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Hodgkin's lymphoma: post- autologous transplantation consolidation therapy

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Abstract. A first-line chemotherapy program based on the ABVD regimen is currently considered the golden standard by most hematologists, being able to achieve a cure without any need of subsequent therapies in >70% of patients with advanced-stage Hodgkin's lymphoma (HL). To increase this percentage, efforts in recent decades focused on the development of new therapeutic strategies. A first major effort was the introduction of the BEACOPP chemotherapy regimen, which is able to increase the response rate and to reduce the need of salvage therapies. However, this result did not demonstrate an advantage in terms of overall survival compared to ABVD, mainly due to an excess of non lymphoma-related events in the follow-up phase. Here we describe three clinical cases of young HL patients who had relapsed/refractory disease after the induction chemotherapy. These three clinical cases provide practical and real world evidence in favor of the use of BV in monotherapy as consolidation treatment after autologous stem cells transplantation in patients with relapsed/refractory HL.

Key words: Hodgkin Lymphoma; consolidation therapy; post-autologous trasplantation

Introduction

Hodgkin's lymphoma (HL) is a highly curable hematologic malignancy treated with combination chemotherapy with or without consolidation radiotherapy (RT). ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) is the preferred first-line combination chemotherapy for HL. Following a treatment with 6-8 cycles of the ABVD regimen, >70% of patients are considered cured (1-4). However, conventional dose chemotherapy is not sufficient to cure refractory or early relapsing disease. High-dose chemotherapy (HDCT), followed by autologous stem cell transplantation (ASCT), is recommended as the standard treatment for those who relapse after the initial therapy (5-6). If this approach fails, most patients can choose to receive a second ASCT, an allogeneic stem cell transplantation (allo-SCT) or a treatment with novel agents, such as brentuximab vedotin (BV), or with the anti-PD-1 agents pembrolizumab or nivolumab.

BV, or SGN-35, is a chimeric anti-CD30 mAb joined through a protease-cleavable linker to a microtubule disrupting agent, the monomethyl auristatin E (MMAE). BV binds to the extracellular domain of CD30 and is internalized and subsequently transferred to the lysosome, causing the enzymatic cleavage of the linker peptide and the release of MMAE into the cytosol, where it binds to tubulin, inhibiting the microtu-

bule polymerization and resulting in mitotic arrest and apoptosis in CD30+ lymphoma cells. MMAE is also diffusible across the cell membranes, possibly creating a bystander antitumor effect into the tumor microenvironment.

In a pivotal Phase II study, BV was tested as single agent therapy in patients with relapsed or refractory HL after ASCT. The study showed a significant efficacy, with an overall response rate (ORR) of 75% and a complete remission (CR) rate of 34% (7-8).

A subsequent Phase III study (AETHERA) in HL patients at risk for relapse after ASCT, showed a me- dian progression-free survival (PFS) of 42.9 months when BV was used as consolidation therapy *vs.*24.1 months reported in the placebo group. In these studies, the most commonly reported side effect was the peripheral neuropathy, affecting 36–56% of patients treated with BV. AETHERA study showed a consistent PFS benefit with BV across pre-specified subgroups, including primary refractory patients and patients who relapsed less than 12 months after a frontline therapy. A post-hoc analysis of PFS in patients with 2 or 3 of any of the following risk factors was also conducted: relapse within 12 months from first CR or refractoriness to frontline therapy, best response or partial response (PR) or stable disease (SD) to the most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-transplantation relapse, ≥2 prior salvage treatments. The 5-year PFS rate (95% CI) was 59% (51-66) with BV *vs.* 41% (33-49) with placebo (HR=0.521; 95% CI, 0.379-0.717). The benefit of BV was more pronounced in patients with additional pre-ASCT risk factors; the 5-year PFS HR (95% CI) was 0.424 (0.302-0.596) in patients with 2 risk factors and 0.390 (0.255, 0.596) in those with 3 risk factors (9-12). BV has been licensed for the treatment of adult patients with relapsed or refractory CD30+ HL, following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option and, more recently, as a consolidation therapy following ASCT in HL patients at risk of relapse or progression. Here we describe 3 different clinical cases in which BV has been used as consolidation therapy following ASCT.

