterapia, chimioterapia de inducție, chimioterapia de salvare și transplantul de celule stem hematopoietice.

Cuvinte cheie: *limfom Hodgkin, histologie, imunofenotip, celula Hodgkin-Reed-Sternberg, chimioterapie.*

Internal Medicine

General Reviews

Hodgkin lymphoma, formerly known as Hodgkin disease, has gone from an incurable disease to one with a cure rate of almost 75%[1]. The disease is defined in terms of its microscopic appearance (histology) and the expression of cell surface markers (immunophenotype), but its biologic behavior and clinical characteristics are also important.

In classical Hodgkin lymphoma (cHL), the neoplastic cell is the Hodgkin-Reed-Sternberg cell (HRS)[2, 3]. Reed-Sternberg cells comprise only 1-2% of the total tumor cell mass (Figure 1). The remainder, the tumoral microenvironment, is composed of a variety of reactive, mixed inflammatory cells consisting of lymphocytes, neutrophils, eosinophils, mast cells and macrophages (Figure 2). Most Reed-Sternberg cells are of B-cell origin, derived from lymph node germinal center, but no longer able to produce antibodies.

To diagnose Hodgkin lymphoma a histologic evaluation is always required, and an excisional tissue biopsy is recommended for this purpose.

Treatment of Hodgkin lymphoma is tailored to disease type, disease stage, and an assessment of the risk of resistant disease. Hodgkin lymphoma is considered to be a curable malignancy, but therapies for this disease can have significant long-term toxicity. General treatment modalities include radiation therapy, induction chemotherapy, salvage chemotherapy, and hematopoietic stem cell transplantation. Treatment seeks to balance the risk of treatment failure with the risk of treatment side effects.

The primary goal of therapy is achievement of a complete remission, but even in patients who fail to do so, there are effective salvage regimens available that can result in long-term survival or cure[4].

When induction chemotherapy fails (Table 1), or patients experience relapse, salvage chemotherapy is generally given. Salvage regimens incorporate drugs that are complementary to those that failed during induction therapy. Commonly used salvage regimens include the following:

- ICE (ifosfamide, carboplatin, etoposide)
- DHAP (cisplatin, cytarabine, prednisone)
- IGEV (ifosfamide, gemcitabine, vinorelbine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin).

Patients with refractory or relapsed Hodgkin lymphoma should be promptly referred to centers capable of high-dose chemotherapy (HDC) with hematopoietic stem cell support. In some cases in which HDC fails, allogeneic stem cell transplantation may be a viable

