Chemotherapy

Anticancer Section / Novel Insights from Clinical Practice

Chemotherapy 2024;69:23–26
DOI: 10.1159/000534784

Received: September 19, 2023
Accepted: October 20, 2023
Published online: November 1, 2023

Prolonged Complete Response with Lenalidomide in a Relapsed Diffuse Large B-Cell Lymphoma, Leg-Type: A Case Report

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Keywords
Primary cutaneous diffuse large B-cell lymphoma · Leg-type · Lenalidomide · Remission

Abstract
Introduction: For primary cutaneous diffuse large B-cell lymphoma, leg-type (PCDLBCL-LT), there are no uniform recommendations for second-line treatment in case of relapse. ***Case Presentation:*** Here, we present the case of an elderly relapsed/refractory PCDLBCL-LT patient who obtained a prolonged clinical complete remission with lenalidomide. ***Conclusion:*** Lenalidomide as single agent led to an unexpected long complete response with manageable toxicity.

Introduction

Diffuse large B-cell lymphoma (DLBCL) represents the most common form of aggressive lymphoma and includes many minor entities [1], such as primary cutaneous diffuse large B-cell lymphoma, leg-type (PCDLBCL-LT). PCDLBCL-LT typically occurs in the eighth decade of life and has a 5-year survival rate between 40 and 60%. Elderly women are more commonly affected, with a male-to-female ratio of 1:3–4 [2]. Approximately 10% of cases involve other cutaneous sites apart from the lower legs, and extracutaneous dissemination is common [3].

Standard first-line treatment is based on polychemotherapy (CHOP regimen, cyclophosphamide, doxorubicin, vincristine, and prednisolone) in combination with rituximab. However, many patients with PCDLBCL-LT are elderly and frail and therefore unfit for chemotherapy.

There are no uniform recommendations for second-line treatment in case of relapse; however, some drugs such as lenalidomide and ibrutinib are showing their efficacy in this setting [3]. Here, we present the case of an elderly relapsed/refractory (R/R) PCDLBCL-LT patient who obtained a prolonged clinical complete remission (CR) with lenalidomide.

Case Presentation

An 84-year-old Caucasian woman came to our institution in July 2020 for nodular lesions on her left ankle that appeared in 2019 and were biopsied in May 2020. Histologic examination showed diffuse infiltration of large lymphoid cells, positive for cluster of differentiation CD20+, BCL6–, BCL2+, MUM1/IRF4+; the final diagnosis was DLBCL-LT.

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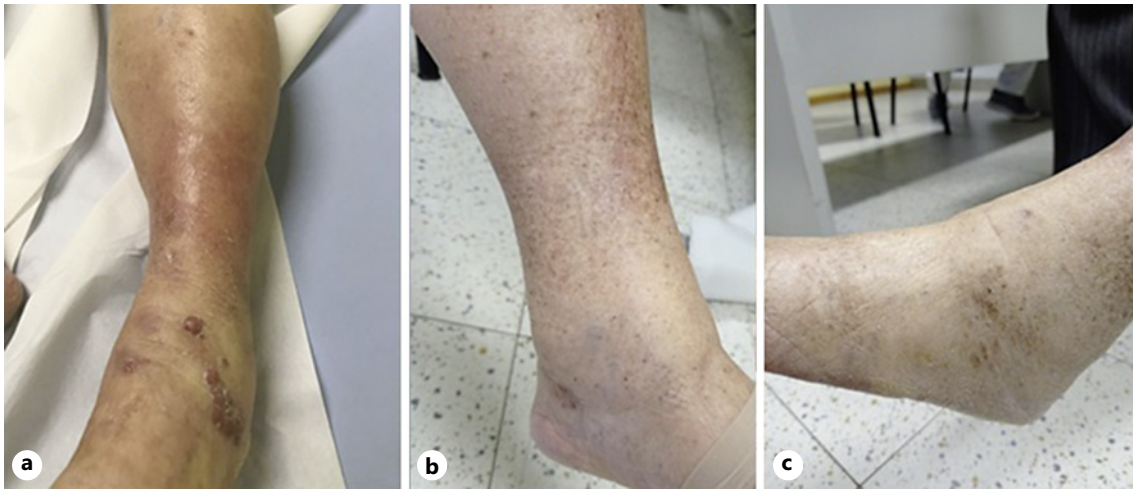

Fig. 1. a Left leg before starting lenalidomide. **b** Left leg after 8 cycles of lenalidomide. **c** Lateral side of left ankle after 8 cycles of lenalidomide.

