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Case Report

Single agent oral selinexor as a key to potential cure in refractory diffuse large B-cell lymphoma: case report and literature review

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Abstract: Relapsed/refractory diffuse large B-cell lymphoma (DLBCL) portends a poor prognosis, with an estimated overall survival of less than 6 months. In the presented case, a female patient with DLBCL refractory to multiple lines of therapy, including chimeric antigen receptor T-cells, was treated with single-agent selinexor, achieving partial response following 5 months of treatment, which allowed the patient to proceed to potentially curative allogeneic stem cell transplantion. This approach enabled the patient, who would otherwise have been considered a candidate for palliative care, to achieve the most prolonged complete response since her first lymphoma-specific treatment. This outcome implies that early identification of relapsed/refractory patients who may benefit most from this drug - either as a single agent or in drug combinations - is imperative.

Keywords: Diffuse large B-cell lymphoma, relapsed/refractory disease, selinexor, allogeneic stem cell transplantation

Introduction

Patients with relapsed/refractory diffuse large B-cell lymphoma (RR-DLBCL) have a dismal prognosis, with an estimated overall survival (OS) not exceeding 6 months [1]. This outcome could even be an overestimation of that expected for patients progressing on novel and highly efficacious therapeutic approaches such as chimeric antigen receptor T (CAR-T) cells [2, 3] and polatuzumab vedotin combinations [4].

Selinexor is a first-in-class oral selective inhibitor of nuclear export (SINE) which reversibly blocks the activity of the transporter protein exportin 1 (XPO1). XPO1 is responsible for the export of ~220 proteins from the cell nucleus to the cytoplasm [5-7]. SINE anticancer mechanisms include nuclear retention and functional activation of tumor suppressor proteins, such as P53, leading to cell cycle arrest and apoptosis [8] and hampered transport of oncogenic messenger ribonucleic acid (mRNAs), such as c-myc, from the nucleus, preventing protein translation.

Preclinical and small clinical studies demonstrated response to selinexor in a variety of malignancies [9-12]. In lymphoma, high XPO1 expression in tissue biopsies was shown to correlate with inferior survival [13].

Phase 1 clinical trials evaluated treatment with selinexor as a single agent in patients with advanced aggressive lymphoma [10] and multiple myeloma [11], as well as in combination with chemotherapy in acute myeloid leukemia [12]. The results of the first-in-human dose-escalation study of selinexor used in B-cell malignancies appeared promising, with an overall response rate (ORR) of 31% [10]. This served as a platform for the pivotal SADAL (selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma) study, where single-agent selinexor was administered to 127 patients with RR-DLBCL after at least two prior systemic therapies, 70% of whom were refractory to their previous line of treatment. The study demonstrated a median ORR of 28%, appearing to be somewhat higher in patients with the germinal center B-cell-like (GCB) subtype as compared to

non-GCB DLBCL, and an encouraging ORR of 39% in patients with DLBCL transformed from low grade lymphoma. Median duration of response (DOR) was 9.3 months in the whole group, and 23.2 months in patients achieving complete response (CR) [14]. These results led to an accelerated approval of selinexor by the United States Food and Drug Administration in June 2020 for DLBCL patients after at least two lines of therapy. Phase 3 studies examining chemo-immunotherapy combinations with this drug are underway.

Here, we present the case of a female patient with DLBCL refractory to multiple lines of therapy including CAR-T cells, who achieved a partial response (PR) following 5 months of single agent selinexor treatment and proceeded to allogeneic stem cell transplantation (allo-SCT).

Case report

A 57-year-old woman with a history of type II diabetes mellitus and hypertension, was diagnosed with GCB type DLBCL, with histologic features suggestive of transformation from follicular lymphoma (FL). The large cells were positive for BCL2, CD10, BCL6 and CD20. Staining was positive for Ki67 in 60% and for c-myc - in 10% of the cells. Fluorescent in situ hybridization (FISH) analysis revealed no c-myc rearrangements. Total-body computed tomography (CT) demonstrated disease sites above and below the diaphragm, including a large retroperitoneal mass, measuring 13×12×17 cm. The CT scan also revealed a large unilateral pleural effusion, suggestive of stage IV disease. However, the presence of lymphoma cells in the pleural effusion was not unequivocally confirmed, as cytology results were normal and flow cytometry data were not available. Staging bone marrow biopsy was negative.

