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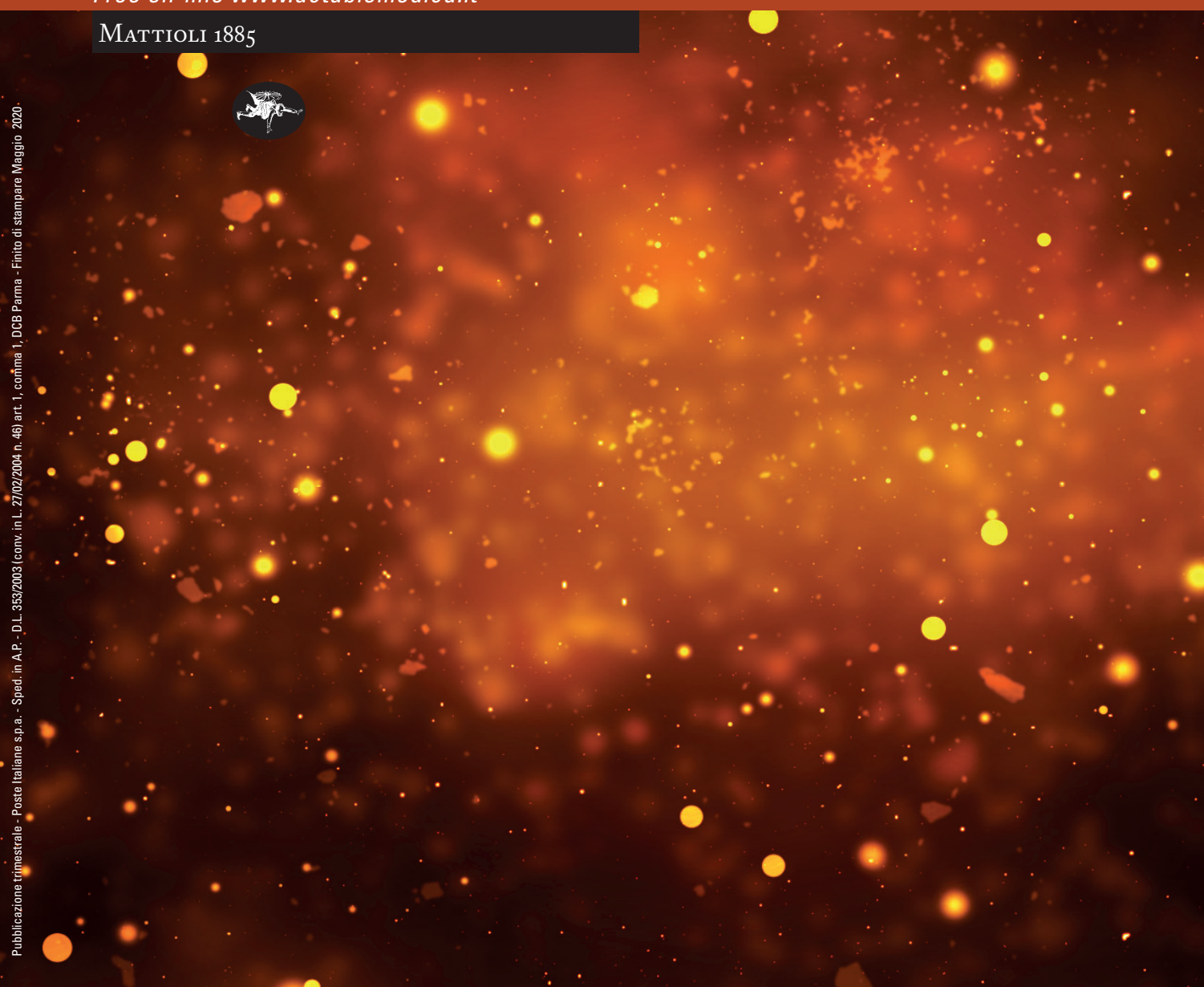

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How I Treat

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Advanced stage Hodgkin Lymphoma: patient management

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Summary. Hodgkin lymphoma (HL) is a rare cancer of the lymphoid system. It clinically presents with swollen lymph nodes and/or systemic symptoms, such as fever, night sweats, or weight loss, as signs of a more advanced stage disease. For the purpose of treatment allocation, HL cases are classified as early-stage favorable, early-stage unfavorable, and advanced-stage disease. Here below we describe four different clinical cases from real life that address some key issues and medical needs that are present in the daily practice with patients affected by advanced stage HL. The four clinical cases are quite heterogeneous, but in each case there are strong inputs to manage a specific category of advanced phase HL patient that is going to be treated with first-line therapy.

Key words: Hodgkin Lymphoma; advanced stage; first-line treatment

Hodgkin lymphoma (HL) is a rare cancer of the lymphoid system. It clinically presents with swollen lymph nodes and/or systemic symptoms, such as fever, night sweats, or weight loss, as signs of a more advanced-stage disease.

HL is one of the most common malignancies in young adults, however it can occur at all ages: recently, an increase of the incidence in people older than 70 years has been reported, while the peak incidence between 20 and 30 years of age appears to be stable. In Europe, 18,525 cases are expected annually (1).

For the purpose of treatment allocation, HL cases are classified as early-stage favorable, early-stage unfavora- ble, and advanced-stage disease (1).

The response rates following a treatment that includes mul-ti-agent chemotherapy in all cases and consolidative radiation therapy (RT) in limited stages of the disease, are high, with long-term remission rates ranging from 80% to 90%, depending on risk group, age, and treatment.

The initial treatment in HL patients with advanced-stage disease is guided by an interim PET scan after 2 cycles of systemic therapy (PET-2), and consists of 6 cycles of multi-agent chemotherapy and localized RT to PET-positive residues thereafter (1).

The combination of doxorubicin, bleomycin, vinblas- tine and dacarbazine (ABVD) has become the widely accepted standard regimen for first-line therapy, as it is associated with a considerably lower acute and long-term toxicity, when compared with the escalated combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) chemotherapy regimen, and is potentially suitable also for elderly patients.

Moreover, the BEACOPP regimen is more often complicated by long-term toxicities, such as sterility

and occurrence of second cancers. However, the risk for refractory disease or re- lapsed HL are significantly higher following the ABVD treatment in comparison to the BEACOPP regimen (1).

The aim of three recently reported large randomized phase III trials, namely the RATHL, HD18 and AHL2011 trials, was to develop individualized approaches, based on an initial therapy with either escalated ABVD or BEACOPP regimens, guided by interim PET scans (1).

The French AHL2011 trial recently reported a non- inferior four-year Progression-Free Survival (PFS) of 87.1% with randomized deescalation to 4x ABVD in patients who achieved a PET-2–negative status after 2x BEACOPP escalated *vs.* 87.4% with full 6x BEACOPP escalated (1).

High-dose chemotherapy (HDCT), followed by autologous stem cell transplantation (ASCT), is administered to patients with primary refractory and relapsed disease, if feasible, and can result in long-term remission in up to 50% of cases (1). Risk factors for relapse after HDCT have been described, as progression/early relapse, involvement of extranodal disease, and residual PET-positive disease before HDCT.

More recently, several targeted agents were investigated in this setting, such as the antibody-drug conjugate brentuximab vedotin (BV) and the checkpoint inhibitors nivolumab and pembrolizumab. The two checkpoint inhibitors nivolumab and pembrolizumab target PD-1 on exhausted T-cells and other immune cells and were approved for the treatment of patients with relapsed/refractory Hodgkin Lymphoma (rrHL). Nivolumab and pembrolizumab showed overall response rates (ORRs) of 69% and 65%, respectively, and a complete response rate (CRR) of 16% with long lasting responses in patients achieving a partial remission (PR) in pivotal phase II trials (1).

Experiences from the clinical practice often allow a better understanding of the patients' needs and can possibly help the tailoring of patient-specific therapeutic strategies.

Here below we describe four different clinical cases from real life that address some key issues and medical needs occurring in the daily practice with patients affected by advanced-stage HL.

Clinical case 1

In March 2018, a young man aged 24 without any significant clinical history, referred to the haematological center because of weight loss, fever and night sweats, with appearance of mediastinal region expansion. A biopsy diagnosed a classical Nodular Sclerosis Hodgkin lymphoma (NSHL). Blood tests and serology were in the normal range. CT/PET scan performed at diagnosis showed:

- A 12 cm mediastinal mass intensely hypermetabolic (standardized uptake value [SUV] max 17), with infiltration of the contiguous pulmonary parenchyma of the upper lobe;
- Multiple intensely hypermetabolic lymphadenomegalies (SUV not available) in laterocervical and bilateral retroclavicular regions, in the axillary cavity deep behind the pectoral muscles and in almost all the mediastinal stations, at the pulmonary hylum, along the mammary chain and in the posterior mediastinum;
- Increased concentration of the radiopharmaceutical agent in the skeletal medulla of almost all the body districts in the field of vision (SUV not available);
- Slight increase of the tracer concentration in the spleen (SUV not available);

The patient was staged IV B International Prognostic Score (IPS) according to the Hasenclever score (2).

The first-line therapy was started and 6 cycles of the ABVD regimen were scheduled.

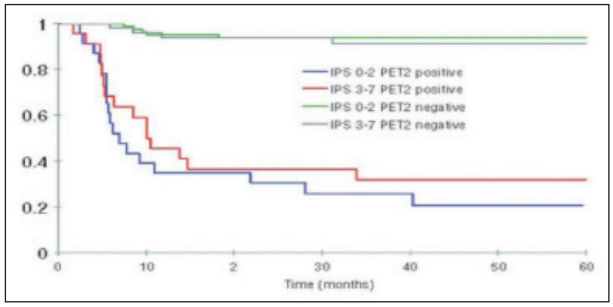
After the second cycle, an Interim PET scan was performed:

- Persistence of hyperfolding area (SUV max 9) in the left anterior mediastinal area, with involvement of the contiguous pulmonary parenchyma of size and uptake with respect to the onset;
- Persistence of bone marrow uptake (with possible influence of the G-CSF use) in all the segments reported, even if reduced (SUV not available);
- Modest and circumscribed fixation area (SUV max 2.8) in the left pulmonary basal area.

Lack of standardized response assessment criteria

- Dimensional mass reduction.

At this stage the answer was doubtful; consequently, the correlation between IPS and PET-2 was evaluated:



Following the interim PET scan, the patient was considered in partial response and continued the first-line therapy with the remaining 4 cycles of the ABVD regimen.

In October 2018, the 6 cycles of ABVD were completed and a restaging was done. The PET scan showed:

- Appearance of the hyperfunctioning area of the radiopharmaceutical agent in the left paratracheal site (SUV max 11), before the trachea in the right paramedian area (SUV max 3.3), left retropectoral (SUV max 93), right paratracheal (SUV max 5.9), anteromedially to the thoracic aorta (SUV max 9.4) and in the left pulmonary ilo-paraxial region (SUV max 10);
- Appearance of the hyperfunctioning area of the radiopharmaceutical agent (most likely lymph nodes) in place: left paratracheal (SUV max 11) unchanged the hyperfolding area in the left anterior mediastinal region (SUV max 9), with involvement of the contiguous pulmonary parenchyma.

The CT scan showed the reduction of the expansive process involving the anterior mediastinal space and extending caudally to incorporate the large vessels.