Clinical case n.1

In May 2015, a 22-year old woman was evaluated for the onset of bilateral supraclavicular nodes and night sweats; an excisional node biopsy revealed classical Hodgkin's Lymphoma (cHL) infiltration. The patient presented an early stage disease (IIB), non bulky and associated to an unfavorable risk profile according to EORTC criteria (increased erythrocyte sedimentation rate, more than 4 nodal sites involved). The patient was treated with 6 courses of ABVD chemotherapy with interim PET/CT scan performed after 2 cycles, showing a complete metabolic response (mCR). The final response assessment performed with a PET/CT scan 40 days after the completion of the sixth ABVD course revealed a laterocervical, supraclavicular and axillary relapse that was confirmed by a core biopsy and histological evaluation. The patient started a salvage treatment with the IGEV (ifosfamide, gemcitabine, vinorelbine, prednisolone) regimen, with the aim to achieve a response, collect the autologous CD34+ stem cells and complete the therapy with ASCT. A PET/CT scan performed after 2 courses confirmed the initial metabolic response but the restaging performed after the fourth cycle showed disease progression in right axillary and supraclavear region), with new sites of the disease in the mediastinal region. Due to disease progression, the patient was considered not eligible for consolidation with ASCT, and was treated with 4 BV courses at standard dose of 1.8 mg/kg, achieving a mCR, as assessed by the FDG-PET scan. The patient was then admitted to the transplantation unit to receive fotemustine, etoposide, cytarabine and melphalan (FEAM) conditioning, and subsequent reinfusion of autologous stem cells, that were collected during the IGEV chemotherapy. Response assessment after ASCT confirmed the mCR. Considering the features of this high risk disease, a BV consolidation program was started. The patient received 12 consolidation doses of BV to achieve the maximum allowed 16 doses as per approved label, also including the four pre-ASCT administrations. A Grade 1 peripheral neuropathy was experienced, that did not require any treatment interruption and that completely regressed after completion of the scheduled administration of BV. Three years after the last BV administration, the patient is still in CR and in good clinical conditions.

Discussion clinical case n. 1

This young patient showed a progressive disease after 6 courses of the ABVD regimen and received a first salvage treatment with a gemcitabine containing regimen (IGEV), showing a subsequent progressive disease at the end of chemotherapy. A second salvage treatment with BV for 4 courses was administered in order to achieve the best response before transplantation. It is known, indeed, that the achievement of a mCR before ASCT is associated with better outcomes in terms of event-free survival (EFS) compared to patients who are not in mCR before ASCT (13-14). In a phase II study, BV was used as salvage treatment before ASCT without any significant toxicity and with 89% of patients able to proceed to transplantation (15). In this case, ASCT was performed in CR after 2 prior salvage treatments. The BV consolidation therapy after the ASCT was scheduled according to the AETHERA published data with the goal to prevent a relapse in a patient with 2 risk factors, and did not cause any significant toxicity. After more than 3 years, the patient is still in complete remission. AETHERA data seem to support the lack of a negative impact on the quality of life (QoL) for patients receiving BV as consolidation treatment (12). However, the cost-effectiveness analysis of this schedule remains debatable, as it has to be compared to the economic burden related to a potential salvage treatment followed by allo-SCT. The literature data do not report a positive cost-effective profile for BV in a consolidative setting. However, this analysis does not include the costs related to late toxicities, duration of subsequent hospitalizations and finally permanent disabilities, all key elements to be evaluated when considering a population of young subjects (16).

