

Treatment of relapsed classical Hodgkin lymphoma in the Brentuximabvedoitn era.

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Introduction:

HL is an uncommon malignancy involving lymph nodes and the lymphatic system. The WHO classification divides HL into 2 main types: classical (CHL) and nodular lymphocyte predominant HL (NLPHL). CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL is characterized by the presence of lymphocytic and histiocytic cells.

HL is now curable in most patients because of the introduction of more effective and less toxic regimens. However survivors may experience late treatment related side effects. Current management of CHL involves initial treatment with chemotherapy or combined modality therapy, followed by re-staging with PET/CT to assess treatment response using the Deauville criteria. The value of interim PET scans remains unclear and the panel emphasizes that all measures of response should be considered in the context of management decisions.

Deauville criteria of PET/CT are scored according to uptake in sites involved by lymphoma as: (1) no uptake, (2) uptake= mediastinum blood pool, (3) uptake= liver, (4) uptake = moderately increased uptake >liver, (5) uptake= markedly increased uptake >liver and/or new lesions. A score of 1-3 was regarded as negative and 4 or 5 as positive.

Combined modality therapy (ABVD plus ISRT or Stanford V) or chemotherapy alone with ABVD are included as treatment options for patients with stage IA or IIA favorable CHL. Chemo-therapy (ABVD or Stanford V or BEACOPP plus ABVD) followed by consolidative ISRT is recommended for patients with stage III-IV disease.

Treatment of relapsed/refractory classical HL:

ASCR/HDT is the best treatment option for patients with relapsed or refractory HL, although it does not improve OS. Second line therapy (RT or conventional-dose second line chemotherapy with or without RT) may be given prior to ASCR/HDT.

ASCR/HDT was compared with conventional chemotherapy in patients with relapsed or refractory HL, showing significant improvement in EFS and PFS and FFTF (with no difference in OS) for patients with relapsed or refractory HL who underwent HDT/ASCR compared with conventional chemotherapy alone. ASCR/HDT is the best option for patients with HL that is not cured with primary treatment, even though it does not improve OS.

Although HSCT with myelo-ablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory HL; however, TRM was more than 50%. Allogenic HSCT with reduced intensity conditioning has been reported to have decreased rates of TRM. Several investigators have developed prognostic models to predict the outcome in patients with relapsed or refractory HL undergoing ASCR/HDT including adverse prognostic factors as end of treatment-to-relapse interval (i.e. CR of < 1 year), extra-nodal disease at relapse, primary refractory disease, clinical stage at relapse, and anemia at relapse, bulky disease at diagnosis, detectable disease at transplant, extent of prior chemotherapy, short time from diagnosis to transplant, pre-transplant functional imaging status and B-symptoms. In patients with none or one factor, 5-year EFS and OS were 83% and 90%, respectively, which decreased to 10% if all factors were present.

Several studies have shown the importance of cyto-reduction with second line chemotherapy before ASCR/HDT. Newer regimens such as GVD (gemcitabine, vinorelbine and pegylated liposomal doxorubicin), IGEV (ifosfamide, gemcitabine and vinorelbine), GCD (gemcitabine, carboplatin and dexamethasone) have also been effective for relapsed or refractory HL. Bendamustine, lenalidomide and everolimus have also shown activity in patients with relapsed or refractory HL. Bendamustine was well tolerated and highly active in heavily pre-treated patients (including those who had failed ASCR/HDT) with relapsed or refractory HL. Lenalidomide and everolimus have also shown single agent activity in patients with relapsed or refractory HL resulting in ORR 19% and 47% respectively. Everolimus is included as an option for second line therapy for patients with relapsed or refractory HL. Bendamustine and lenalidomide are included as options for third line therapy for patients with relapsed or refractory HL.

Second line radiotherapy was reported to be effective in a subset of patients with relapsed or refractory HL. The 5 year–FFTF and OS rates were 28% and 51% respectively. Second line RT may be effective in patients who are in good performance status with limited stage late relapses and without B-symptoms. It may be very effective salvage regimen for patients with initial favorable stage I-II disease who are treated with chemotherapy alone and relapse in initially involved sites.

Individualized treatment is recommended for patients with relapsed or refractory HL since there are no data available to support a superior outcome with any of the treatment modalities.

