Lenalidomide and Carfilzomib in Relapsed and Refractory T Follicular Helper Lymphomas

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Abstract

Non-Hodgkin T-cell lymphomas represent a heterogeneous group of aggressive haematological malignancies with a high risk of early relapse or resistance to standard treatment protocols. One significant drawback is that chemotherapy protocols were initially designed for B-cell lymphomas, and targeted studies for T-cell lymphomas were only recently developed. Due to the rising incidence of peripheral T cell lymphomas (PTCL) in recent years, there is a need for new therapies to effectively treat these types of malignancies. Incorporating gene expression profile (GEP) studies in the standard diagnostic tests could enable treatments specifically tailored to each patient's needs. In this article we present the case of a patient diagnosed nodal-T follicular helper cell lymphoma, who exhibited early relapse following the standard chemotherapy protocol in our country. After multiple lines of treatment without favorable response, we conducted an off-label treatment combining Lenalidomide (an immunomodulatory drug) and Carfilzomib (a selective irreversible proteasome inhibitor). This therapeutic approach was previously done in other studies, but it involved also the use of Romidepsin, a histone deacetylase inhibitor (HDACi). We did not use Romidepsin in this patient as it is not approved in the European Union for patients with PTCL.

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Introduction

T-cell lymphomas constitute only 10 to 15% of all Non-Hodgkin Lymphomas and are recognized as some of the most aggressive chronic lymphoid malignancies (1). They originate from post-thymic T lymphocytes. In Europe, peripheral T cell lymphoma, not otherwise specified (PTCL NOS) and angioimmunoblastic T cell lymphoma (AITL) are the two most common types of T-cell lymphomas, comprising 34.3% and 28.7% of T cell lymphomas, respectively. Nodal PTCL with a TFH phenotype accounts for only 1% of all T-cell Lymphomas (1). AITL typically affects middle-aged and elderly patients, with a higher incidence in men than women. It is more prevalent in the white population and has a higher mortality rate in men (2).

In the WHO 2016 classification, a new type of lymphoma was introduced as nodal peripheral T cell lymphoma with a T follicular helper phenotype, initially classified as a subcategory of PTCL NOS (3). In the WHO 2022 Classification of Haematolymphoid Tumours, this category of lymphomas is termed nodal T-follicular helper cell lymphomas (nTFHLs) and it includes three entities: nTFHL angioimmunoblastic-type, nTFHL follicular-type and nTFHL-not otherwise specified (4).

Through genetic studies, it was discovered that AITL and PTCL with TFH phenotype share a range of common mutations, including RHOA, TET2, DNMT3A, and IDH2(5). Furthermore, the fusion gene t(5,9)(q33;q22) leading to ITK-SYK fusion is described in 20% of PTCL with TFH phenotype and in rare AITL cases, while it is absent in other T-cell lymphomas(6).

Research has shown that TET2 and DNMT3A mutations are premalignant, leading to the malignant transformation of affected cells. Specifically, TET2 mutation induces hypermethylation of the Blc6 gene, ultimately promoting proliferation of TFH lymphocytes. RHOA, a GTPase protein with a crucial role in thymus development, is found in 70% of TET2 positive AITLs, and its inactivation is implicated in T-Cell Lymphomas (7). Additionally, RHOA G17V is described in 25% of PTCL with FTH phenotype and in ATLL as well. IDH2 R172 mutation is also frequently observed in AITL (33%), but it is not expressed in other types of PTCL (8). Interestingly, despite being described separately in acute myeloid leukaemia (AML), TET2 and IDH2 mutations frequently co-occur in AITL, an unexpected phenomenon given that IDH2 inhibits TET2 enzyme activity (9).

AITL and nodal PTCL with TFH phenotype exhibit similar immunophenotyping and immunohistochemistry characteristics, requiring a minimum of two or three positive markers of follicular T helper cells, including CD10, PD1 (CD279), BCL6, CXCL13, CXCR5, ICOS, and SAP (3). Both AITL and PTCL with FTH phenotype manifest histopathological features such as endothelial venules proliferation and extrafollicular expansion of dendritic cells surrounding the vasculature. However, FTH lymphoma represents a tumour-rich variant of AITL (1, 3, 5).