Clinical case n. 2

A 23-year old woman was admitted in an infectious dis- ease unit complaining fever unresponsive to antibiotics, cough and night sweats. A CT scan revealed multiple mediastinal and hilar enlarged lymph nodes. A PET/CT scan revealed FDG-avid areas in the regions already described by CT scan, with additional lesions in the neck and in paraortic regions, and with a diffuse marrow uptake. An excisional lymph node biopsy revealed a pathological infiltration by CD30+, CD15-/+, BSAP/PAX-5 +, IRF-4/MUM-1+, CD20-, CD79a-, CD3-, EBV- neoplastic cells, leading to the diagnosis of cHL, nodular sclerosis subtype. A bone marrow biopsy excluded the marrow involvement. The patient was then considered as stage IIIB, IPS 4, for the presence of anemia, lymphopenia, leucocytosis and hypoalbuminemia. ABVD chemotherapy was started with 6 scheduled courses. The interim PET/CT scan, performed after 2 courses, showed a moderate uptake (SUV max 2.3) in a retrosternal residual lymph node, inferior to liver background (Deauville Score 3). The scheduled treatment program of 6 ABVD cycles was then completed and the final PET/CT scan documented the achievement of a mCR.

Three months after the end of treatment, the patient presented B symptoms recurrence. A PET/CT scan revealed an early relapse in mediastinum and right lung hilus and showed hypermetabolic lung nodules as well. A salvage treatment consisting in 4 courses of IGEV chemotherapy was administered, with stem cell collection after the second course. A PET/CT scan was performed after the second IGEV cycle, showing a residual uptake located in the lung lesions. A tru-cut biopsy was performed, but the procedure was unsuccessful. Nevertheless, a CT scan showed a dimensional reduction of the lesion and the patient could proceed through the scheduled 4 cycles of treatment. Pre-ASCT PET/CT scan evaluation showed a mCR and allowed to proceed to ASCT with FEAM as conditioning regimen. A post-transplantation PET/CT scan confirmed the mCR, but, considering the features of this high risk disease, the patient started a consolidation treatment with BV. The treatment was carried out without any side effect. However, the treatment was discontinued due to the patient's choice after 6 courses of therapy. At the most recent follow-up visit, 21 months after the last BV administration, the patient was confirmed in CR and in optimal clinical conditions.

Discussion clinical case n. 2

Several aspects of this case need to be discussed, starting from the staging assessment. Considering the bone marrow involvement, only a PET/CT scan of fo-

cal uptake can be considered sensitive for bone marrow positivity, while a diffuse uptake warrants osteomedullar biopsy, being more frequently the expression of reactive hyperplasia (17,18). According to recently published literature data, this latter presentation is relatively uncommon in HL (9.3%), not associated to positive bone marrow biopsies. No data are available about TAC or PET/TC scan guided biopsies and the iliac crest could not necessarily be involved (19-21).
Considering the disease features at relapse, our patient presented 3 risk factors negatively affecting the survival outcome: despite showing a chemosensitive disease, the patient presented an early relapse (<12 months) characterized by extranodal involvement and B symptoms. In this case, the probability of a long-term remission, even if the patient underwent ASCT in CR, was presumably low and the risk of severe toxicity related to a salvage treatment followed by allo. SCT was also not negligible. In a setting like this, post-ASCT BV consolidation certainly represents an advisable choice. Very impressive results in terms of ORR, CR and response duration have been reported in the pivotal phase II study where, despite a median of 10 cycles administered, only 18% of patients received all the scheduled 16 cycles (7). Similar outcomes were reported by Gopal in the same setting of patients, treated with a median of 13 cycles, and by Garciaz and Gibb, who treated small cohorts of subjects eligible to receive an allo-SCT with a median number of cycles of 4 and 5.5, respectively (22-24). It is debatable whether the patients receiving a consolidation treatment should be treated with the same number of doses as relapsing patients (25).