Peripheral blood examination revealed mild multifactorial anemia (10.5 g/dL) without leukopenia or decreased platelet count. Renal function was impaired (estimated glomerular filtration rate 36 mL/min) and there was a mild lactate dehydrogenase elevation (271 U/L). Hepatic function was normal. Serum markers for HBV and HIV were negative, while IgG for HCV were positive.

Subsequently, staging procedures were carried on: an abdominal ultrasound exam excluded abdominal lymphadenopathy and organomegaly; a fluorodeoxyglucose positron emission tomography scan showed increased uptake of the skin nodules and excluded any other disease localizations (Fig. 1). After collegial discussion, considering the patient comorbidities (diabetes on pharmacologic therapy, HCV-related treated in 1994, hypertensive heart disease, and atrial fibrillation with ejection fraction of about 70%), histology, and age, we decided to begin vincristine therapy associated with steroids. The patient received 4 weekly vincristine (1 mg) administrations (the last one in September 2020) with oral prednisone (25 mg/day), without important toxicities and with progressive reduction of cutaneous nodules.

One month after the end of therapy, the patient experienced an episode of congestive heart failure concurrently with a decrease of hemoglobin levels and simultaneous erysipelas on her left leg. After some days of diuretics and antibiotics administration (amoxicillin and clavulanic acid followed by clarithromycin), the episode resolved. Afterward, the patient was evaluated for radiation therapy, but the radiotherapy specialists contraindicated treatment due to the multifocality of the cutaneous lesions.

After a 4-month follow-up period, in January 2021, a PET scan showed hypermetabolic subcutaneous lesions with appearance of new focalities on metatarsal bones. Clinically, the nodular lesions appeared stable (Fig. 1a, 2a).

On March 24, 2021, the patient was started on single-agent lenalidomide (15 mg/day for 21 days in a 28-day cycle). The following disease reassessments documented a progressive improvement from both a clinical and a radiological point of view: after 4 cycles, the patient achieved a clinical CR with disappearance of the skin lesions and with reduction of FDG uptake on subcutaneous nodules (Fig. 1b, c, 2b).

Considering the good tolerance, the clinical and radiological response, and the patient age, we decided to prolong lenalidomide until progression or unacceptable toxicity. Dose was adjusted according to renal function, and starting from cycle 20, the dose was reduced to 10 mg due to a grade 4 neutropenia.

The patient completed 24 cycles of treatment without any considerable toxicity and maintained a clinical CR for 16 months. Radiation therapy was not considered because of the CR obtained: another treatment would have caused adverse events in a frail cutaneous area without clinical benefits.

On January 9, 2023, a PET scan showed disease progression, albeit without clinical worsening (Fig. 2c). For this reason, lenalidomide therapy was interrupted and on February 13, 2023, daily oral cyclophosphamide was started. Patient gave consent to publish her data.

Discussion

PCDLBCL-LT is a rare form of aggressive lymphoma with a high incidence of relapse and poor outcomes [4]. This disease is characterized by a challenging course starting from diagnosis and carrying on with therapy choice.

The recommended first-line treatment is polychemotherapy in combination with the anti-CD20 antibody rituximab, considering the similarities between PCDLBCL-LT and systemic DLBCL. In a French study, Grange et al. [5] showed how rituximab in combination with CHOP is superior to all other possible combinations (polychemotherapy without rituximab, R-CHOP without doxorubicin, or doxorubicin monotherapy).