A disease progression was evaluated, and consequently the patient started a second-line therapy with the ifosfamide, gemcitabine, vinorelbine and prednisone (IGEV) regimen, followed by ASCT. The PET scan after the second cycle of IGEV treatment revealed:

- Permanence, but reduced intensity, of accumulations in the left paratracheal site (SUV max 6), ipsilateral retropectoral (SUV max 3.3) and in the left pulmonary hilum-paraxial region (SUV max 3.7);
- The hyperfolding area was substantially unchanged (SUV max 9), perhaps slightly less extensive in the left anterior mediastinum, with involvement of the contiguous pulmonary parenchyma;
- An area of modest uptake at the left pulmonary base was still present as well.

Considering these results, the disease was evaluated persistent and therefore the patient started a therapy with BV as a bridge to transplantation. The treatment is still ongoing.

Case 1 discussion

There are some considerations for this case:

- The persistence of bone marrow uptake could be influenced by the use of G-CSF.
- The interim PET scan was evaluated as partial response but there is no indication about the criteria used for the evaluation.
- The patient was evaluated as affected by progressive disease; nevertheless, he was not submitted to biopsy of the significant lymphoadenopathy to histologically confirm the persistence of HL.
- We should consider that the response to pre-transplantation salvage chemotherapy remains the most important prognostic factor for the outcome in HL patients. The decision to use IGEV instead of the bendamustine, gemcitabine, and vinorelbine (BEGEV) regimen as a bridgeto transplantation found a rational in strong previous experience: Santoro *et al.* reported the encouraging results derived from the induction regimen obtained in 91 patients with refractory or relapsed HL that were treated prospectively with ifosfamide 2000 mg/m^2 on days 1 to 4, gemcitabine 800 mg/m^2 on days 1 and 4, vinorelbine 20 mg/m^2 on day 1, and prednisolone 100 mg on days 1 to 4 (IGEV).

The 53.8% of patients achieved a CR and the 27.5% a partial response for an ORR of 81.3%. Adequate CD34+ cell collection was achieved in 98.7% of mobilized patients. The regimen appeared to be well tolerated and manageable from the patients.

The high response rate and the low toxicity profile, and the very high mobilizing potential of the IGEV regimen strongly confirmed that patients with relapsed/refractory HL may benefit from the use of this salvage induction regimen (2).

Clinical case 2

In April 2012, a 27 year-old female was referred to the haematological center for an enlargement of the supraclavicular lymph nodes and night sweats.

A biopsy was performed and a diagnosis of classical NSHL was done.

After bone marrow biopsy, PET and CT scans, a stage IV x B was deter- mined according to the Ann Arbor staging system based on the presence of disease in left supraclavicular nodes, mediastinum, liver (PET positive for nodular lesions in segment III) and lung (bulky disease in the upper left lobe 8 x 4.8 x 9 cm; SUV max 20.41). A diffuse and homogeneous marrow uptake was not considered as disease involvement.

The IPS score was 3, consistently with stage, leucocytosis, lymphocytopenia.

The patient was enrolled in the HD0801 protocol and started the treatment with the ABVD regimen.

In the protocol, PET-2-positive patients were able to shift to an intensified treatment with IGEV followed by ASCT, while PET-2-negative patients completed 6 cycles of the ABVD regimen.

As per protocol, the patient underwent a PET scan after 2 ABVD cycles. The interim PET scan showed:

- The disappearance of all lesions detected at the baseline PET scan;
- A focal uptake in the maxillary bone, considered secondary to an odontogenic infection.

The patient completed the 6 cycles of the ABVD regimen and a restaging with CT and PET scans was performed. The CT scan showed:

-A residual lesion measuring 2 cm in the major axis in the upper lobe of the left lung;

- The resolution to less than 1.5 cm of the nodal lesions. Consequently, considering the absence of pathological uptakes at the end of the treatment, a CR was evaluated.

According to the HD0801 protocol, the patients in CR were randomized to consolidative RT of the bulky lesions at baseline or to observation. The patient was randomized to observation only but, after a preliminary internal discussion and the subsequent discussion with the patient, it has been decided to start the RT considering the site (the lung), and the dimension of the baseline bulky lesions.

So, the patient withdrew from the protocol and received 30.6 Gy in 17 fractions of 1.8 Gy each.

After 70 months, the patient is still in CR without any treatment toxicity.

Case 2 discussion

There are some considerations for this case:

Indeed, the protocol regimen that was applied for this patient was a real effective approach.

The phase II HD0801 study involved 519 patients with advanced-stage *de novo* HL submitted to an initial treatment with the ABVD regimen and an early ifosfamide-containing salvage treatment, followed by stem cell transplantation if they showed a positive PET scan evaluation after 2 cycles of chemotherapy (PET-2).

The primary endpoint was the 2-year PFS calculated for both PET-2-negative patients (who completed a full treatment of 6 cycles of the ABVD regimen) and PET-2-positive patients.

Overall, 103 out of the 512 evaluable patients were PET-2-positive. On intention-to-treat analysis, the 2-year PFS was 76% for the PET-2-positive patients (regardless of the salvage treatment they received) and 81% for the PET-2-negative patients (3).

Clinical case 3

In February 2015, a 67-year-old male was referred to the haematology outpatient clinic because of a swelling of the right axilla associated with B-symptoms, consisting in periodic fever higher than 38°C, and drenching night sweats. On clinical examination, the patient had a palpable lymph node of 5 x 3 cm in the right axilla.

Lymph node biopsy was performed and histological ex- amination showed CD30+ Reed-Sternberg cells with weak PAX5 and sporadic CD15 expression, organized in microgranulomas and surrounded by a rich infiltration of CD3+ lymphocytes and macrophages. Diagnostic conclusion was HL.

The CT scan revealed enlarged axillary lymph nodes, and thoracic and abdominal lymph nodes of about 1 cm.

The staging PET-CT scan revealed:

- ^{18}Fluorodeoxyglucose (^{18}FDG)-avid disease in the right retroclavicular, axillary and retropectoral area, in the anterior mediastinum, the paratracheal, right hilar, right cardiophrenic angle, in the upper abdomen (celiac, interportocaval, left paraortic) and right iliac area.

– The spleen showed diffuse and irregular uptake. Bone marrow biopsy was negative for lymphoma infiltration.

Stage was defined as IIIsB, while the IPS was 2 because of age >45 years and of male sex.

The medical history was positive for surgery of aneurysm of the ascending aorta, with replacement by a tubular prosthesis in 2013. The patient was a former smoker.

He was in medical treatment for hypertension with the beta-blocker agent bisoprolol 2.5 mg, 1 tablet/die, and the angiotensin II receptor antagonist telmisartan 80 mg, 1 tablet/die, and received prophylaxis with acetylsalicylic acid 100 mg/die.

Echocardiography documented a slight enlargement of the left atrium and ventricle, with preserved ejection fraction (65%).

The N-terminal pro-hormone natriuretic peptide (NT- proBNP) level was slightly high (296 pg/mL, *vs.* the upper normal value of 150 pg/mL).

Pulmonary function tests, including diffusing capacity of the lung for carbon monoxide (DLCO) and arterial blood gas analysis, resulted in the normal range.

In March 2015, the patient started a treatment with the first of 6 cycles of the ABVD regimen at standard dose. Supportive therapy included the administration of the myeloid growth factor G-CSF on days 8 and 9 following each administration of chemotherapy. Therapy was administered as scheduled.

The interim PET-CT scan documented a complete metabolic response with a minimal uptake in supradiaphragmatic lymph nodes, above the mediastinal blood flow but lower than liver (score 2 according to the 5-point Deauville scoring system), and absence of FDG uptake in the abdominal lymph nodes.

The patient continued the therapy as scheduled.

Monitoring of NT-proBNP showed slightly high, but stable levels (336 pg/mL), while the troponin test was negative.

In July 2015, after the fourth cycle of the ABVD regimen, the patient reported shortness of breath during physical activity. Auscultation of the lung was normal, chest X ray did not reveal any abnormality. The pulmonary function test showed normal DLCO, but a significant reduction of arterial pO_2 (from 100 mmHg to 71 mmHg).

Bleomycin was omitted from the last 2 cycles of chemotherapy, and the patient completed the 6 cycles. Respiratory symptoms resolved, and pulmonary function tests at end of therapy documented an increase of arterial pO_2, and DLCO in the normal range.

The PET-CT scan at end of therapy was unchanged with respect to interim PET scan (Deauville score 2).

Four years after the diagnosis, the patient continues to be in CR and in a good health status.

Case 3 discussion

There are some considerations for this case:

-PET-CT scan resulted in an upstaging of disease with respect to CT scan, detecting also FDG-avid disease in abdominal pericentrimetric lymph nodes and spleen.

– The change from stage IIB without bulk to stage IIIsB resulted in a change of the treatment strategy from a potential combined treatment modality with an abbreviated chemotherapy to a full course of 6 cycles of the ABVD regimen.

– The patient had cardiac and limited pulmonary comorbidity, as he was a former smoker, but the patient did not experience cardiotoxicity despite the full dose doxorubicin. Doxorubicin replacement with the liposomal formulation (Myocet), while maintaining the ABVD regimen as backbone, did not result in a better tolerability of the regimen in an Italian multicenter study for elderly HL patients.

– The patient developed respiratory symptoms after the fourth cycle of the ABVD regimen. Bleomycin is associated with an increased risk of pulmonary toxicity in elderly patients, most often observed after the third or fourth cycle. Although the patient did not show the typical clinical and radiological signs of bleomycin-induced pneumonitis, the decrease in arterial pO_2 could have been an early sign of lung damage. This patient did not require therapy with corticosteroids, and the omission of bleomycin was sufficient to normalize the lung function.

– The RATHL study recently demonstrated that bleomycin can be safely omitted following a negative interim PET scan in patients with advanced HL, with excellent results for disease control. Omission of bleomycin after the negative PET scan result fol-

lowing the second cycle in our patient could have been a safe strategy to avoid initial lung injury. Another potential strategy to avoid pulmonary toxicity in advanced-stage patients at risk is bleomycin replacement with BV.
- The A-AVD regimen is associated with a reduced pulmonary toxicity and an increased efficacy.

In conclusion, the treatment of elderly HL patients remains challenging, as efficacy optimization and reduction of the risk of toxicity should be combined.

Clinical case 4

In March 2015, a 42-year-old woman was referred to the haematological center for a large mediastinal mass (21 x 15 cm) with dyspnea, dry cough and shortness of breath on minimal exertion.

On presentation, the patient was febrile (38.5°C), referring night sweats, and weight loss; blood pressure was 117/81 mm Hg and pulse was regular (140 bpm). The respiratory rate was 28/min, with oxygen saturation of 93% on room air. Heart sounds were diminished, while lung auscultation showed a reduced right side air entry. Other outcomes of the physical examination were in the normal range.

CT-scan and ^{18}FDG-PET scan revealed active disease in the chest due to:
- A large anterior mediastinal mass encasing the great vessels, including the right upper pulmonary artery and the superior vena cava;
- There was at least 50% tracheal compression by mass;
- The right lung was collapsed, with massive pleural effusion and pericardial effusion;
- Laterocervical and supraclavicular right lymph nodes (30 x 40 mm), paraesophageal, para-aortic, mesenterium lymph nodes and liver were also involved.