Clinical case n. 3

A 31-year old woman was admitted to the Hematological Department after experiencing fever and swelling on the left axillary region. Her past medical history did not show other comorbidities, but she referred fever (>38°C), night sweats and pruritus for a month. The physical examination revealed the presence of enlarged fixed and painless lymph nodes in bilateral axillary region. Laboratory results showed increased erythrocyte sedimentation rate (ESR), lymphopenia, anemia and hypoalbuminemia. A CT scan confirmed enlarged nodes in the left and right axillary regions, also showing pathological lymph nodes in the upper mediastinum, a bulky lesion in the abdomen (10x12 cm) and a hepatic lesion. All CT scan findings were confirmed by a FDG-PET scan. Excisional biopsy of the left axillary node revealed a cHL, nodular sclerosis subtype. The patient disease stage was classified as IVB, with an IPS of 4. Because of the high risk prognostic features, the patient started an escalated BEACOPP chemotherapy (bleomycin, etoposide, doxorubicin, cyclophosfamide, vincristine, procarbazine, prednisone), that was scheduled for 6 cycles. A PET/CT scan performed after 2 cycles showed partial metabolic response due to the residual pathological uptake on the bulky abdominal lesion (Deauville score 4). The treatment with esc-BEACOPP was confirmed and 6 cycles were administered without any major complication. After completion of the scheduled treatment, a new FDG-PET scan showed progressive disease in the liver and in axillary and abdominal regions (Deauville score 5). The patient then started a salvage therapy with 4 cycles of Be-GEV chemotherapy (bendamustine, gemcitabine, vi- norelbine, metilprednisolone). After the fourth course, a PET/CT scan documented a partial metabolic response due to the persistence of nodal and hepatic disease. In order to obtain a better control of the lymphoma, the patient was treated with 4 BV cycles, leading to an additional reduction in the pathologic sites, that however were still positive at PET/CT scans (Deauville score 4).

We decided to proceed with ASCT following FEAM conditioning. The procedure was well tolerated but a PET/CT scan confirmed a partial metabolic response due to persistent uptake in the abdominal lesion. Considering the high risk of disease progression, a BV consolidation program was started. A mCR was documented with a FDG-PET after 6 and 12 BV cycles. A G2 peripheral neuropathy and EBV reactivation was experienced during the BV administration that prompted the BV therapy discontinuation. Sixteen months after last BV administration, a relapse was documented in the left axillary region. The patient was treated with nivolumab followed by haploidentical allo-SCT conditioned with thiotepa, busulfan, fludarabine. Currently, the patient is in CR with non-

extensive chronic graft versus host disease (GVHD) and an acceptable QoL.

Discussion clinical case n. 3

The patient was treated with escalated BEACOPP as first-line treatment: this approach, especially in very high-risk settings at presentation, has been proved to improve PFS (26). However, no clear advantage in terms of overall survival (OS) has been proven and this is probably related to a major risk of both early and late toxicities (2). Nevertheless, the patient showed a progressive disease after 6 courses and received a salvage treatment with the BeGEV regimen: this approach allowed CR and PR achievement in 73% and 10% of patients, respectively, and is related to a 2-year PFS of 80% for those who proceeded to ASCT (27). After 4 BeGEV courses, a PR was documented and a treatment with BV was scheduled in order to achieve a better response before ASCT. Despite the use of a biological drug, the PET/CT scan before ASCT still documented a PR and the response did not improve even after transplantation. BV consolidation was scheduled and, after 6 doses, a mCR was achieved and maintained until completion of the scheduled 12 cycles. No G3-G4 serious adverse event occurred and the CR lasted for 16 months. At relapse, the patient was treated with the anti-PD-1 nivolumab and complete response was consolidated by allo-SCT. Nowadays, the use of novel drugs as a bridge to allo-SCT is a widely applied approach: check-point inhibitors are associated to an ORR of 65-69% in heavily pretreated patients (28-29). However, due to their strong immunomodulating action, this class of drugs has been related to a significant increase in acute and chronic GVHD incidence and GVHD-related mortality and comorbidity (30). A recent analysis performed by the EBMT Lymphoma Working Party reported a lower risk for GVHD in patients who underwent allo-SCT after being exposed to BV (31).