The patient originally received rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). An interim positron emission tomography-computed tomography (PET-CT) performed after 2 courses of this therapy demonstrated stable disease; hence, the treatment was intensified with 4 additional courses of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R). Following the first 2 cycles of DA-EPOCHR, PET-CT showed complete metabolic response; however, unfortunately, the end-of-treatment exam demonstrated disease progression. The patient proceeded to a platinum-based salvage therapy with rituximab, ifosfamide, carboplatin, etoposide (RICE), leading to a 50% reduction in the size of the largest abdominal mass. An attempt to improve this response with a reduced-dose bis-chloroethylnitrosourea-etoposide-ARA-C (cytarabine)-melphalan (miniBEAM) regimen failed, and the patient did not ultimately proceed to the preplanned autologous stem cell transplantation (ASCT).

To that end, she was referred to anti-CD19 CAR-T cell therapy, preceded by a bridging combination of bendamustine, polatuzumab vedotin and rituximab. One month after CAR-T cell infusion, PR was demonstrated; however, 3 months post-treatment the disease progressed. At that time, reimbursement restrictions precluded retreatment with polatuzumab vedotin combinations, and single-agent oral selinexor was started. The drug was provided by Karyopharm Therapeutics through an expanded access program. Treatment was initiated at the recommended twice-weekly dose of 60 mg, accompanied with twice-weekly dexamethasone (8 mg×2/week) for the first 2 months. Since nausea had been reported to be a major selinexor-related adverse event, interfering with adherence to the treatment protocol, prophylaxis with netupitant/palonosetron was given once weekly. On day 1 of this treatment, nodal disease was evident on both sides of the diaphragm, including a retroperitoneal mass measuring 14 cm (standard uptake value [SUV] 13.4 MBq/g) and a mesenteric mass measuring 12 cm (SUV 12.8 MBq/g) (**Figure 1A**).

Adverse effects included asymptomatic hyponatremia as well as neutropenia and thrombocytopenia (all grade 3 without clinical sequelae). Consequently, the selinexor dose was lowered to 100 mg once weekly and granulocyte colony-stimulating factor (G-CSF) support was given. Hyponatremia resolved with the administration of intravenous 0.9% saline on several consecutive days, with no further recurrence. No other significant adverse effects, including nausea, emesis or lethargy, were observed.

PET-CT performed 3 months following selinexor initiation demonstrated minimal metabolically active disease. The fluorodeoxyglucose (FDG) uptake was limited to a very small area within