Excisional biopsy of supraclavicular right lymph node revealed cHL, nodular sclerosis subtype, not Epstein-Barr virus (EBV)-associated in advanced-stage, unfavorable disease (stage IVB and IPS of 4 based on stage, hemoglobin level of 9.8 mg/dL, absolute white cells count 16500 cells/mm^3, absolute lymphocyte count 450 cells/mm^3).

The patient started a treatment with the ABVD regimen.

^{18}FDG-PET scan after 2 cycles was positive and, based on the promising results of PET-2-adapted therapy, the switch to a most efficacious regimen, such as stem cell collection and ASCT, was proposed.

However, due to her religious beliefs, the patient re- fused any high-dose regimen that could expose her to both autologous and heterologous blood component. For this reason, she accepted the salvage treatment followed by early evaluation, according to standard BEACOPP regimen.

Since after 4 BEACOPP courses the patient achieved only a partial remission, and the ^{18}FDG-PET scan was still positive, the patient accepted an early further salvage treatment with the IGEV regimen, and with 40,000 UI EPO twice a week in place of blood transfusions.

After 2 IGEV courses, the patient achieved only a par- tial remission, and the ^{18}FDG-PET scan was still positive, so she was referred to further salvage treatment with 1.8 mg/kg BV administered every 3 weeks by IV infusion, in a named national program.

After 4 cycles, the CT-PET scan showed a reduction in size and intensity of the ^{18}FDG uptake, so the scheduled treatment was completed with additional 12 BV cycles, obtaining the PET-scan negativity after 8 cycles.

The CT scan confirmed a not-active mediastinal mass with a progressive size reduction during the treatment (7.5 x 5 cm after 8 cycles, 6 x 4 cm after 12 cycles, 5 x 3 cm after 16 cycles), and an excellent performance status.

The patient completed the treatment in August 2017, and she is still in follow-up.

Case 4 discussion

This clinical case can suggest some considerations:

The potential benefits of a PET/TC scan-adapted therapy are:

1) Negative interim PET scan: reduce the treatment intensity in rapid response after 2 cycles of chemotherapy, perceived to be at low risk of treatment failure; 2) Positive interim PET scan: intensify the treatment in patients for whom the initial treatment has been less effective (20%) (1). Retrospective studies of patients treated with the ABVD regimen suggested that the FDG-PET scan performed after 2 cycles of treatment

can be highly predictive of treatment success or failure (4). This appears to provide better prognostic information than CT scans, (5) with a high negative predictive value, giving a 2-year PFS of approximately 95% and a reasonable positive predictive value, with PFS between 13% and 27% (6,7).

- The international Response Adjusted Therapy for Hodgkin Lymphoma (RATHL) study (4) tested the use of FDG-PET scans after 2 initial cycles of the ABVD regimen in more than 1200 patients, after which those with an interim PET scan score ranging from 1 to 3 were randomly assigned to either continuation of the ABVD treatment or to receive doxorubicin, vinblastine, and dacarbazine (AVD) without bleomycin to determine whether the pulmonary toxicity could be reduced for patients with a good prognosis. Conversely, patients with an interim PET scan score from 4 to 5 proceeded to intensification with the BEACOPP regimen every 3 weeks or with the similar BEACOPP-14, administered at 2-week intervals.
- The Italian lymphoma group study (9) used a similar approach, with interim FDG-PET scans after 2 cycles of the ABVD regimen followed by intensification to the BEACOPP regimen for patients with positive scans. The rates of metabolic remission after 2 cycles of theABVD regimen were very similar in all the 3 trials, at about 85%. The results of treatment in the PET-positive group were also similar and appeared to be superior to the historical controls used in previous studies, with subsequent metabolic response rates of 75% or more and projected failure-free survival figures at 2 years of 65- 75%.

The antibody-drug conjugate BV combines an antibody to the CD30 molecule, which is expressed on Reed-Sternberg cells, with an antitubulin, monomethyl auristatin E. The efficacy seen in early-phase studies has been impressive, with 76 objective responses (and 34% CRs) among 102 patients with recurrent disease who had already undergone high-dose therapy and autologous stem cell rescue (10-11-12).

- Pembrolizumab and nivolumab are two anti-PD-1 antibodies that have undergone phase 1 trials, with re- ported response rates of 53% and 87%, respectively (13). Nivolumab is currently being assessed in a phase 2 trial in patients whose disease has progressed after ASCT (14).
- A range of salvage therapies has been tested in the 20-30% of patients with advanced disease whose HL was refractory to, or relapsed after initial treatment. The salvage regimens appear to be largely interchangeable. The single-arm phase 2 trials performed did not offer a direct comparison between regimens, but ORR of 60% to 80% have been found (15). A randomized comparison of sequential single-agent high-dose therapy *vs.* continued conventional salvage therapy did not show any difference in efficacy (16).

Favored salvage regimens in our center include ifosfamide, carboplatin and etoposide (ICE), epirubicin in place of carboplatin (IVE), and cytarabine and cisplatin (DHAP).

- Patients who are eligible and achieve a complete metabolic response should proceed ASCT in second remission (17).
- Assuming a successful mobilization of stem cells, the standard high-dose regimen used prior to stem cell transplantation is carmustine, etoposide, cytarabine, and melphalan (BEAM). This regimen is based on 2 randomized controlled trials that compared high-dose chemotherapy followed by ASCT to conventional chemotherapy in patients achieving a second remission. Both studies showed a significantly improved freedom from progression in the group receiving high-dose therapy, although the small number of patients enrolled prevented the conclusive demonstration of improved OS (18,19).

Conclusion

The four clinical cases we reported are quite heterogeneous but in each case there are strong inputs to manage a specific category of advanced-phase HL patient that is going to be treated with first-line therapy.

Indeed, we discussed both young and elderly patients' cases. Patients with an early relapse and the role of PET scans in treatments and in disease evaluation were discussed as well.

It is important to remind that new drugs and clinical trials are allowing to treat in advance the patients with a sort of tailored therapy that could bring to a long disease remission and a good quality of life. An early

identification of the most appropriate regimen for the patient is crucial for the treatment outcome.

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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Treatment of very high-risk classical Hodgkin Lymphoma: cases' selection from real life and critical review of the literature

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Summary. Over the last 4 decades, advances in radiation therapy and the addition of combination chemotherapy have significantly increased the cure rate of patients with HL, with a 5-year OS of about 90% . However, despite high rate of cure after first line of therapy, 5%-10% of HLs are refractory to the treatment, and 10-30% of patients have a disease relapse after a complete response (CR). Relapsed HL can be treated with salvage therapies with a long-lasting complete remission in 80% of cases. In recent years, novel drugs are available for the patients with relapsed/refractory HL, like Brentuximab Vedotin and immune checkpoint inhibitors. These drugs have been able to rescue a cohort of patients who subsequently could receive an allogeneic stem-cell transplant. Our cases have been chosen because they are representative of critical issues in the management of relapsed/refractory HL; our experiences are consistent with what reported by other Authors.

Key words: Hodgking Lymphoma, high risk HL patien, relapsed/refractory disease, salvage treatments

Background

Over the last 4 decades, advances in radiation therapy and the addition of combination chemotherapy have significantly increased the cure rate of patients with classical Hodgkin Lymphoma (cHL), with a 5-year overall survival (OS) of about 90% in patients younger than 60 years (1). However, 5%-10% of HL patients are refractory to first line treatment, and 10-30% of patients relapse after achieving a complete response (CR) (2). Relapsed HL can be managed with salvage therapies with a long-lasting complete remission in about 50 % (3).

Numerous studies have shown that high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is superior to conventional chemotherapy in terms of long-term disease-free survival (DFS) and OS. Outcome of second line therapy is strongly influenced by sensitivity to second line chemotherapy and consequently by disease status at transplantation (4-6), and patients refractory to salvage chemotherapy or relapsing after ASCT present a

dismal prognosis (2, 7). Moreover, some patients with relapsed/refractory HL are not considered suitable for ASCT, due to both co-morbidities and age: for this subgroup, a standard of care is lacking and outcome is unsatisfactory (8).

In recent years, landscape of relapsed/refractory cHL has been deeply modified by novel drugs availability, being brentuximab vedotin (BV) and immune checkpoint inhibitors (CPI) the most effective (9-14).

Brentuximab vedotin is an antibody-drug conjugate active against CD30-positive cells, such as Reed Sternberg cells, and delivers the antimicrotubule agent monomethyl auristatin E inside HL and Reed-Sternberg cells, inducing apoptosis. Brentuximab vedotin has shown capability to rescue about two thirds of cHL relapsing after, or not eligible to, ASCT (9, 10). Additionally, it has shown to induce high, long lasting ORR and PFS rates when used as post ASCT consolidation in patients with classical Hodgkin lymphoma (cHL) at high risk of relapse or progression, with an acceptable tolerability and safety profile (13, 15-17). Based on these data, Brentuximab vedotin as single agent has been approved for treatment of cHL who relapse after autologous ASCT or following two prior therapies in those unsuitable for ASCT (18). More recently, Brentuximab-Vedotin has been tested as debulking pre-transplant strategy in relapsed/refractory cHL failing at least one salvage chemotherapy with promising efficacy (19).

Checkpoint inhibitors target the interaction of the programmed death (PD)-1 immune checkpoint receptor, and its ligands PDL1 and PDL2, and have shown a significant activity in many tumors (7). Nivolumab and pembrolizumab are anti-(PD)-1 monoclonal antibody currently approved for the treatment of relapsed/refractory classical Hodgkin's lymphoma cHL (20, 21).

In this paper we report 6 real life cases treated in different Italian hematological centers, selected because representative of critical and high-risk areas in the relapsed/refractory cHL management, due to the lack of a clear and well recognized standard of treatment and to the patients' clinical heterogeneity. With the aim of picturing how challenging clinical choices might be in the real-life setting, we report two different therapeutic choices for each situation, including the use of BV either in monotherapy (in label) or combined with chemotherapy (off label), and we provide a critical review of the literature.

Cases 1A and 1B Young patient, eligible to ASCT

Treatment options for incomplete response to second-line therapy: BV or conventional third-line chemotherapy ?