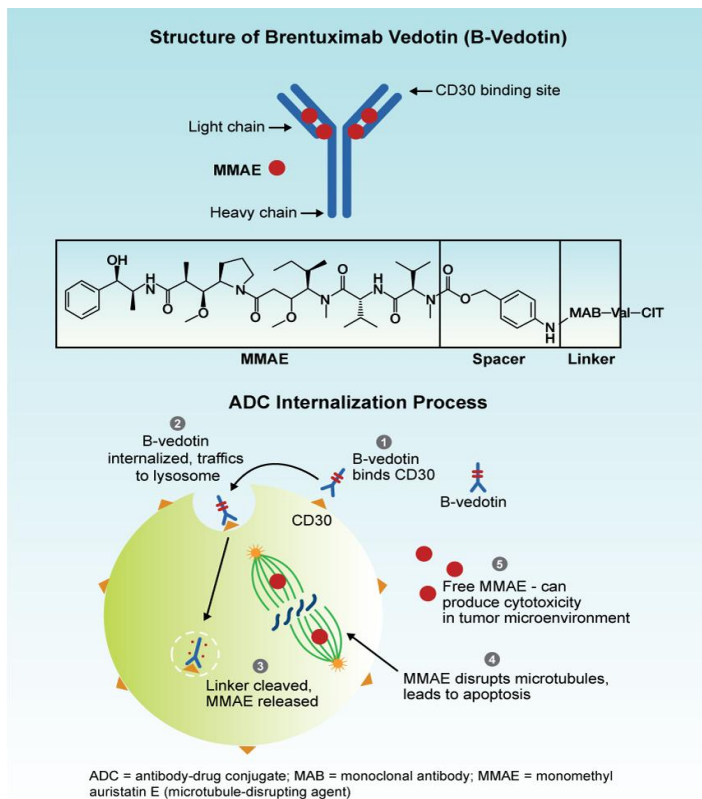
Brentuximab role in relapsed/refractory CHL:

Brentuximabvedtoin induced objective responses and complete remissions in 75% and 34% of patients, respectively, with a median follow up of more than 1.5 years. The median PFS for all patients and median duration of response for those in CR were 5.6 months and 20.5 months, respectively. Based on the results of this study, the FDA approved Brentuximabvedtoin for the treatment of patients with relapsed HL after failure of ASCR/HDT or at least 2 prior chemotherapy regimens in patients who are not candidates for ASCR/HDT.

Brentuximabvedtoin was now included as an option for patients with progressive or relapsed or refractory HL disease after ASCR/HDT or at least two prior chemotherapy regimens for all patients regardless of their eligibility for ASCR/HDT.

Brentuximab drug information:

Brentuximabvedotin is an antibody-drug conjugate (ADC) that selectively delivers monomethylauristatin E, an anti-microtubule agent, into CD30-expressing cells. Brentuximabvedotin demonstrated significant activity with a favorable safety profile in patients with relapsed or refractory CD30-positive lymphomas (licensed for HL & anaplastic cell lymphoma).



Brentuximabvedotin maximally tolerated dose is 1.8 mg/kg by intravenous infusion over 30 minutes given every 3 weeks. In the absence of disease progression or prohibitive toxicity, patients can receive a maximum of 16 cycles. The most common ($\geq 10\%$) treatment-related adverse events were peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), neutropenia (19%), diarrhea (18%), pyrexia (14%), vomiting (13%), arthralgia (12%), pruritus (12%), myalgia (11%), peripheral motor neuropathy (11%), and alopecia (10%). The most common events leading to dose delays or reductions (from 1.8 to 1.2 mg/kg) are neutropenia (16%) and peripheral sensory neuropathy (13%) and grade 4 thrombocytopenia. Most adverse events associated with Brentuximabvedotin are managed through standard supportive care, and the most common events are typically grade 1 or 2. Neuropathy typically develops after prolonged exposure to the drug, with a median onset of grade 2 at 27.3 weeks. The neuropathy was also largely reversible after treatment is completed or discontinued or the dose is reduced.

Improvements in the use of combined chemotherapy and radiotherapy in advanced-stage, newly diagnosed Hodgkin's lymphoma (HL) have resulted in durable remission rates of approximately 60% to 80%. However, a large fraction of patients with HL are not cured. The standard of care for patients with relapsed or refractory HL is salvage chemotherapy followed by autologous stem-cell transplantation (auto-SCT), which can induce long-term remissions in approximately 50% of patients. For patients who experience relapse or progressive HL within 1 year after auto-SCT, the prognosis is exceedingly poor, with a median survival time of approximately 1.2 years.

The malignant Hodgkin's Reed-Sternberg cells of classical HL are characterized by the expression of CD30, a member of the tumor necrosis factor superfamily. Because normal CD30 expression is restricted to a relatively small proportion of activated B cells, T cells, and eosinophils, it represents an ideal target for monoclonal antibody therapy.

Brentuximabvedotin is an antibody-drug conjugate (ADC) comprising an anti-CD30 antibody conjugated by a protease cleavable linker to the potent anti-microtubule agent, monomethylauristatin E (MMAE). Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment, releasing MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

NCCN recommendations for refractory CHL:

Histologic confirmation with biopsy is recommended before initiating treatment for refractory disease. Although further cyto-reduction and ASCR/HDT (with RT if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of RT or chemotherapy with or without RT. Conventional dose second line chemotherapy may precede ASCR/HDT . ISRT is recommended when the sites of relapse have not been previously irradiated. In radiation naïve patients, TLI may be an appropriate component of ASCR/HDT.