While AITL presents more frequently, both AITL and TFH Lymphoma may exhibit B-cell blasts, often infected with the Epstein-Barr Virus (EBV). The T neoplastic cells function as helper cells, stimulating B cell proliferation, leading to the development of another lymphoma (10).

The standard first-line treatment for PTCLs involves the CHOP protocol, with the option to add etoposide in young and fit patients, in a higher overall response rate (ORR) compared to classic CHOP. To enhance treatment response, Autologous Stem Cell Transplantation (ASCT) consolidation should be considered, potentially increasing overall survival (OS) up to 48% at 5 years, compared to 26% in patients who did not undergo ASCT (1).

For patients with relapsed or refractory disease, Allogenic Stem Cell Transplantation (AlloSCT) is the standard protocol after achieving the first remission. If AlloSCT is proposed, a more aggressive pre-transplant regimen, such as ICE (Ifosfamide, Carboplatin, and Etoposide) or DHAP (Dexamethasone, Cytarabine, Cisplatin), is recommended (1). However, aggressive chemotherapy protocols may not be suitable for patients unable to undergo transplantation, as they do not yield sustained responses and can pose significant toxicity.

Patients unsuitable for AlloSCT may receive new lines of treatment, such as HDACi inhibitors (e.g., Romidepsin, Belinostat), immunomodulating agents (Lenalidomide), or proteasome inhibitors (Carfilzomib, Bortezomib), which are associated with less pronounced toxicity and can be administered over an extended duration. A trial involving the use of romidepsin, carfilzomib and lenalidomide showed promising results in the relapsed/refractory PTCL, especially in the subset of nTFHL angioimmunoblastic-type (11).

Case presentation

We present the case of a 55-year-old patient, a former heavy smoker, with the following medical history: recently treated pulmonary tuberculosis, chronic obstructive pulmonary disease (Gold stage II), chronic respiratory failure, hepatitis B virus (HBV)-related

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cirrhosis. Antiviral treatment for HBV was started one year prior and was complicated after a couple of months by the appearance of lymphocytic alveolitis and pulmonary thromboembolism, at which point the treatment was stopped. The patient also had with multiple haemorrhagic events due the rupture of oesophageal varices. During a liver transplantation evaluation, he was found to have important supradiaphragmatic and subdiaphragmatic lymph node enlargement, 32/22 mm and 36/16 mm respectively. Other imaging findings were emphysematous pulmonary changes associated with multiple nodules, a cirrhotic-configured liver and an enlarged spleen with a bipolar axis of 18.7 cm with a homogeneous structure.

Axillary and paratracheal lymph node excisions were performed, with the histopathological and immunohistochemical results revealing diffuse non-Hodgkin malignant lymphoma with small non-specific peripheral T cells with a follicular helper phenotype. The immunohistochemistry report showed CD20 positivity in follicular B structures, as well as in rare small B lymphocytes in the paracortical area and in rare large Sternberg-like cells, many of them were also positive for CD30 (an activated lymphocyte marker). The kappa/lambda ratio was 3:1, suggesting a polyclonal pattern in plasma cells. CD3 was positive in very frequent small T cells which were also positive for PD1 (follicular T helper marker). Most of the T cells were CD4+ CD8- and had low Ki67 proliferation index (~20%).

The bone marrow biopsy showed marrow infiltration of approximately 18-20% T lymphocytes, compatible with a non-Hodgkin malignant T cell lymphoma.

At that time of diagnosis, the patient had an ECOG score of 1 and except for HBV positive serology, the patient had normal laboratory tests. HTLV I/II infection screening was negative.

A diagnosis of stage IVB, nodal T-follicular helper cell lymphomas (nTFHLs)- not otherwise specified was made. The patient had high-intermediate prognostic score according to the age-adjusted international prognostic index.

Considering the patient's multiple comorbidities, we opted for CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) without the addition of etoposide.

After three cycles of CHOP chemotherapy, the patient had a partial remission with more than 50% reduction of supra and subdiaphragmatic adenopathies and a reduction of the spleen size from 180 mm to 150 mm, all the while maintaining signs of portal hypertension.

The treatment was completed after a total of six CHOP chemotherapy cycles, at the end of which the PET CT examination showed a complete metabolic remission.

Seven months later, the patient returned with clinical evidence of spleen enlargement, beyond the last taken measurements. A CT scan was performed, and it revealed relapsed supra- and subdiaphragmatic adenopathies with a maximum size of 39/18 mm and an enlarged spleen with a bipolar axis of 163 mm.