Case 1A (Re)

A 26-year-old male attended to our center with fever, irritating cough, and night sweats, without benefit after antibiotic therapy. He complained a slight weight loss. A chest X-Ray was negative; a chest computer tomography (CT) scan showed mediastinal lymphadenopathies (up to 7 cm). An echo guided core needle biopsy of mediastinal mass demonstrated classical Hodgkin Lymphoma (cHL). ^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) showed ^{18}FDG uptake in hilar and mediastinal lymphadenopathies, and in small bilateral lymph nodes of the neck; below the diaphragm, ^{18}FDG-PET demonstrated lymphomatous disease with paraaortic lymph nodes and focal splenic uptakes. An abdomen CT scan confirmed four hypodense lesions of the spleen (up to 1.2 cm). The patient was then diagnosed advanced-stage cHL (stage IIIB), with International Prognosis Score of 3 (based on gender, stage, and albumin level of 3.8 mg/dL). Cardiac and pulmonary function tests were found within the normal range. He received a first line therapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with filgrastim as secondary prophylaxis. ^{18}FDG-PET after 2 cycles showed disappearance of all uptakes. He completed 6 cycles and achieved a complete response (the post-treatment ^{18}FDG-PET demonstrated resolution of previous abnormal uptake and the CT scan showed nodal size consistent with partial response by International Working Group criteria). Eight months after completing chemotherapy, a CT scan revealed a 2.6 cm retrosternal lymph node and a slight increase in one epiaortic lymph node (maximum diameter 3.6 cm), both with ^{18}FDG-PET pathologic uptake. No extranodal disease was evidenced. Incisional biopsy of mediastinal lymph nodes with video-assisted thoracic surgery approach revealed recurrent cHL, classified as

stage IA, non-bulky. Considering the young age of the patient, we decided to start a salvage chemotherapy and a subsequent high dose chemotherapy with autologous stem cell transplant (ASCT), if responsive. He received 2 cycles of salvage treatment with ifosfamide, gemcitabine, and vinorelbine (IGEV), which were well tolerated. ^{18}FDG-PET after the second cycle showed a partial response, with persistence of pathologic uptake in the epiaortic lymph node. The CT scan revealed nodal size reduction of 40% of product of the main diameters. We then decided to treat the patient with 2 cycles of esc-BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). At hematologic recovery after the first esc-BEACOPP, 9x10^6/Kg CD34+ cells were collected. After the second cycle the patient was hospitalized for neutropenic fever, resolved with broad spectrum antibiotics. The response to the treatment was then re-evaluated: CT scan showed no disease, and ^{18}FDG-PET was negative. He proceeded to ASCT after a carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning regimen. High dose chemotherapy was well tolerated. After post-transplant recovery, radiotherapy on sites of previous relapse was administered (30 gray). Since then, the patient has been followed for 3 years after ASCT with no relapse.

Case 1B (Rusconi)

A 40-year-old Caucasian male, with no significant co-morbidities in the medical history, presented with fever, significant weight loss (8 kilos in the last two months) and cough. A chest X-ray detected a mediastinal enlargement, while an echocardiography examination showed a pulmonary hypertension (65 mmHg) and a 2 cm pericardial effusion without impairment of the left ventricle ejection fraction. Patient was therefore referred to the emergency department, where a CT scan detected a bulky mediastinal mass (up to 10 cm) and multiple supradiaphragmatic adenopathies (up to 4 cm). Patient was admitted in the Hematology department, and an excisional biopsy of a supraclavicular lymph node was performed. Histological examination showed a classical Hodgkin lymphoma (cHL), nodular sclerosis (CD30 positive, CD15 positive, CD20 negative). ^{18}FDG-PET revealed ^{18}FDG uptake in the large mediastinal lymphadenopathies (SUV max 8.32) and in hilar and cervical (bilateral) and axillary (left) lymph nodes; a diffuse, low intensity uptake in the skeleton was described as well. Bone marrow biopsy was negative for cHL CD30+ localization. The disease was classified as Ann Arbor stage IIB, with an Hasenclever score of 2 (due to male gender and low albumin). Pulmonary function test was normal. Six cycles of ABVD plus radiotherapy on bulky mediastinal mass were planned. Chemotherapy was administered with a 25% reduction of the dacarbazine dose only on day 14 of the first cycle due to transaminitis (G3); neither further dose reduction nor delay were registered. Interim ^{18}FDG-PET performed after two ABVD cycles resulted negative, with a Deauville Score (DS) of 2; the co-registered basal CT scan showed a reduction of tumor size consistent with partial remission. A contrast-enhanced CT scan was performed after 4 ABVD cycles and demonstrated a reduction of the mediastinal bulky adenopathy (maximum diameter 4 cm) and the complete resolution of the pericardic localization, together with the other sites of disease. ^{18}FDG-PET after 6 ABVD cycles showed the reappearance of a mediastinal uptake (DS: 4). A CT guided core needle biopsy of the mediastinal residual mass showed the persistence of cHL. After 2 cycles of non-cross-resistant salvage chemotherapy with bendamustine, gemcitabine, vinorelbine (BeGEV), ^{18}FDG-PET was repeated, and was consistent with stable disease, while the co-registered CT scan showed a further reduction in the mediastinal lymphadenopathy (maximum diameter 3 cm). Patient was therefore considered not eligible to autologous stem cell transplantation due to the persistence of disease, even if an adequate stem cell harvest was obtained after the first BeGEV cycle (8.8x10^6 CD34+/kg). Patient was further treated with single-agent BV at a standard dose of 1.8 mg/kg iv every 3 weeks as an attempt to obtain a metabolic response and proceed to consolidation with ASCT. Treatment with BV was well tolerated and no significant toxicity was detected. After 4 BV cycles, ^{18}FDG-PET was performed, with a negative result (DS: 2), while no changes in the mediastinal lymph node was detected. The patient underwent ASCT following carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning regimen. After transplant recovery, radiotherapy on previous mediastinal bulk as additional consolidation was administered (30 Gy). ^{18}FDG-PET 8 weeks after

radiotherapy completion was negative (DS: 2). Patients is now in continuous complete remission 2 years after ASCT and radiotherapy and undergoes a periodic regular clinical follow-up.

Discussion case 1A and 1B (Zanni)

Several studies on r/r HL have shown that high-dose chemotherapy followed by ASCT exerts a better control of the disease as compared with conventional chemotherapy, curing approximately 50% of patients (4-6, 22). Therefore, ASCT is currently considered the standard of care in this setting (23). To overcome drug resistance, many salvage regimens incorporating compounds never used in first-line (e.g. ICE, DHAP or IGEV) have been investigated before ASCT, showing approximately 80% of ORR and CR ranging from 20% to 50% (24-27). Recently, an Italian phase 2 trial showed the high efficacy of the "BeGEV" regimen as an induction before ASCT, describing 73% of CR and 10% of PR, with a 2-year PFS and a OS of 62% and 77%, respectively (27). As of today, however, no results are available from prospective randomized trials comparing diverse salvage regimens before ASCT. Moreover, the overall therapeutic impact of ASCT relies on the chemo-sensitiveness of the disease to salvage therapy, which remains one of the most important predictive factors of long-term outcome (24). ^{18}FDG-PET remains the best detection method of residual active disease, and several studies have suggested that its negativity during salvage chemotherapy and before ASCT strongly predicts PFS (28-30). Indeed, a retrospective analysis of 153 r/r HL patients showed a significant difference in 5-year event free survival (EFS) between pre-transplant PET-positive and PET-negative patients (31% vs 75%) (30). On the other hand, novel approaches are warranted for patients showing incomplete response after second-line treatment. Third-line conventional chemotherapy reached acceptable ORR in a few studies, including the one by Moskowitz et al. showing the capacity of 2 cycles of gemcitabine, vinorelbine and doxorubicine to induce a 53% of CR in patients who were PET-positive after ICE-based salvage chemotherapy, an outcome that was even similar to PET-negative ones (31). An Italian retrospective analysis on a few r/r HL patients treated with BEACOPP regimen, also demonstrated the usefulness of a third-line non-cross resistant chemotherapy for achieving the best disease response before ASCT (32). Consistently, BV may represent another effective option as a bridge to ACST, but only few data are currently available in the transplant-naive setting of patients failing at least one salvage therapy. The study by Zinzani et al. investigated the efficacy of BV monotherapy in 30 r/r patients before ASCT. After a median of 4 cycles, OR and CR rates were 40% and 30%, respectively, according to ^{18}FDG-PET evaluation (14). Another retrospective study from UK reported an ORR of 56% and a CRR of 29% in the same setting of patients (16). These results were also confirmed by a prospective multicenter study reporting an ORR of 50%, which allowed 47% of patients to proceed to ASCT (33).

Cases 2A and 2B. Young patient, eligible to ASCT

Treatment options for refractoriness to third line brentuximab-vedotin: check-point inhibitors or a rechallenge with BV with the addition of chemotherapy?

Case 2A (Puccini)

A 25-year-old man presented with a dry cough and pruritus in October 2012. Physical examination identified enlarged lymph nodes (in particular supraclavicular, 3 cm) in both sides of the neck. Excisional biopsy from the supraclavicular lymph node showed stage I nodular sclerosing Hodgkin lymphoma. ^{18}FDG-PET scan showed increased uptake in bilateral cervical, supraclavicular, mediastinal, and bilateral axillary nodes. CT scan evidenced multiple mediastinal lymph nodes of a maximum diameter of 4 cm. A bone marrow biopsy was negative for cHL localization. The stage was Ann Arbor IIA without a large mediastinal tumor. According to the German Hodgkin Study Group (GHSG) risk allocation, the patient was classified as early unfavorable classical Hodgkin lymphoma. In January 2013 the patient started 4 cycles of ABVD followed by 30 Gy involved field radiotherapy (IFRT). Post-treatment PET showed a complete metabolic response (DS 2). Nine months after the end of the radiotherapy, the patient presented with itching and a new increase in the neck lymph nodes. PET and biopsy confirmed the relapse (CD30-positive/CD15-positive and CD20-negative classical Hodgkin lymphoma of nodular sclerosis subtype). The

patient was treated with four cycles of IGEV, with the aim to proceed to high-dose BEAM chemotherapy and autologous stem cell transplant. After 2 cycles, CT showed a partial remission, and an adequate autologous stem cell harvest was obtained. PET performed after the fourth IGEV course was consistent with stable disease. Therefore, in September 2014, patient began therapy with esc-BEACOPP for 4 cycles. CT and ^{18}FDG-PET at the end of the therapy showed persistence of disease (DS 5). In February 2015 patient was thus treated with BV at the standard dose of 1.8 mg/kg every 3 weeks intravenously, with a partial remission after 4 cycles. After 8 doses, he presented with a grade 2 peripheral sensory neuropathy and BV dose was therefore reduced to 1.2 mg/kg; peripheral neuropathy improved to grade 1. Re-staging after 8 BV cycles evidenced a partial remission, with a residual DS of 4 in the mediastinal and supraclavicular lymph nodes. Considering the opportunity to participate in the nivolumab Expanded Access Program (EAP), we decided to introduce the anti-PD1 antibody as a bridge to autologous stem cell transplantation (ASCT). In October 2015 our patient started treatment with nivolumab at 3 mg/kg dose every two weeks, with good hematological and extra-hematological tolerability. Re-staging after 3 months of treatment revealed a partial response, and after 6 months a complete response (DS 2). An HLA identical donor was not available, and patient received ASCT with BEAM conditioning. During aplasia he had 2 episodes of fever of unknown origin (FUO). No relevant complications occurred during the post-transplant period. At 24 month follow up the patient showed good general condition without disease relapse.