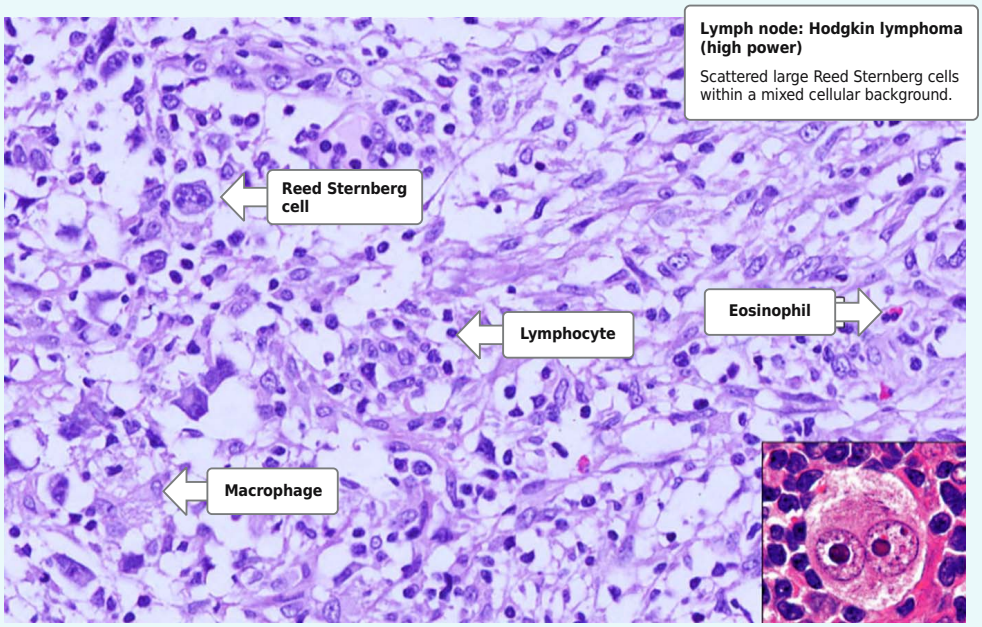

Figure 1. *Microscopic appearance of a lymph node biopsy, copyright*

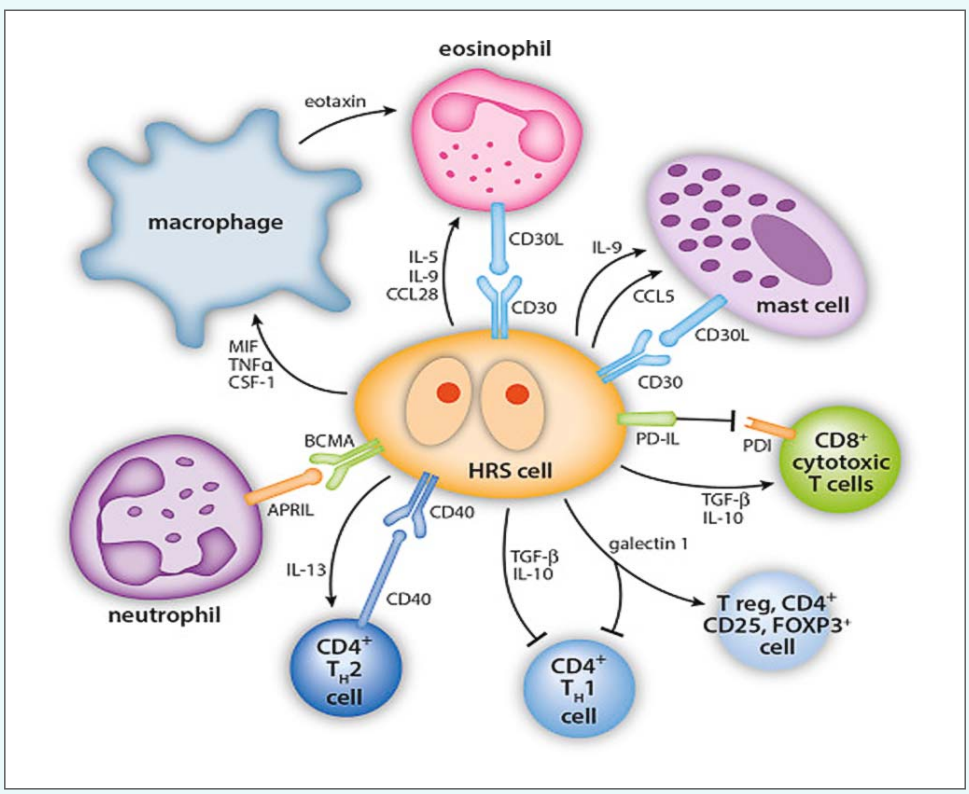

Figure 2. *Links between cells in the tumoral microenvironment, copyright*

option. Historically, allogeneic stem cell transplantation for Hodgkin lymphoma has been considered too high-risk for most patients, due to high transplant-related mortality.

Immunotherapy is emerging for use in hematologic malignancies, including Hodgkin lymphoma.

Brentuximab vedotin was approved by the US Food and Drug Administration (FDA) in August 2011 for treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplantation or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for a stem cell transplant. This agent is a CD30-directed antibody-drug conjugate consisting of IgG1 antibody cAC10, specific for human CD30, and the microtubule disrupting agent, monomethyl auristatin E (MMAE, or vedotin)[5].