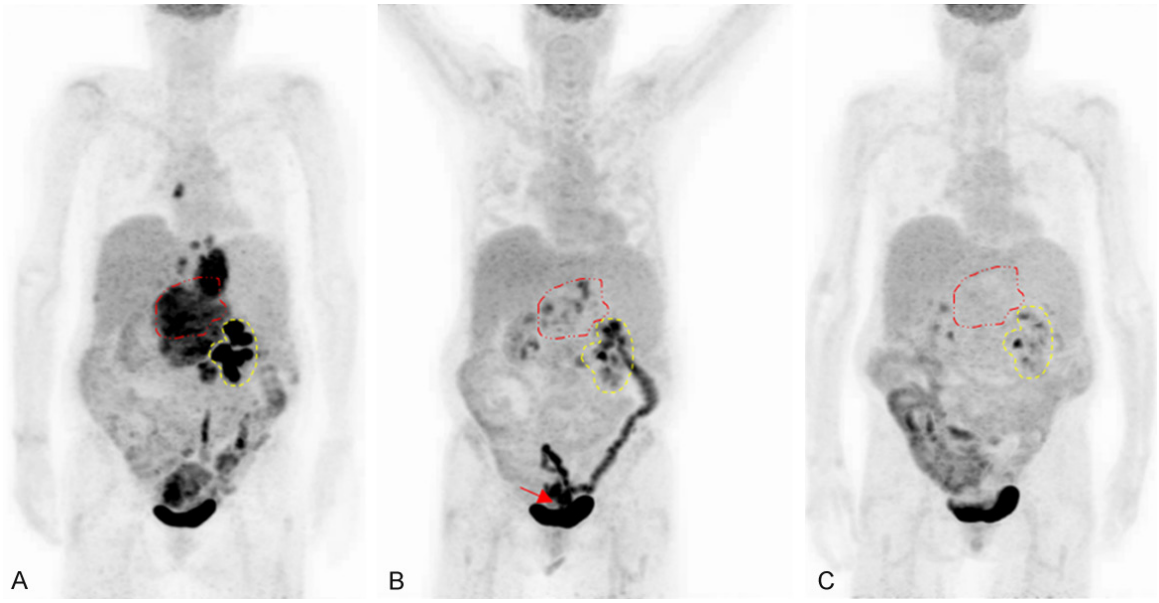

Figure 1. Fluorodeoxyglucose-positron emission tomography-computed tomography images before and after selinexor therapy. A. A positron emission tomography-computed tomography (PET-CT) image performed 3 months after chimeric antigen receptor T (CAR-T) cell therapy demonstrating progressive disease with pathological uptake in a mediastinal lymph node and in retroperitoneal, mesenteric and pelvic masses, obstructing urine flow from the left kidney (dashed line). B. A PET-CT image performed 3 months after selinexor initiation, demonstrating marked improvement with small foci of increased fluorodeoxyglucose (FDG) uptake (Deauville score =4) in residual mesenteric and retroperitoneal masses (solid line), and a new uptake focus above the urinary bladder. C. A PET-CT image performed 6 months after allogeneic stem cell transplantation (allo-SCT) and 11 months after selinexor initiation, demonstrating a complete metabolic response.

the original mass (which in itself reduced from 12 cm to 7.6 cm) and a lymph node (1.7×2 cm) adjacent to the urinary bladder (**Figure 1B**).

After 5 months of therapy, while in PR, the patient discontinued selinexor and underwent a matched related donor allo-SCT. Reduced-intensity conditioning (RIC), including fludarabine 30 mg/m^2 for 5 days, and melphalan 140 mg/m^2 on day -2 was used. Graft-versus-host disease (GVHD) prophylaxis, consisting of methotrexate and cyclosporine, was given as per the institutional protocol.

Early post-transplant events were mainly related to GVHD (grade 2 diarrhea and skin involvement), which developed on day +27 and was managed with steroids and once-weekly photopheresis. Now, 8 months post-transplant, despite complete donor chimerism, the patient remains moderately pancytopenic with a hypocellular bone marrow (10% cellularity). She still suffers from grade 1 GVHD and has been admitted to hospital several times due to infectious complications. However, her Eastern Cooperative Oncology Group (ECOG) performance status is good (0-1), and she is in CR, as confirmed by a follow-up PET-CT scan, performed 6 months after the transplant (**Figure 1C**).

Discussion

To the best of our knowledge, this is the first report of a patient with highly refractory DLBCL, resistant to multiple rounds of chemoimmunotherapy and CAR-T cell therapy who underwent allo-SCT following the achievement of deep PR with single-agent oral selinexor. Now, over one year after selinexor initiation, and following allo-SCT, the patient is in CR.

Currently available data on the outcome of patients undergoing allo-SCT for RR-DLBCL are conflicting. Beneficial effects of this procedure on survival have not been unequivocally proven, which could be explained, at least in part, by the heterogeneity of patient populations analyzed in the large retrospective studies [15-20] as well as by significant differences in the