Case 2B (Sorio)

A 22-year-old male, with no significant past medical history, underwent hematological evaluation in February 2015, due to night sweats and neck adenopathies. A lymph node biopsy allowed to diagnose classical Hodgkin Lymphoma, nodular sclerosis. CT scan showed multiple supra-diaphragmatic adenopathies with a mediastinal bulky mass (10 cm, SUV max 15.8). A bone marrow biopsy was negative for HL. Ann Arbor stage was IIB with bulky mediastinal involvement. First line chemotherapy with 6 ABVD cycles was started; interim PET after 2 courses was consistent with complete metabolic response (DS 3). Consolidation radiotherapy to bulky sites was delivered after chemotherapy (30 Gy). Post-radiotherapy ^{18}FDG-PET was negative. After 6 months, a first biopsy confirmed a relapse. ^{18}FDG-PET scan showed a pathological uptake (SUV max 9.7) at right lung hilum and at mediastinal level. After two R-DHAOx (rituximab, dexamethasone, cytarabine, oxaliplatin) cycles, $13.38x10^6$ CD34+ cells/Kg were harvested. ^{18}FDG-PET after the 2 salvage cycles showed progressive disease, and patient reported night sweats reappearance. Patients was treated with four BV cycles at standard dose (1.8 mg/kg IV every 3 weeks), obtaining a partial metabolic remission (DS 4). Bendamustine was added to BV, and administered for 4 cycles. ^{18}FDG-PET after 2 salvage cycles showed a complete remission (DS 2), and no systemic symptoms were reported. Autologous stem cells consolidation after BEAM conditioning was performed in May 2018. Since then, clinical and radiological follow-ups have been negative for disease recurrence.

Discussion (Vanazzi)

In chemo-refractory patients, once excluded (whenever possible) the occurrence of a different histology (grey zone lymphoma, NHL or non-malignant process) on a second biopsy, BV and checkpoint inhibitors represent valuable therapeutic options (2). As single agent, BV was shown to induce CR in approximately one-third of patients and, in combination with chemotherapeutics as gemcitabine, bendamustine or cisplatin, it results in therapeutic outcomes mostly comparable with those obtained using more aggressive strategies (34-38). In the study by LaCasce et al., evaluating the combination of BV with Bendamustine as first-salvage regimen in r/r HL, fifty-five patients received the standard dose of BV on day 1 with bendamustine 90 mg/m^2 on days 1 and 2 every 3 weeks for up to 6 cycles. Patients could undergo ASCT at any time after cycle 2. Following ASCT or completion of combination therapy, if not proceeding to ASCT, patients could receive BV monotherapy for up to 16 cycles. After a median of 2 cycles (range, 1-6), the objective response rate (among 53 efficacy-evaluable patients) was 92.5%, and 39 patients (73.6%) achieved CR. Forty patients underwent ASCT. Thirty-one patients, including 25 transplanted patients, received BV monotherapy (median 10 cycles; range 1-14). After a median of

20.9 months of follow-up, the estimated 2-year progression-free survival was 69.8% (patients who had received ASCT) and 62.6% (all patients) (38). When combined with nivolumab, BV produced 82% of OR, including 61% of CR (39). Overall, 87% of patients proceeded to ASCT, and 68% underwent transplantation with no need of additional salvage therapy. Also nivolumab alone has been reported as valid bridge-to-transplantation option in the refractory setting. In a phase 2 study, 243 patients received nivolumab, showing OR and CR rates of 65% and 29%, respectively, in BV-naïve patients (n = 63), 68% and 13% in those who had undergone prior ASCT followed by BV (n = 80), and 73% and 12% in patients who had received BV before and/or after ASCT (n = 100) (40). Similarly, a retrospective analysis of 82 r/r HL treated by nivolumab for 12 weeks showed ORR and CR of 64% and 22%, respectively. Twenty patients underwent subsequent transplantation. Among 11 patients receiving allogeneic stem-cell transplantation, 5 reached a durable CR. The main reason of nivolumab discontinuation was the occurrence of disease progression, while the safety profile of the drug was acceptable, with only 4 patients displaying serious adverse events. The 6-month OS and PFS rates were 91.2% and 77.3%, respectively (41). Thus, nivolumab represents a good option for BV-refractory HL patients, and may be a useful bridge to transplantation, although associated with a slightly increase of toxicity. Similar results were also achieved using pembrolizumab, which produced OR and CR rates of 74% and 22%, respectively, in patients who underwent prior ASCT and BV, 64% and 25% in never transplanted patients, as well as 70% and 20% in BV-naïve patients who failed ASCT (42).

Cases 3A and 3B Elderly patient

Treatment options for r/r cHL accordingly to fitness status: beyond age?

Case 3A (Flenghi)

A 71-year-old caucasian women without significant anamnestic co-morbidities, referred to our centre for the occurrence of night-sweating and itching. An abdominal ultrasound showed right pleural effusion, confirmed by chest X-ray; thoracic-abdominal CT-scan showed also the presence of a mediastinal bulk (92 x 65 x 160 mm). Blood tests, ECG and Echocardiogram resulted normal, and ECOG score 0; the geriatric assessment showed ADL (Activities of Daily Living) score of 6, IADL (Instrumental Activities of Daily Living) 7, CIRS (Cumulative Illness Rating Scale) 1. The PET-CT scan showed a high ^{18}FDG uptake (SUV_{max} 22.6) of the mediastinal mass, without other lesions. The subsequent mediastinal biopsy was diagnostic for nodular sclerosis type II Hodgkin's lymphoma. The pleural effusion cytology resulted negative for neoplastic cells. The final diagnosis was Hodgkin's lymphoma stage IB bulky, with Hasenclever score 1. The patient was treated with 2 cycles of ABVD. We observed persistence of disease at the revaluation with PET-2 scan (Deauville score 4) and CT-scan (50 x 45 mm vs 92 x 65 mm). A second line IGEV regimen was then started, with hematopoietic stem cells harvesting. The PET-CT scan after the third cycle was consistent with a stable disease, therefore we started immunotherapy with brentuximab vedotin, obtaining after 6 infusions a complete remission, consolidated with fotemustine, etoposide, cytarabine, melphalan (FEAM) high-dose chemotherapy (reduced at 75% of the total dose because of the patient's age), followed by autologous stem cell transplant. Subsequent radiotherapy was not performed because the patient denied the consent. The patient is currently in persistent complete remission 15 months after the transplant.

Case 3B (Fabbri)

An 80 year old male patient was admitted to our institution on February 2014, due to persistent fever, increased ESR and multiple abdominal lymphadenopathies documented by an abdominal ultrasound scan. Previous Medical History included hypertension, an episode of atrial fibrillation, successfully drug reverted, and mild chronic renal failure. Neck-thorax and abdominal contrast enhanced-CT scan confirmed the presence of multiple pathological lombo-aortic and right common iliac lymph nodes, with longest diameters of 3 and 6 cm respectively. The patient underwent laparoscopic excisional lymph node biopsy without complication and the diagnosis was classical Hodgkin lymphoma, nodular sclerosis type I. Bone marrow biopsy was negative. Ann Arbor stage was II B. The patient

was classified as "unfit", according to the comprehensive geriatric assessment (CGA) scale reported by the Italian group in DLBCL setting (43) and started an induction treatment with the VEPEMB (vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin) regimen, specifically designed for elderly HL patients. Patient compliance and tolerability were non-satisfactory, since his general condition and PS worsened during treatment (PS 2), and he experienced a grade 3 hematological toxicity, requiring RBC support; a CT scan performed after 2nd cycle showed a marked reduction of lymph nodes volume (75%) and, due to this encouraging result, the patient continued treatment with acceptable dose intensity (>70%). A CT scan performed after the 4th cycle unfortunately showed disease progression, despite patient had again a good PS (ECOG 1) and no systemic symptoms. Single agent gemcitabine was administered as second line treatment, starting in August 2014. Treatment was again not well tolerated, as patient required one more time HGFs and RBC support and had two grade 2 infective episodes. CT scan performed after the 3rd cycle showed a stable disease (NR) and ^{18}FDG-PET/CT scan confirmed the disease persistence. Third line treatment with brentuximab vedotin was started in February 2015 (1.8 mg/Kg q 3 wks). Treatment was quite well tolerated: the patient maintained a good PS (1) and did not experience infections or require blood transfusions; a CT scan performed after the 4th cycle showed a 50% reduction of lymph nodes volume and TC/PET scan was negative (Deauville 2). After the VI cycle the patient again experienced a febrile episode (FUO) with PS worsening and occurrence of grade 2 peripheral sensitive neuropathy; when the patient recovered from infection, we decided to administer 2 additional cycles of BV at a reduced dosage (1.2 mg/Kg), but unfortunately the peripheral neuropathy (PN) progressed to grade 3; at that time the TC showed a stable condition with a persistent negative PET scan, and the decision was to stop the treatment and start a follow-up program. The clinical follow-up was negative after 3 months, with satisfactory PS (ECOG 1); PN improved from grade 3 to grade 1. Patient is now 84 years old and in good clinical condition, with an ECOG score of 1, without evidence of disease at the last follow up visit.

Discussion (Ciavarella)

Despite progressive therapeutic advance for younger HL patients, treatment choice in the elderly population remains an unsolved issue. This is primarily due to the lack of prospective clinical trials designed for or including large numbers of elderly subjects, although recent registry data indicate that one third of first-diagnosed HL patients are above the age of 60 years (44**).** On the other hand, reduced compliance to standard chemotherapies, development of excessive toxicities, treatment delays and dose reductions that commonly occur in elderly patients make clinical results controversial, slowing the knowledge improvement in these setting. The reported cases exemplify some of current controversies in this field, pointing out crucial aspects of therapeutic decision, as well as the increasing usefulness of new targeted drugs, as brentuximab vedotin, for these vulnerable patients. As one of the earliest steps of disease assessment, the staging procedure in old patients requires a formal co-morbidity evaluation, a detailed screening for frailty and scoring systems that, beyond the sole evaluation of performance status (ECOG), help in treatment modulation. It is increasingly clear, indeed, that comorbidities, frailty and ECOG, but not age per se, are factors significantly associated with therapeutic response (45). In both the reported cases, patients were >60 years old and diagnosed with advanced disease, but the geriatric scales indicated different level of co-morbidity and fitness, making the treatment plan challenging. At this regard, only few and small-sized studies have provided data about clinical features and outcome of elderly HL patients assessed by objective comorbidity scales as CIRS, ADL, IADL, ACE-27 (8, 46**).** Overall, while growing data emphasize that high frailty levels identify patients who are unlikely to benefit from or tolerate chemotherapy, an objective concept of "fitness" is difficult to achieve in the daily practice due to the lack of a unique, standardized tool for geriatric assessment. This practical discrepancy also emerges comparing the reported cases. Authors of case 3A applied classical geriatric scales to support a treatment plan with a curative intent, including high dose chemotherapy and ASCT. In the case 3B, authors categorized the patient as "unfit" according to the CGA scale (43), and chose a chemotherapy-based induction strategy. In both cases, patients underwent a front-line polychemotherapy, which in the case 3B satis-

fied the intent of a less toxic approach. To this respect, several attempts have been reported to evaluate regimens with apparent less toxicity than ABVD in elderly, advanced-stage patients. VEPEMB has been shown to produce lower toxicity, while failing in term of efficacy. Therefore, the use of novel targeted compounds active in HL recently appeared as the ideal front-line strategy to overcome the ABVD toxicity, especially for "frail" patients. Forero-Torres et al. reported that BV monotherapy may represent an effective option for older patients who cannot tolerate conventional chemotherapy, with no substantial impact of age to the drug's pharmacokinetics (47). In the cases reported here, patients showed disease progression after the first-line approaches and were treated by salvage chemotherapies including gemcitabine in monotherapy or in combination with other agents, resulting, however, only in partial remissions. At this regard, the curative perspective of using targeted drugs as BV acquired a double value. While in the case regarding the "unfit" relapsed/refractory patient the BV administration produced a stable remission with no remarkable toxic effects, in case 3A it resembled, *de facto*, a bridging strategy to ASCT, which indeed resulted in durable remission and good quality of life. In both cases, BV was used after >1 previous lines of treatment in accordance to the Italian authorization, and produced high therapeutic responses with acceptable toxicity. As reported by some Authors, in patients with relapsed/refractory HL, PET- positive after conventional chemotherapy salvage treatments, the administration of BV can lead to a normalization of PET in about 30% of cases, allowing the ASCT (14, 15). The efficacy observed in young patients suggests to design of trials exploring BV also within selected elderly populations with either refractory/relapsed or previously untreated disease. Both the clinical cases here reported underscore the role of BV as a valuable option for elderly vulnerable and heavily pre-treated patients, and support the conducting of studies aimed at validating its role in early lines of treatment (48, 49). Most importantly, current trials including older HL patients incorporate objective geriatric evaluation tools in early patient assessment, providing additional elements for a continuous optimization of BV use in this specific clinical setting. Finally, new combinations of BV with alternative agents, as bendamustine, dacarbazine or nivolumab has resulted promising in elderly patients, although with considerable incidence of adverse effects. Future studies are needed to define the best combination and position of BV in an ideal therapeutic algorithm for older patients with HL.