Second line chemotherapy followed by response assessment with PET is recommended for all patients. Patients with a score of Deauville 1-3 should be treated with ASCR/HDT or observation (short interval follow up with PET-CT every 3-6 months until Deauville 1-2 or until no progression for 12 months or more), if ASCR/HDT is contraindicated. Additional second line therapy (ISRT or second line chemotherapy with or without ISRT) followed by another restaging is recommended for patients with a PET

score of Deauville 4 or 5. Alternatively, those with a score of Deauville 4 can be treated with ASCR/HDT. If the repeat PET score (after additional second line therapy) is Deauville 1-4, ASCR/HDT or observation (only if the patient has achieved CR and ASCR/HDT is contraindicated) is recommended. If the PET remains Deauville 5, patients should be retreated with ISRT or second line chemotherapy with or without ISRT. Brentuximab vedotin is included as an option for patients with a score of Deauville 4 or 5 following second line chemotherapy with or without RT.

Some studies have suggested that patients with CR to second line therapy prior to ASCR/HDT or those with chemo-sensitive disease to second line chemotherapy have improved outcomes following ASCR/HDT compared to those with resistant disease. The consensus of the panel was that patients who are refractory to second line chemotherapy should not proceed to ASCR/HDT and patients with refractory disease who are not chemo-sensitive after 2 second line chemotherapy regimens should be given a trial of Brentuximab vedotin prior to ASCR/HDT even though they may be candidates for transplant. Therefore, the panel has included Brentuximab vedotin as an option for patients who have failed ASCR/HDT or at least two prior chemotherapy regimens, regardless of their eligibility for ASCR/HDT.

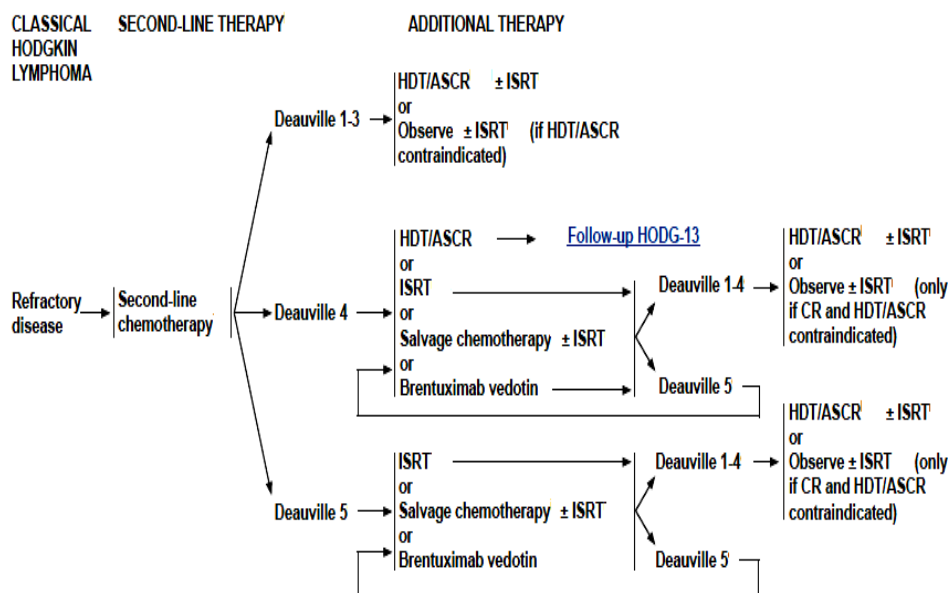
NCCN recommendations for relapsed CHL:

While second line chemotherapy is an appropriate treatment for any patient with relapsed disease, regardless of the length of initial remission, some studies have also suggested that second line chemotherapy may not be essential before proceeding to ASCR/HDT for patients with minimal residual disease at relapse. In selected patients with long disease free intervals and other favorable features, the selection of second line chemotherapy should be individualized.

Suspected relapse should be confirmed with biopsy. Observation (with short interval follow up with PET/CT) is appropriate if biopsy is negative; however, clinical circumstances may warrant additional therapy even if the biopsy is negative. Restaging, with or without bone marrow biopsy is recommended for patients with positive biopsy.

Second line chemotherapy is recommended for all patients experiencing disease relapse after initial treatment with chemotherapy or combined modality therapy. Second line chemotherapy with or without ISRT (followed by restaging) is the preferred treatment option for patients with stage IA to IIA disease who were initially treated with chemotherapy alone and experienced failure at the initial sites followed by restaging. ISRT alone may be appropriate for selected patients. Patients with a score of Deauville

1-3 should be treated with ASCR/HDT or observation (in selected patients). Those with a score of Deauville 4-5 should be managed as described above for refractory disease.



Algorithm of management of refractory CHL (from NCCN 2015 guidelines).

Abbreviations:

ASCR/HDT: autologous stem cell rescue/high dose therapy, HL: Hodgkin lymphoma, ISRT: involved site radiation therapy, TRM: treatment related mortality.

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