focus of each study. A large analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) including 1183 patients <65 years with non-Hodgkin lymphoma [(NHL); only 30% had DLBCL] who underwent RIC allo-SCT, showed 4-year OS of 51%, and progression-free survival (PFS) of 37% [15]. Encouraging results were also reported by the European Society for Blood and Marrow Transplantation (EBMT) on 101 RR-DLBCL patients (half of whom received RIC), demonstrating 3-year PFS and OS of 41.7% and 52.2%, respectively, along with a low non-relapse mortality (NRM) rate of 20% [16]. At the same time, high NRM rates were reported in another sub-analysis from the CIBMTR database evaluating allo-SCT in NHL patients [17]. Moreover, neither this nor other studies revealed an association between improved survival and the presence of GVHD [15, 16], both findings questioning the relevance of allo-SCT in this setting. Data that still advocate for the allo-SCT benefit in this patient population come from a smaller study (68 RR-DLBCL patients) by the French Society of Marrow Transplantation and Cellular Therapy Registry (SFGM-TC) demonstrating a positive impact of chronic GVHD on OS [18], and the evidence from the National Cancer Institute, documenting responses to donor lymphocyte infusion or immunosuppression withdrawal [19].

Another retrospective analysis comparing the outcome of RR-DLBCL patients based on the type of conditioning, showed that RIC or non-myeloablative conditioning (NMAC) reduced NRM; however, this came at the expense of increased 5-year progression rates as compared to myeloablative conditioning (MAC) [21]. An additional important negative prognostic factor emerging in that study was a refractory disease status prior to transplant. Overall, the available data preclude formulating general guidelines and thus, the decision regarding patient referral to allo-SCT in this indication has to be made on an individual basis. Clearly, in order to reserve allo-SCT as a promising therapeutic option for RR-DLBCL patients, minimizing NRM and improving CR rates prior to transplant are imperative [15, 16, 18, 20].

The fact that selinexor has been shown to be effective in RR-DLBCL patients [14] makes it an attractive choice. Yet, the accumulating clinical experience with selinexor points to substantial interpatient variability in response to this drug. While the SADAL study [14] demonstrates a moderately better ORR in patients with GCB versus non-GCB DLBCL (34% vs 21%, respectively), and a comparatively good response in patients with transformed lymphoma relative to historical data [22], precise clinical and biological characteristics of patients who would benefit most from SINEs are still a subject of active investigation. Since the cell-of-origin classification actually encompasses an array of mutations and genetic signatures, defining 5 different clusters [23], whole-exome sequencing may become a useful tool for the identification of patients whose disease is expected to respond most profoundly to selinexor. Preclinical data in mantle cell lymphoma cell lines show that lymphoma cells, originally resistant to Bruton's tyrosine kinase (BTK) inhibition, undergo apoptosis when treated with selinexor, which is mediated by NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling attenuation [24]. This suggests that lymphomas dependent on NF-κB signaling, such as part of the activated B-cell (ABC) DLBCLs, and the "cluster 4" DLBCLs [23], would be responsive to XPO1 inhibition. Moreover, new data show that mutations in the XPO1 gene are prevalent both in RR-DLBCL and primary mediastinal B-cell lymphoma [25]. As these mutations might support lymphomagenesis [26], the subgroups harboring such aberrations could be preferentially sensitive to SINEs.

A number of ongoing studies are evaluating selinexor in combination with multiple other standard and novel regimens for the treatment of lymphoma (NCT04442022; NCT02303392; NCT03147885) in an attempt to improve response rates and extend the duration of response, as has been observed in myeloma studies [27, 28].

Until the results of new studies become available, treating physicians intending to provide optimal management for patients on selinexor, who are in PR or CR, will have to decide between the following two options: early referral to a subsequent potentially curative therapy or continuous selinexor treatment as long as the response is maintained and adverse effects are manageable. Since cumulative or major organ toxicities are uncommon, responding patients could potentially remain on this therapy until disease progression [29].

Conclusions

In the presented case, a DLBCL patient with a disease refractory to multiple lines of treatment, including CAR-T cell therapy, was treated with single-agent selinexor, which provided her an opportunity to undergo a potentially curative allo-SCT. This approach allowed the patient, who would have been otherwise considered a candidate for palliative care, to achieve the most prolonged CR since her first DLBCL treatment. Given that patients with RR disease could be salvaged with oral selinexor as a platform for further treatment, early identification of individuals who are expected to benefit most from this drug used either as a single agent or in drug combinations, is imperative.

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Disclosure of conflict of interest

None.

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