Conclusions

The six cases we described have been chosen because they can be considered representative of critical issues in the management of relapsed/refractory cHL patients; our experiences are consistent with those previously reported. Cases 1A and 1B regard young patients with relapsed/refractory cHL who failed standard second line therapy, and were therefore considered ineligible to ASCT due to unsatisfactory disease control. In this setting, BV proved to be an equally effective and less toxic alternative to additional classical chemotherapy; both strategies described allowed to proceed to ASCT in second complete response, thus hitting the set goal. Cases 2A and 2B focused on an even more difficult situation: both relapsed cHL patients were candidate to receive ASCT, but failed 2 salvage attempts, the first with chemotherapy regimens and the second with BV monotherapy. As third salvage strategy in case 2A a check-point inhibitor was chosen, while in case 2B BV was combined with chemotherapy. Both therapeutic strategies allowed to obtain a complete metabolic response and finally proceed to ASCT as consolidation. Finally, for elderly-patients, the majority of whom are not candidates for multi-agent salvage chemotherapy and autologous stem cell transplant, effective and less toxic new agents are warranted. Case 3A and 3B illustrated successful BV utilization in elderly cHL patients, despite different fitness categories and disease phases, without unexpected toxicity. In the setting of elderly cHL patients, a standard of care is lacking, both for first and subsequent therapeutic lines; due to this uncertainties, objective and standardized tools should be developed, in order to assist physicians' choice between different treatment options, characterized by different intensity.

In summary, the present clinical cases selection highlights a potential role of novel drugs such as Brentuximab Vedotin and check-point inhibitors for high risk relapsed/refractory cHL patients, as a valid alternative to additional standard chemotherapy.

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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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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Relapsing/refractory HL after autotransplantation: which treatment?

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Abstract. For advanced-stage Hodgkin lymphoma (HL), front-line chemotherapy, alone or in combination with radiotherapy, leads to 5-year progression-free survival (PFS) rates and freedom-from-treatment failure (FFTF) rates of 70-85%, regardless of the chemotherapy regimen applied. Patients with HL experiencing disease progression during or within 3 months of front-line therapy (primary refractory) and patients whose disease relapses after a complete response have a second chance of treatment. The standard of care for relapsed or refractory HL is second-line chemotherapy followed by autologous stem cell transplantation (ASCT), which can induce long-term remission in approximately 40-50% of patients. However, HL recurrence occurs in about 50% of patients after ASCT, usually within the first year, and represents a significant therapeutic challenge. Allogeneic transplantation from HLA-matched donors represents the standard of care for patients with HL relapsing after- or refractory to ASCT.

Key words: Hodgkin Lymphoma, Relapsing/refractory HL, autologous transplantation

Introduction

For advanced-stage Hodgkin lymphoma (HL), front-line chemotherapy, alone or in combination with radiotherapy (RT), leads to 5-year progression-free survival (PFS) rates and freedom-from-treatment failure (FFTF) rates of 70-85%, regardless of the chemotherapy regimen applied. Patients with HL experiencing disease progression (DP) during or within 3 months of front-line therapy (primary refractory), and patients whose disease relapses after a complete response, have a second chance of treatment. The standard of care for relapsed or refractory HL is second-line chemotherapy followed by autologous stem cell transplantation (ASCT), which can induce a long-term remission in approximately 40-50% of patients. However, HL recurrence occurs in about 50% of patients after ASCT, usually within the first year, and represents a significant therapeutic challenge.

Several factors have been associated with an increased risk of relapse following ASCT, including the number of prior regimens, less than a complete remission to salvage treatment prior to ASCT evaluated by PET-CT scan, the short duration of first remission, the poor performance status and extranodal involvement. Many regimens or single agents have been tested in patients with relapse after ASCT, showing an overall response rate of 20- 86%, including a complete response of 4-50%, with a short median duration of response, usually ranging from 5 to 20 months.

Allogeneic transplantation from HLA-matched

donors represents the standard of care for patients with HL relapsing after or refractory to ASCT. Unfortunately, not all the patients are eligible for this potentially curative therapeutic approach because of donors' unavailability, advanced age and/or comorbidities. Although a second ASCT may be an option in patients who do not have a donor for an allogeneic stem cell transplantation (allo-SCT), it is not routinely recommended, especially nowadays that new drugs such as brentuximab vedotin (BV) and the checkpoint inhibitors (CPI) nivolumab and pembrolizumab are available. How these drugs should be integrated in the therapeutic strategy for treatment of patients with HL relapsing after ASCT will be discussed.

Do we trust in PET scans?

Case report 1

A 25-year-old man was diagnosed with stage IIA classical Hodgkin lymphoma (cHL) involving bilateral cervical nodes and mediastinum (bulky). A staging PET/CT scan revealed a 2 x 3.9 cm right cervical node, with a standardized uptake value (SUV) of 10.5, a 1.9 x 2.5 cm right paratracheal node with a SUV of 8.0, and a 10.3 x 5.7 cm bulky mediastinic involvement with a SUV of 12.6. The therapeutic program was ABVD regimen for 4 cycles with an interim PET scan evaluation and Involved-field radiotherapy (IFRT). PET/CT scan performed after 2 cycles of the ABVD regimen demonstrated a persistent positivity on mediastinum (Deauville score: 4), with decreased mediastinal mass at CT scan. Therefore, the treatment was shifted to the BEACOPP regimen. Two cycles of BEACOPP and RT were scheduled. After 2 cycles, the PET/CT scan was persistently positive, with a Deauville score of 4 in the residual mediastinal mass, which was further reduced at CT scan. A CT scan guided biopsy of the positive PET area did not show any evidence of lymphoma. The patient was treated with 4 cycles of therapy following the BeGEV scheme, with stem cell collection after the second cycle. Pre-transplantation PET/CT scan showed again a persistent mediastinal PET scan positivity; a new biopsy was performed, suggesting again fibrotic tissue, in absence of lymphoproliferative disease. The patient received a high dose chemotherapy and ASCT, followed by a consolidation RT on mediastinal bulk. A CT scan after 45 days showed a reduction of the residual mass (3.8 x 2 cm) and a PET/CT scan performed after 3 months showed a reduction of the SUVmax and a Deauville score of 3. A new CT scan was performed after 3 months and showed a further minimal reduction of the residual mediastinal mass. No signs of active disease were observed during the follow-up.

Discussion

Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan is without any doubt the best currently available predictor for HL patients. However, it should be used carefully due to the well-known false positivity issues.

Our case clearly points out the wide variability of PET scan interpretation before and after stem cell transplantation, which could possibly lead to overtreat the patient or, by the contrary, underestimate a PET scan positive signal. According to the wide literature data, we probably overtreat some interim PET scan-positive patients (10-15%) or undertreat some interim PET scan-negative patients (5- 10%) (1-3).

The role of interim PET scan in advanced HL has been supported by several prospective studies, confirming that an early intensification in interim PET scan-positive patients significantly improves PFS (4-7). Moreover, with the interim FDG-PET scan evaluation, we avoid to use in all the patients a very intensive treatment such as the BEACOPP regimen.

In localized-stage HL patients, the role of FDG-PET scan is less consolidated and the literature data are conflicting (8-10). In particular, in bulky disease we can frequently observe a persistence of positivity either in interim PET scan or in end-of-treatment PET scan (11).

Several papers and clinical trials tried to understand whether the PET scan results could be used to spare RT in HL patients. However, the chemotherapy in association with RT still remain the golden standard (12,13).

In uncertain cases, a CT scan-guided biopsy is mandatory in order to demonstrate the presence of residual disease. The possibility of PET scan false positivity is well known and reported in several studies, and every clinical decision should be supported whenever possible by a CT scan-guided biopsy. The possibility

to overtreat patients should be considered in particular in localized-stage with bulky mass, due to the high frequency of false positive PET scans. Unfortunately, the persistence of positivity, even if intense, is usually very limited, the attempt to perform a biopsy to identify the cause very often fails, and in a CT scan-guided biopsy this result cannot be considered certain. The only reliable technique is the PET/CT scan-guided biopsy, but it is not applicable in all the centers (14,15).

Thus, a biopsy result suggesting the absence of lymphoma should always be carefully discussed, in order to exclude a false negative specimen and not to lose or undertreat the patient.

Another issue about the PET-CT scan is its role in the peri-transplantation period. The literature has focused on pre-transplant PET scan, which is known to be important and predictive of good clinical outcomes: several authors reported a better PFS obtained with high dose chemotherapy with a negative PET scan (16). The role of PET scans after transplantation is more controversial (17,18). Some studies reported that persistence of PET scan positivity is associated with lower PFS and OS (19), however the data in this field are still limited. As a matter of fact, post-transplantation management, such as maintenance BV, is so far guided by pre-transplantation patient's characteristics (20). Therefore, PET scan interpretation is a really critical issue, because it is not known which patients could be treated with RT only, or could be rescued by new agents, or in which patients an allo-SCT would be indicated (21,22).

After an allo-SCT, the PET scan role is far more complicated, as false positivity has been described in case of graft versus host disease (GVHD) and other transplantation-associated complications (23,24). The case we described here is paradigmatic of all PET scan issues discussed above. The patient was probably overtreated. We should have continued with the scheduled therapy also with a PET scan positivity and with a Deauville score of 4 on bulky mass, considering that RT is curative in HL, omitting the high dose chemotherapy. In that moment, we had a persistent PET scan positivity on residual bulky disease, with a negative histological test, which however did not guarantee the absence of disease. However, considering the increasing SUVmax of the mediastinal mass, the young age and the very good conditions of the patient, and the global low therapeutic load as well, we proceeded to intensification. Clearly, the interim PET scan positivity could underlie a spread of the disease due to an insensitivity to chemotherapy, but this situation is much more likely with a Deauville score of 5 (25-27), when all the statements about PET scan false positivity are not applicable.