Conclusions

A first-line chemotherapy program according to the ABVD regimen is currently considered the standard of care by most hematologists, being able to achieve a cure without any need of subsequent therapies in >70% of patients with advanced-stage HL. To increase this percentage, efforts in recent decades have been focused on the development of new therapeutic strategies. A first major effort was the introduction of the BEACOPP chemotherapy regimen, which is able to increase the response rate and to reduce the need of salvage therapies. However, this result did not demonstrate an OS advantage compared to the ABVD regimen, mainly due to an excess of non lymphoma-related events in the follow-up phase. A second important result has been achieved by the use of PET scan after two cycles of chemotherapy (PET-2) as a decisional prognostic factor in the continuation of first-line chemotherapy. Indeed, it was observed that patients with negative PET-2 had a better prognosis than patients with positive PET-2. From this observation, phase 2 and 3 studies have shown that an early intensification leads to an increase in ORR rate up to values >80%. Finally, the introduction of new molecules in the first-line regimens such as BV seems to improve the response rates, as well as PFS, but to date no conclusive data are available for OS and long-term toxicity (32).

With regard to the treatment of patients with relapsed/ refractory HL (rrHL), the therapeutic standard requires the administration of salvage chemotherapy with mobilization of stem cells followed by ASCT. There are currently several available chemotherapy regimens proposed and among them, the BeGEV chemotherapy scheme, whose data have been recently published and that has shown response rates >80% in patients with relapsed or refractory HL is noteworthy. The importance of salvage chemotherapy has been emphasized by studies that showed that the achievement of a negative PET scan before the ASCT is an important requirement to grant for good outcome. For this purpose, patients who do not achieve disease control with salvage chemotherapy, can benefit from the use of additional treatment, BV administration being one of the most frequently adopted strategies in Italy. This strategy allows the recovery of a good number of patients with a possible improvement in outcomes.

In addition to strategies that are useful to improve the quality of response before ASCT, relapsed patients are at high risk of experiencing further disease relapse

after HDCT, with an overall estimated risk of 50%. Consequently, another possible strategy to improve patients' outcome is to act on the post ASCT phase using the available drugs to consolidate the response achieved with the myeloablative phase. This has been done in the AETHERA randomized study that compared the efficacy of the use of a consolidation therapy with BV to standard observation in rrHL patients. The trial was successful and showed that patients randomized to BV consolidation therapy had a better PFS compared to those who were only observed, with manageable adverse events and without worsening of patient QoL, according to an ancillary study on patient reported outcome. The AETHERA study was not able to show a difference in terms of OS. This was mainly due to the crossover design of the study that allowed the patients included in the observation arm to receive BV at time of disease progression. Most importantly, the ancillary analysis showed that the higher benefit in terms of PFS was achieved in patients with a high risk profile, mainly defined by advanced stage lymphoma and by the presence of extranodal disease. Based on available evidence, the use of BV as consolidation therapy is a reasonable and feasible option for patients with rrHL that are ASCT-responsive.

In conclusion, we described 3 clinical cases of young HL patients affected by relapsed/refractory disease after frontline chemotherapy. All patients started salvage therapy with the aim to proceed to ASCT. In all cases but one the conventional salvage therapy did not achieve a pre-ASCT complete response and BV was used as a bridge to ASCT, allowing the achievement of a mCR in one of them. ASCT was administered in all patients, achieving CR in 2 cases, and was followed by consolidation BV in all of them. The decision to administer BV after ASCT was based on the positive results of the AETHERA randomized trial. Of note, all the patients showed high risk features that were also associated with an increased efficacy of BV in the original report. Additional high risk features were also considered and included the lack of pre-ASCT mCR, and the short duration of response to first-line therapy. In all the 3 reported cases, the toxicity profile of BV therapy was confirmed to be safe, with main adverse events related to reversible, mild-to-moderate peripheral neuropathy.

These 3 clinical cases provide practical and real world evidence in favor of the use of BV monotherapy as consolidation treatment after ASCT in patients with rrHL.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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