Brentuximab vedotin is indicated as consolidation therapy following autologous hematopoietic stem cell transplantation (HSCT) in patients with classic Hodgkin lymphoma who are at high risk of relapse or progression. Approval for this indication was based on the AETHERA clinical trial, in which median progression-free survival was 42.9 months in the brentuximab group versus 24.1 months in the placebo group, a statistically significant improvement of 18.8 months (P=0.001)[6].

Current NCCN guidelines recommend brentuximab vedotin as maintenance therapy for 1 year after high-dose therapy with autologous stem cell rescue (HDT/ASCR). In addition, in selected patients, brentuximab vedotin can be used as second-line therapy prior to HDT/ASCR to minimize the use of more intensive chemotherapy.

Regarding the microenvironment, PD-1 and related target PD-ligand 1 (PD-L1) are expressed on the surface of activated T cells under normal conditions. PD-L1/PD-1 interaction inhibits immune activation and reduces T-cell cytotoxic activity when bound (Figure 3). This negative feedback loop is essential for maintaining normal immune responses and limits T-cell activity to protect normal cells during chronic inflammation.

A monoclonal antibody which inhibits suppression of T-cells by blocking the interaction between programmed cell death-1 protein and its ligands is Nivolumab. In May 2016, the FDA approved the monoclonal antibody nivolumab for the treatment of classic Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and posttransplantation brentuximab vedotin. Approval was based on a combination of the phase 2 CheckMate 205 and phase 1 CheckMate 039 trials with an efficacy analysis conducted on data from 95 patients. Treatment with nivolumab showed

Regimen	Dose and route	Frequency
ABVD (28-day cycle)		
Doxorubicin	25 mg/m2 i.v.	Days 1 and 15
Bleomycin	10,000 iu/m2 i.v.	Days 1 and 15
Vinblastine	6 mg/m2 i.v.	Days 1 and 15
Dacaebazine	375 mg/m2 i.v.	Days 1 and 15
BEACOPP escalated (21-day cycle)*		
Bleomycin	10,000 iu/m2 i.v.	Day 8
Etoposide	200 mg/m2 i.v.	Days 1-3
Adriamycin (doxorubicin)	35 mg/m2 i.v.	Day 1
Cyclophosphamide	1250 mg/m2 i.v.	Day 1
Vincristine	1.4 mg/m2 i.v. (max. 2 mg)	Day 8
Procarbazine	100 mg/m2 orally	Days 1-7
Prednisolone	40 mg/m2 orally	Days 1-14