In the case we described, even the peri-transplantation PET scan was meaningful, in the era of post-transplantation maintenance with BV. Pre-transplantation PET scan was still positive, again with a negative biopsy. High dose chemotherapy was performed, but a softer approach, with strict clinical follow-up and PET scan, should have been another rational approach, as clearly demonstrated in the post-transplantation follow-up.

Post-transplantation PET scan showed a SUV reduction of the known lesion, which was treated with local RT on initial bulky mass, showing a progressive disappearance in the follow-up. It could be speculated that a follow-up-based approach could have led to the same result.

In summary, the answer to the starting question is that, in our opinion, we can trust in PET scan, even if not blindly, and we should have a good knowledge of PET imaging technique and of PET scan interpretation.

In a localized stage with bulky disease, an interim positive PET scan with a Deauville score of 4 suggests to proceed with the scheduled therapy with a new PET evaluation before the start of RT. In our opinion, in case of PET scan positivity, and regardless of biopsy result, the patient should be treated with RT at the end of the pharmacological treatment. In case of persistent positivity at the end of treatment, a CT or PET/CT scan guided biopsy is mandatory, and if positivity is confirmed, the patient should undergo a salvage treatment. If the biopsy is negative, without any other sign or symptom of active disease, it could be useful to repeat a PET/CT scan after 2 or 3 months.

Post-autotransplantation therapy: which treatment?

Case report 2 Post-autotranplantation brentuximab

On February 2017, a 36-year-old male presented weight loss, low-grade fever and sweating. A CT scan revealed a voluminous enlargement of all lymph nodes

(left LC, axillary and inguinal lymph nodes, with a maximum diameter of 5 cm, and right LC with a 9 cm diameter), with bilateral pulmonary micronodules; in the spleen was 3 cm and in the liver 2 cm, without parenchymal lesions. All lesions were PET scan-positive, and the patient was diagnosed with stage IVB cNS HL, type 2 BNLI. In March 2017, the patient started a treatment with the ABVD regimen; during the second cycle, despite a reduction of superficial nodes (diameter 3 cm), a fast progression of the disease was observed, with discomfort and enlargement of LC nodes (7 cm). Therefore, the treatment was switched to BEACOPP escalated for 3 cycles, with stem cell mobilization. After an initial significant node reduction, during the third cycle a new enlargement was observed, with a PET scan result of partial response (PR). In July 2017, the patient started 3 cycles of BeGV, and in October the PET scan was negative. HLA investigation identified a matched sibling donor. During pre-transplantation exams, a biopsy of the right LC node revealed a new progression. A treatment with 2 cycles of brentuximab was started, with PR. After the addition of bendamustine for 2 additional cycles, PET and abdomen ultrasound scans resulted negative. In May, the patient underwent autotransplantation with complete remission (CR), but he presented a symptomatic relapse after 2 months, with PET scan positive for nodes, bones, spleen and liver. CT and NMR scans revealed a diffuse positivity for nodes (max 3 cm), spleen hypodense lesions (max 2.6 cm), focal liver lesions (max 1.6 cm), and intertrochanteric femoral lesion (2 cm). In September, a new PET scan revealed a further increase of dimension and metabolic activity of part of the abdominal nodes, with new vertebral lesions (D9, D10, L2, L4), and with a slight regression of other sites. Four cycles of brentuximab were scheduled, with a concomitant administration of low dose corticosteroid. In December 2018, a treatment with nivolumab was started, with a good clinical response and symptoms regression, and the corticosteroid administration was discontinued. After 4 cycles of nivolumab, a DP (affecting spleen, liver, bones, and mediastinal, abdominal, LC and axillary nodes) was revealed by PET scan and confirmed by NMR.

Nivolumab therapy is currently ongoing. A hepatic bi- opsy was scheduled but not performed as no lesions were identified with ultrasound scan. The patient is currently free from systemic symptoms. A PET scan re-evaluation is scheduled, and a HLA identical donor is currently available.

Discussion

Before the development of BV and CPI, the median survival of HL patients relapsing after ASCT was 25 months (28). Allo -SCT could potentially cure about 40% of these patients, particularly when performed in the setting of a chemosensitive disease (29).

In patients relapsed after ASCT, BV demonstrated an Overall Response Rate (ORR) of 74% with 34% of cases with a CR; estimated PFS and Overall Survival (OS) were 9.3 and 40.5 months, respectively, with longer survivals in CR patients (30). Moreover, Chen *et al.* showed that BV- treated patients had a better 2-year PFS after allo-SCT compared to patients re-induced with standard chemotherapy (59.3% *vs*. 26.1%), with reduced cumulative incidence of relapse or progression (23.8% *vs*. 5.65%) due to better disease control prior to allo-SCT (31).

BV could be considered the most suitable drug to "bridge" the patients to allo-SCT. However, 38% of complete BV responders could maintain a sustained response over time, also without allo-SCT consolidation (30). For this reason, a delay of allo-SCT to the time of DP during or after the BV treatment is now considered reasonable, provided that a salvage treatment with a CPI (nivolumab and pembrolizumab) is available. In this setting, pembrolizumab demonstrated an ORR of 73.9%, with 21.7% CR (32), and nivolumab an ORR of 68%, with 13% CR (33).

Nevertheless, only a minority of CPI-responding patients obtain a long-term remission, and allo-SCT remains the only potentially curative therapy. However, its timing in patients treated with CPI is matter of debate. Patients undergoing allo-SCT after CPI appeared at increased risk of grade 4 acute graft versus host disease (GVHD), veno-occlusive disease (VOD), and noninfectious febrile syndrome, requiring a prolonged steroid treatment. It should be underlined that the relapse rate was lower than previously reported (16% at 1 year), with an encouraging 1 year PFS of 74% (34). Recently, a large pooled analysis suggested that allo-SCT after CPI is feasible and not associated with higher mortality, provided that a careful consideration is given to prevention, early detection and treatment of GVHD

(35). As questioned by Broccoli and Zinzani in a recent review, should allo-SCT be performed only in patients achieving a CR, in all patients with at least stable disease, or only in patients progressing while on CPI? (36). Herbaux and colleagues suggest keeping CR and PR patients on therapy instead of stopping it to proceed to allo-SCT (37). This is motivated, on one hand, by the relative safety of CPI compared to allo-SCT and, on the other, by the possibility to reinduce remission after CPI failure. In a retrospective analysis, salvage chemotherapy following CPI resulted in an ORR of 53% (38,39). Nevertheless, the authors recommend referral to a transplantation center for a potential transplantation at the time of CPI failure, considering an early allo-SCT only for patients in remission, with heavily pretreated refractory disease and no viable post–CPI salvage options. Shah and Moskowitz proposed an algorithm (40) where the patients achieving CR continue the CPI therapy for 3 additional months: if the CR is maintained, the authors suggest to stop the therapy and restart only in case of progression. For PR patients, the authors continue the therapy due to a possible late conversion to CR, but consider allo-SCT sooner. Finally, if there is stable disease on CPI treatment, the authors suggest to continue the therapy until DP, followed by an alkylator-based therapy or a clinical trial as a bridge to allo-SCT in case of responding disease. If allo-SCT is scheduled, CPI treatment should be hold for 6 weeks before transplantation. A reduced intensity conditioning, a bone marrow source and a post-transplantation cyclophosphamide treatment should be considered to minimize the risk of GVHD and VOD (37). Interestingly, these algorithms take into account the response to CPI treatment as outlined by PET/CT scans. However, CPI-induced activation of antitumor immune cells could theoretically increase the ^{18}F-FDG uptake, masking the CPI efficacy. This so-called pseudoprogression, with imaging findings suggestive of progression, followed by later response, has been described in solid tumors and confirmed in HL patients. In 2016, the LYmphoma Re- sponse to Immunomodulatory therapy Criteria (LYR-IC) introduced the concept of indeterminate response to indicate the time interval until a biopsy or subsequent imaging confirm either a pseudoprogression or a true progression (41). On the other hand, hyperprogression, a condition in which CPI initiation leads to a paradoxal increase in tumor growth rate, seems to be associated with a worse prognosis (42). The literature data reported above led us to continue the CPI treatment in our patient, due to a satisfactory clinical response despite the progression at first PET/CT scan re-evaluation, but also to schedule allo-SCT despite the subsequent response, in consideration of the high probability of relapse and of the lack of suitable salvage therapy.

Post-allotransplantation therapy: which treatment?

Case report 3:Post-allotransplantation brentuximab (with lymphocytes infusion)

A 22-year-young boy was diagnosed with stage IIIA cHL (mixed cellularity). He started the ABVD chemotherapy. The PET/CT scan after 2 cycles revealed a partial response, with residue in right retroclavicular lymph node, bilateral laterocervical and mediastinum. Therefore, he received 4 BEACOPP escalated cycles achieving RC (no evidence of hypermetabolic disease localization with PET/CT scan) and then other 4 BEACOPP baseline cycles. PET/CT scan showed CR.

Four months after the end of therapy, the PET/TC scan revealed a relapse. A novel excisional biopsy (axillary node) confirmed cHL (nodular sclerosis). The patient was treated with 4 IGEV cycles (achieving PR) and with 4 cycles of BV infusion and subsequent ASCT with FEAM conditioning (CD34+ PBSC: 5x10^6/Kg).

The post-ASCT PET scan revealed a good but partial response to treatment (persistent uptake in bilateral submandibular lymph nodes, considerable reduction in laterocervical nodes, resolution of other nodal sites: mediastinal, axillary, jugular nodes).

Within 3 months before the SCT, the patient received another brentuximab infusion and RT (30 Gy in bilateral sub- mandibular and laterocervical nodes).

The patient underwent allogeneic haploidentical stem cell transplantation, fludarabine (30mg/m^2/day, from day -6 to day -2), cyclophosphamide (450mg/m^2/day, on days -6 and -5) and TBI 2 Gy (on day -1) conditioning, achieving a complete allogeneic engraftment. The patient received GVHD prophylaxis with CSA, MMF and cyclophosphamide. He did not present

acute GVHD but the hospitalization was complicated by haemorrhagic cystitis and by cytomegalovirus reactivation.

After 11 months, the disease relapsed (mixed cellularity with scleronodular areas at biopsy). The PET/CT scan showed a relapse in multiple lymph nodes above and under diaphragm, in pectoralis muscle and in spleen.

The patient started a treatment with bendamustine (90 mg/m^2 on day +1 and +2) and brentuximab (1,8 mg/kg on day +1) every 21 days for 4 cycles.

The PET/CT scan revealed a CR. Brentuximab was well tolerated, Bendamustine determined third and fourth grade hematologic toxicity.

The patient continued the treatment combining brentuximab infusion (day +1, 1.8 mg/Kg every 21 days) with donor lymphocyte infusion (DLI) administration (day +8, in increasing doses) in alternating regimen. Treatment was repeated every 28 days. The patient received 8 brentuximab infusions on day +1 (3 in association with bendamustine) with 5 DLI (day +8, increasing doses: the first two at the dose of 1x10^5/kg, the third and the fourth at the dose 5x10^5/kg, the fifth at 1x10^6/Kg).