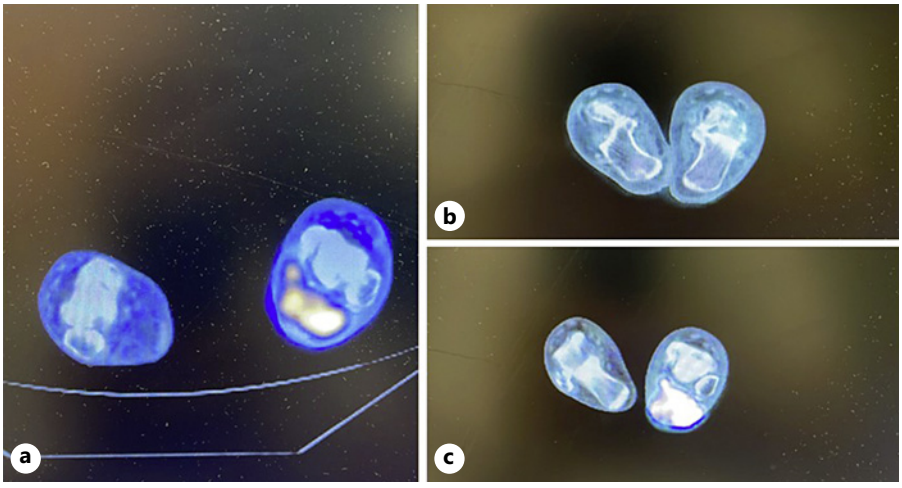

Fig. 2. a Baseline PET. **b** PET after 4 cycles of lenalidomide. **c** PET showing progression of disease.

However, PCDLBCL-LT often occurs in elderly people, who are usually unfit for this type of immunochemotherapy and who can benefit from less aggressive treatment strategies, such as lenalidomide. The mechanism of lenalidomide is based on the stimulation of T and natural killer cells activity: the drug decreases the expression of PD1 on both T and natural killer cells, thus restoring their cytotoxic functions, and causes the release of various cytokines. Moreover, lenalidomide abrogates the cross-talk between tumor cells and stromal microenvironment [6]. Lenalidomide presents a good toxicity profile: most common adverse events are represented by severe neutropenia, pneumonia, thrombosis, diarrhea, and renal impairment.

The present case report confirms how single-agent lenalidomide can be effective and well-tolerated in an elderly patient with a relapsed PCDLBCL-LT and multiple comorbidities. Lenalidomide as single agent led to an unexpected long complete and response with manageable toxicity.

The patient achieved a clinical CR after approximately 4 cycles of therapy which was maintained for 16 months. Considering her optimal tolerance of the drug, we decided to prolong the treatment with lenalidomide even after the completion of the usual 12 cycles. Overall, the patient received 24 cycles of therapy without experiencing any relevant side-effects apart from asymptomatic skin lentigo and grade 4 neutropenia, which resolved with dose reduction.

Few other cases have been described, some of which show the efficacy of lenalidomide in combination with other anticancer agents: in a small phase II study ($n = 19$), the 6-month overall response rate with single-agent lenalidomide in R/R PCDLBCL-LT was 26%, including four CR and one partial response. At 12 months, there were still two CR and one partial response. A case report of a 78-year-old man with R/R PCDLBCL-LT showed that combination therapy with ibrutinib, lenalidomide, and rituximab succeeded in obtaining a clinical and metabolic CR after 4 cycles [7].

Another case report illustrates the successful use of lenalidomide, rituximab, and pembrolizumab as combination therapy to treat an elderly patient with R/R PCDLBCL-LT: the patient remained in CR for 7 months [8]. Nowadays, many therapeutic options can be evaluated for patients with a diagnosis of PCDLBCL-LT, although we certainly need more studies and more details about the use of these new strategies.

Acknowledgment

We thank Massimo Agostini for data entry.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The work reported in this publication was funded by AIL Bologna OdV (prot 2CSAIL21 Argnani).

Author Contributions

Sabrina Zoli, Cinzia Pellegrini, Beatrice Casadei, Alessandro Broccoli, Lisa Argnani, Laura Nanni, Vittorio Stefoni, and Pier Luigi Zinzani conceived the case report, collected data, wrote the manuscript, provided advice, assisted with data interpretation, and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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