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Relapsing/refractory HL after autotransplantation: which treatment?

Nicola Di Renzo[1], Francesco Gaudio[2], Carmelo Carlo Stella[3], Sara Oppi[4], Matteo Pelosini[5], Roberto Sorasio[6], Caterina Stelitano[7], Luigi Rigacci[8]

[1]Department of Hematology and Stem Cell Transplant, Presidio Ospedaliero Vito Fazzi, Lecce, Italy; [2]Department of Emergency and Transplantation, Hematology Section, University of Bari Medical School, Italy; [3]Department of Hematology and Oncology, Humanitas Cancer Center, Humanitas Clinical and Research Center - IRCCS, Rozzano (MI), Italy; Department of Biomedical Sciences, Humanitas University, Rozzano, Milano, Italy; [4]Bone Marrow Transplant Center, R. Binaghi Hospital, ASL 8, Cagliari, Italy; [5]Hematology Division, Pisa University Hospital, Pisa, Italy; [6]Division of Hematology, A.O. Santi Croce e Carle, Cuneo, Italy; [7]Division of Hematology, Azienda Ospedaliera "Bianchi Melacrino Morelli", Reggio Calabria, Italy; [8]Haematology Unit and Bone Marrow Transplant Unit, San Camillo Forlanini Hospital, Rome, Italy

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.

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Correspondence:
Nicola Di Renzo
E-mail: direnzo.ematolecce@gmail.com