The treatment was well tolerated and stopped on April 14, 2015. The patient did not experience any no side effect. One month after the end of the therapy, the patient presented pruriginous maculopapular erythema on hand and feet palm, volar forearm and neck, treated with a steroid cream. After 5 months, a treatment with cyclosporine (with an initial dose of 3mg/Kg/day, reduced to 0.5mg/kg/day) was started for limited chronic cutaneous GVHD on hands and nails (nail dystrophy).

Forty-eight months after the end of therapy, the patient is still in CR and presents limited chronic GVHD, well controlled with cyclosporine at the dose of 0.5 mg/Kg/day.

Discussion

For patients developing disease recurrence or progression after allo-SCT, the prognosis is fatal and the treatment is challenging because most of these subjects are heavily pretreated and often are affected by a chemotherapy- resistant disease (43-46).

CPI are increasingly used in this setting and appear to be highly effective, although with conflicting safety results as they can be complicated by the rapid onset of transplantation disease against the severely affected and treatment-resistant host (GVHD) (47,48). Anecdotal reports and some small series of cases suggested that BV, alone (49,50) or in combination with DLI, could be effective in a post-allograft setting (51).

It is interesting to note that the BV ORR was not in- fluenced by whether or not the patients received BV before undergoing allo-SCT, suggesting that rechallenge with BV could be advantageous in HL patients developing recurrent disease after allo-SCT, although theyhave received BV before transplantation.

Treatment of HL patients developing recurrence or DP after allo-SCT remains a real challenge and an unmet medical need (43-46).

DLI, with or without previous chemotherapy, resulted in a response rate ranging from 43% to 56%, at the expense of a grade 2-4 GVHD, ranging from 32% to 38% (52,53).

Currently, the treatment options for HL patients failing the allo-SCT are BV, with or without DLI, or CPI.

There is a shortage of data on the efficacy and safety of BV, either alone or in combination with DLI, for the treatment or prevention of relapse after allo-SCT.

In a recent study, the administration of BV after allo- SCT to 16 high-risk and highlypretreated HL patients led to an objective response rate of 73% (51). This high efficacy rate should not be attributed only to BV but rather to the combination of BV and DLI. The safety and efficacy of BV after allo-SCT were evaluated in a prospective study of 25 BV-naive patients with recurrent HL. Toxicity was minimal and easily manageable, while the overall response and CR rate were 50% and 38%, respectively. Median PFS was 7.8 months while the median OS was not achieved at the time of publication (49).

In another study, 16 previously BV-naive patients with recurrent HL after allo-SCT were included in a program of compassionate use. The treatment was safe, with anemia, neutropenia, thrombocytopenia and peripheral sensory neuropathy reported as the most frequent side effects. ORR was 69%, with five patients achieving CR. Median PFS and OS were 7 and 25 months, respectively (50).

Both the association of chronic GVHD with reduced incidence of relapse and the efficacy of DLI in inducing remissions in patients with relapsing HL after

allo- SCT support the concept of a graft effect with respect to the HL effect (45, 46).

The largest body of data on the efficacy of DLI in HL patients comes from the cooperative study group in the United Kingdom. Seventy-six consecutive patients with relapsed/refractory HL underwent allo-SCT following reduced intensity conditioning. DLI was effective in restoring donor chimerism to 86% of patients. A lasting response to DLI was observed in 79% of patients treated for relapse, while DLI-related 3-year mortality was 7% and was mainly attributed to GVHD (54).

However, it should be noted that these results were not reproduced from other studies evaluating the efficacy of DLI in the treatment of progressive or recurrent HL disease after allo-SCT. In these studies, the responses to the DLI were inconsistent and of short duration, as no patient reached a PFS in the long term (52, 55, 56).

In conclusion, the administration of BV in combination with DLI is safe and induces a significant anti-HL activity. Furthermore, it is strongly suggested that a BV-induced immunomodulatory effect resulted in a reduction in the incidence and severity of GVHD associated with DLI. The combination of BV plus DLI should be prospectively tested in a greater number of patients with high-risk HL after allo-SCT. It is conceivable that this approach will be more effective if used as a consolidation therapy for HL in response to allo-SCT rather than as a treatment for a confirmed relapse or a post-SCT progressive disease.

The working hypothesis supporting the combined BV-DLI treatment suggests that selective targeting of lymphoma cells could improve the graft response against leukemia by inducing immunogenic cell death (57). Furthermore, BV could potentially reduce GVHD by targeting CD30+ T cells (58). Adverse events were generally manageable and were not worse than expected in heavily pretreated patients. The most common events were generally of grade 1 or 2. Based on the hypothesis that antigen targeting on activated T cells could further compromise cell-mediated immunity in this high-risk population, particular attention was paid to a close monitoring of clinical infection. No grade III or IV infections were recorded and no CMV reactivation occurred. BV is a highly effective therapy with a good toxicity profile that can be offered to HL patients with relapse or progression after allo-SCT, in order to achieve an effective but transient disease control. Future studies should explore the combination of BV with DLI, conventional chemotherapy (e.g. bendamustine) or targeted agents (eg PI3K inhibitors or anti-PD-1 agents), to improve the tumor burden reduction and increase the rate of CR, thereby improving the disease control. The BV therapy, with or without DLI, could also be considered a prophylaxis strategy in patients at high risk of relapse after allo-SCT. Recent data regarding the reprocessing of BV support this therapeutic approach in patients that have previously received BV regimens during the course of the disease (59). Future studies could be justified to explore these new BV-based strategies in BV-naive and BV-sensitive patients.

Case report 4: Post allotransplantation nivolumab

In 2012, a 49-year-old male patient with Parkinson's disease in his past medical history, was diagnosed with stage IIIB cHL, and with International Prognostic Score of 4. He received 5 therapy lines: 6 cycles of ABVD regimen, resulting in a PR, 4 cycles of IGEV regimen followed by ASCT, with PR, 4 cycles of BV, resulting in DP, and then 6 cycles of bendamustine, with no response, showing a chemorefractory disease. Therefore, in 2014 we performed an allo-SCT from a matched sibling donor, due to the lack of other treatment options. The patient achieved a PR, that lasted for 28 months after allo-SCT. Subsequently, DP required additional treatments. The patient started a treatment with the anti-PD-1 nivolumab, at the standard dose of 3 mg/kg every 2 weeks. After 3 cycles, the patient developed a grade 2 elevation of liver enzymes and a grade 2 cutaneous and ocular GVHD. The nivolumab treatment was discontinued and corticosteroid treatment started, with a consequent normalization of the liver enzymes and the regression of cutaneous and ocular signs after 4 months. At that time, disease revaluation showed a CR.

Discussion

Allo-SCT is a treatment option for patients with re- lapsed or refractory HL, when a previous autologous transplantation failed. Since the allo-SCT -related mortality continues to decline, with preparative regimens

characterized by a lower-intensity and a better supportive care, the treatment of relapsed disease is increasing. Approximately 30% of allografted lymphoma patients relapse after allo-SCT (43).

For patients who develop disease recurrence or progression after allo-SCT, the prognosis is unfavorable and the treatment is challenging as most patients are heavily pretreated, and often have a chemotherapy-refractory disease.

Aside from rapidly minimizing the systemic immunosuppression, no standard strategy is currently available.

The scientific basis for the use of CPI in HL is real and strong. In tumor tissue, HL cells are scanty and surrounded by a large number of inflammatory tumor-infiltrating lymphocytes. In particular, Reed-Sternberg cells are characterized by the 9p24 amplification, encoding for both the PD-1-/PD-2-ligands and for the Janus kinase (JAK)-2. The latter activates the JAK/STAT pathway (60), leading to a further enhancement of PD ligand expression on Reed-Sternberg cells. Additionally, around 40% of patients with cHL are positive for Epstein-Barr virus, which is associated with high expression of PD-1 and PD-2 ligands (61).

Recently, early-phase clinical trials on PD-1–blocking antibodies nivolumab and pembrolizumab showed a substantial therapeutic activity and an acceptable safety profile in patients with relapsed or refractory HL (62-64).

Of note, both trials excluded patients with a previous history of allo-SCT, because of concerns about GVHD reactivation.

Current strategies for relapsed HL after allo-SCT are discouraging (50,65). Using different approaches (DLI with or without chemo- therapy, BV, or bendamustine), poor results were reported, with a median PFS ranging from 6 to 18 months.

The immune-mediated graft-versus-tumor (GVT) effect endows the allo-SCT with the potential to cure malignancies refractory to all other treatments. Nevertheless, it is associated with the risk of donor cell-mediated GVHD, which mainly contributes to its relevant morbidity and mortality. In theory, the GVT effect might be enhanced by immune CPI such as ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4), nivolumab (anti-PD-1) or pembrolizumab (anti-PD-1), by releasing the brakes on GVT conveying tumor-suppressed lymphocytes. Nevertheless, severe GVHD reactions might be unleashed as well.

CPI administration has also been tested for post allo-SCT relapse, and, although the response rates are high, the toxicity is substantial as well. A multicenter retrospective trial of 31 lymphoma patients, 29 with HL, treated either with nivolumab or with pembrolizumab after allo-SCT relapse, found a high ORR of 77%. However, a treatment-related GVHD occurred in 55% of patients and tended to be highly refractory to conventional GVHD management, with a mortality of 26% (48). Another retrospective trial on 20 HL patients receiving nivolumab after allo-SCT found an ORR of 95%, with a 30% incidence of GVHD, and 10% of the patients died of GVHD (47).

While the preliminary data demonstrated no significantly increased GVHD in patients treated with ipilimumab post allo-SCT, there is still a substantial concern regarding the safety of PD-1 inhibitors in this setting. In fact, increased GVHD-related lethality has been demonstrated in a murine model of acute GVHD when blocking PD-L1 (66).

There is a possibility that anti–PD-1 administration during the early phase of transplantation would trigger severe GVHD secondary to decreased PD-1/PD-L1 ligation soon after the allo-SCT (67).

Donor source, type of GVHD prophylaxis, history of GVHD, dose and timing of anti–PD-1 therapy, and immunosuppression at time of anti–PD-1 administration should be considered as variables potentially influencing the development of GVHD in clinical trials that evaluate the treatment with checkpoint blockade after allo-SCT.

In phase 1 studies with nivolumab and pembrolizumab for treatment of relapsed and refractory HL, grade 3 hepatic and dermatologic toxicities were observed in 5% of patients, and there were no drug-related grade 4-5 events (62-64).

One case of fatal hepatic toxicity has been reported in a lung cancer patient after the treatment with an anti-PD-1 monoclonal antibody (68).

Nevertheless, early onset of severe and fatal events occurred more frequently than expected when anti–PD-1 monoclonal antibodies were administered post allo-SCT.

There are context-dependent functions of the PD-1/PD-L1 axis in allo-SCT, including timing of pathway activation and organ-specific immunogenicity, donor *vs.* host expression, and peripheral tolerance, which affect the risk of aGVHD and cGVHD.

However, while reversing the suppression of allogeneic GVT effects with PD-1 inhibition appears particularly appealing, special caution has to be taken in the context of an allogeneic immune system, given the role of the PD-1 axis in the pathophysiology of GVHD as well. In conclusion, CPI are increasingly being used in this setting and appear to be effective, although with conflicting safety results, because their administration can be complicated by the rapid onset of severe and treatment-refractory GVHD.

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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