Table 1. *First line chemotherapy in cHL, copyright*

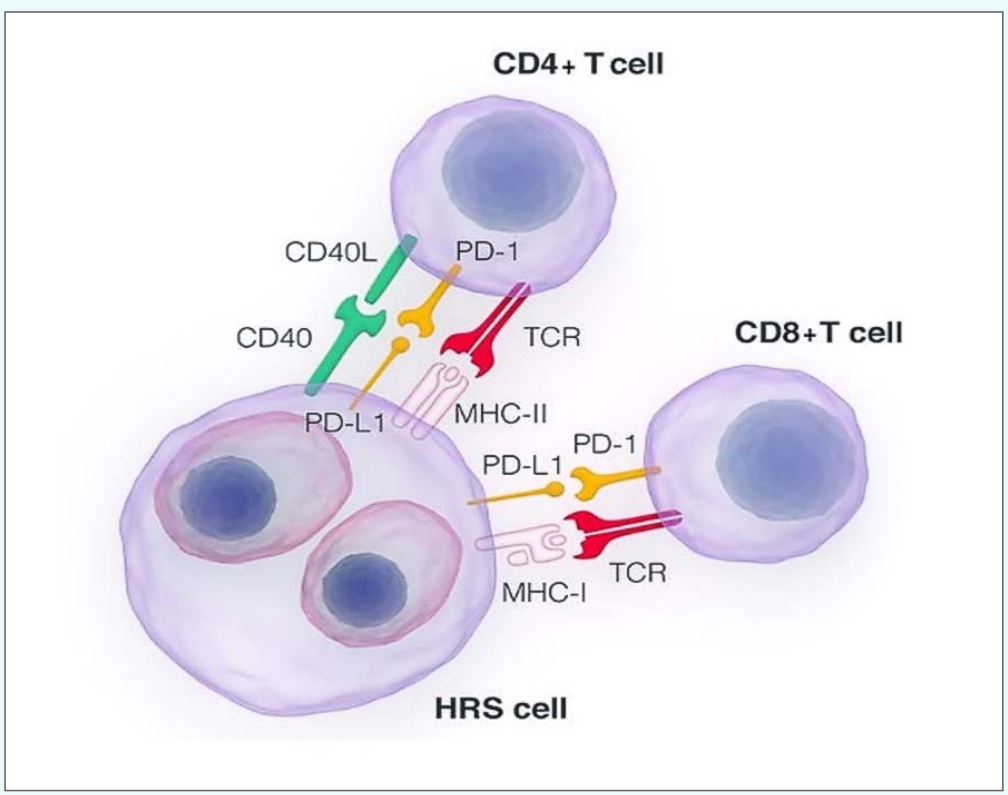

Figure 3. *PD-L1/PD-1 interaction, copyright*

an objective response rate (ORR) of 65% (CI 95%: 55-75; 62/95), a complete response rate (CRR) of 7% (CI 95%: 3-15; 7/95), and a partial response rate (PRR) of 58% (CI 95%: 47-68; 55/95). Among responders, the median duration of response was 8.7 months (CI 95%: 6.8-NE; range 0.0+, 23.1+)[7,8].

In March 2017, pembrolizumab, another monoclonal antibody to programmed cell death-1 protein (PD-1) gained accelerated approval from the FDA for cHL. It is indicated in adults and pediatric patients who have refractory cHL or have relapsed after 3 or more prior lines of therapy. Approval was based on data from the KEYNOTE-087 trial (n=210), which demonstrated an ORR with pembrolizumab averaging ~67% (95% CI: 62, 75), a CRR of 22%, and a PRR of 47%. The median follow-up time was 9.4 months. In the 145 patients who responded to treatment, the median duration of response was 11.1 months[9].

Single-agent salvage therapy is given as follows:

- Brentuximab vedotin, 1.8 mg/kg once every 3 weeks for up to 16 cycles
- Nivolumab, 3 mg/kg once every 2 weeks until disease progression or unacceptable toxicity
- Pembrolizumab, 200 mg every 3 weeks until disease progression or excessive adverse effects, for a maximum of 24 months.

Nivolumab and pembrolizumab are used as salvage therapy in Hodgkin lymphoma and can have numerous autoimmune side effects as a result of immune checkpoint inhibition. This can include pneumonitis, colitis, nephritis, hypothyroidism, hypopituitarism, and adrenalitis. High-dose corticosteroids may be required to treat these side effects. Hypothyroidism requires thyroid hormone replacement and adrenal insuffiency requires physiologic replacement of corticosteroids and mineralocorticoids.

As discussed earlier, single-agent brentuximab vedotin, nivolumab, and pembrolizumab may be used in the relapsed/refractory setting either post-transplant or in transplant-ineligible patients. Data comparing these regimens are not yet available, but phase 3 trials are ongoing, including a trial comparing brentuximab vedotin versus pembrolizumab and another phase 3 trial comparing brentuximab vedotin plus nivolumab versus nivolumab. Brentuximab vedotin plus nivolumab is also being studied in the frontline setting in a phase 2 trial for older patients (NCT02758717). Efforts are also under way to incorporate these novel agents into earlier lines of therapy with the hopes of improving outcomes and minimizing toxicities. Early phase studies are ongoing to determine how to use them prior to transplant in the second-line setting. These studies currently include various combinations of brentuximab vedotin

and chemotherapy[10,11,12,13] or brentuximab vedotin plus immunotherapy (nivolumab)[14], with preliminary data showing high response rates. To date, there are no randomized trials to establish a standard pre-transplant regimen. In the frontline setting, the combination of nivolumab followed by nivolumab plus AVD (A – doxorubicin (Adriamycin), V – vinblastine, D – dacarbazine) is being studied in patients with advanced-stage disease[15], with promising early results.

