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

Chiara Rusconi[1], Sabino Ciavarella[2], Alberto Fabbri[3], Leonardo Flenghi[4], Benedetta Puccini[5], Alessandro Re[6], Marco Sorio[7], Anna Vanazzi[8], Manuela Zanni[9]

[1]Division of Haematology, Department of Haematology and Oncology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano; Niguarda, Milan, Italy; [2]Hematology and Cell Therapy Unit, IRCCS-Istituto Tumori "Giovanni Paolo II", Bari, Italy; [3]Unit of Hematology, Azienda Ospedaliera Universitaria Senese & University of Siena, Siena, Italy; [4]University of Perugia, Institute of Hematology, Italy;: [5]Haematology Unit, Careggi Hospital-University of Florence, Largo Brambilla 3, 50134, Florence, Italy; [6]Department of Hematology, ASST Spedali Civili di Brescia, Italy; [7]Department of Clinical and Experimental Medicine, Hematology and Bone Marrow Transplant Unit, University of Verona, Verona, Italy; [8]Division of Clinical Hemato-Oncology, Istituto Europeo di Oncologia, Milan, Italy; [9]Hematology Unit, Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy

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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Correspondence:
Chiara Rusconi
E-mail: chiara.rusconi@ospedaleniguarda.it