Finally, an emerging area of research is the use of chimeric antigen receptor (CAR) T-cells to treat Hodgkin lymphoma. This will be an ongoing area of investigation[16]. The current treatment of Hodgkin lymphoma seeks to maximize the risk-benefit ratio of treatment. Thus, treatment focuses on tailoring therapy to each patient according to age, risk of short-term and long-term toxicity, and risk of relapse.

References

1. DeVita VT - A selective history of the therapy of Hodgkin's disease, Br J Haematol. 2003; 122(5):718-27 (ISSN: 0007-1048)

2. Thomas RK, Re D, Wolf J, et al. - Part I: Hodgkin's lymphoma--molecular biology of Hodgkin and Reed-Sternberg cells, Lancet Oncol. 2004; 5(1):11-8 (ISSN: 1470-2045)

3. Re D, Küppers R, Diehl V - Molecular pathogenesis of Hodgkin's lymphoma, J Clin Oncol. 2005; 23(26):6379-86 (ISSN: 0732-183X)

4. Connors JM - State-of-the-art therapeutics: Hodgkin's lymphoma, J Clin Oncol. 2005; 23(26):6400-8 (ISSN: 0732-183X)

5. Moskowitz CH, Nademanee A, Masszi T, et al. - Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial; Lancet. 2015; 385(9980):1853-62 (ISSN: 1474-547X)

6. Younes A, Bartlett NL, Leonard JP, et al. - Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas, N Engl J Med. 2010; 363(19):1812-21 (ISSN: 1533-4406)

7. Ansell SM, Lesokhin AM, Borrello I, et al. - PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma, N Engl J Med. 2015; 372(4):311-9 (ISSN: 1533-4406)

8. Ansell S, Armand P, Timmerman JM, et al. - Nivolumab in Patients (Pts) with Relapsed or Refractory Classical Hodgkin Lymphoma (R/R cHL): Clinical Outcomes from Extended Follow-up of a Phase 1 Study (CA209-039), Blood 2015 126:583

9. 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 (ISSN: 1527-7755)

10. Moskowitz AJ, Schöder H, Yahalom J, et al. - PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study; Lancet Oncol. 2015; 16(3):284-92 (ISSN: 1474-5488)

11. Garcia-Sanz R, Sureda A, Alonso-Alvarez S, et al. - Evaluation of the Regimen Brentuximab Vedotin Plus ESHAP (BRESHAP) in Refractory or Relapsed Hodgkin Lymphoma Patients: Preliminary Results of a Phase I-II Trial from the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO), Blood 2015 126:582

12. Cassaday RD, Fromm J, Cowan AJ, et al. - Safety and Activity of Brentuximab Vedotin (BV) Plus Ifosfamide, Carboplatin, and Etoposide (ICE) for Relapsed/ Refractory (Rel/Ref) Classical Hodgkin Lymphoma (cHL): Initial Results of a Phase I/II Trial, Blood 2016 128:1834

13. LaCasce AS, Bociek RG, Sawas A, et al. - Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma, Blood. 2018; 132(1):40-48 (ISSN: 1528-0020)

14. 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(11):1183-1194 (ISSN: 1528-0020)

15. Ramchandren R, Fanale MA, Rueda A, t al. - Nivolumab for Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma (cHL): Results from the Phase 2 Checkmate 205 Study, Blood 2017 130:651

16. Wang CM, Wu ZQ, Wang Y, et al. - Autologous T Cells Expressing CD30 Chimeric Antigen Receptors for Relapsed or Refractory Hodgkin Lymphoma: An Open-Label Phase I Trial, Clin Cancer Res. 2017; 23(5):1156-1166 (ISSN: 1078-0432).