Second line GemOx (gemcitabine, oxaliplatin) chemotherapy was initiated, taking into account the patients past medical history and the fact that he was not deemed eligible for allogeneic or autologous stem cell transplantation. After three cycles, CT imaging showed progression of mediastinal and subdiaphragmatic adenopathies.

Because of the unfavourable course of the disease, as well as the limited therapeutic options in regard to the patient associated comorbidities and also the already studied and established fact that relapsed T-cell lymphoma have limited response to other chemotherapy agents, we decided to change the treatment to a non-chemotherapy approach.

Considering the existence of trials (7) that showed promising results with the combination of lenalidomide, carfilzomib and romidepsin, especially in the nTHFLs, we decided to give Lenalidomide and Carfilzomib as an off-label treatment. Romidepsin was omitted as it was not approved for use in Europe.

The regimen consisted of 15mg of lenalidomide given orally on days 1-14 and intravenous Carfilzomib 36 mg/m2, on days 1 and 8 of a 21-day cycle.

Afte 4 cycles, the imaging examination showed a regression of the adenopathies by approximately 50%, which justified the continuation of the treatment. The treatment was stopped after the 10th cycle of Lenalidomide-Carfilzomib because the patient developed grade 3 thrombocytopenia, which temporarily contraindicated the administration of the treatment.

Subsequently, he had a cirrhosis decompensation developing ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and massive variceal haemorrhage. He also had a cerebrovascular ischemic stroke, with persistent severe thrombocytopenia majorly influencing the treatment.

Because of all the complications related to the non-haematological comorbidities, the patient was deemed

unfit to continue the treatment for the lymphoma and was referred to a palliative care centre. He had a duration of response of eight months to the combination of Carfilzomib and lenalidomide.

Discusions

Since a lot of nTFH lymphomas occur in elderly patients that can't undergo an AlloSCT, new treatment regimens that are not associated with great toxicity, should be developed. We opted for an off-label treatment with Lenalidomide and Carfilzomib and this option did not bring high toxicities. Lenalidomide, an immunomodulatory agent studied as a solo agent in PTCL and cutaneous T-cell Lymphoma presented an ORR between 22-42% (11). Carfilzomib is an irreversible proteasome inhibitor that binds to the enzyme, delaying cellular proliferation and inducing apoptosis. Although not properly studied, the combined treatment with Lenalidomide and Carfilzomib showed a great disease control in our patient.

The studies that we based our treatment on also included Romidepsin, a HDAC inhibitor that is not yet approved in the European Union. When associated, Romidepsin and Lenalidomide have a synergistic effect that induces apoptosis through forming of reactive oxygen species. The triple therapy with Lenalidomide days 1-15, Carfilzomib days 1 and 8 and Romidepsin days 1, 8 and 15 showed a favourable response, ORR being 50% and 31% of the patients obtained CR. The median survival was 21.9 months (11). Possibly with the addition of Romidepsin, which was not available in the European Union, the patient's duration of response (DUR), would have been a better one.

Malignant cells' treatment resistance occurs through multiple mechanisms: during the treatment there is a selection of drug-resistant clones, that will later multiply and lead to a progressive disease. Also new mutations can develop, that finally lead to chemotherapy resistant cells and subsequently a relapse of the disease due to drug tolerant persistent (DTP) cells (12). This is the main reason that the standard chemotherapy protocols are not the best option, at least in the setting of relapsed/refractory (R/R) PTCL.

TET2 mutations that are present in almost 85% of AITL cases, are responsible for DNA hypermethylation (1. Genetic tests are essential in modern medicine in order to develop specific treatments for the new emerging mutations, especially for cancer patients that would benefit the most by receiving targeted medications designed for their needs. By discovering the TET2 mutation, new therapies with hypomethylating agents could be a possible cure for AITL. The usage of 5-Azacitidine administered in monotherapy for 7 days was associated with an ORR of 75% and CR of 50% in patient with AITL (13). Molecular testing of this patients could indicate that some of them may benefit from hypomethylating agents in the R/R setting.

Pralatrexate, which is a folate analogue metabolic inhibitor, could be a valid option for patients with Relapsed/Refractory PTCL, but it is also not approved in the European Union.

New therapies approved for PTCL that showed a favourable response are the monoclonal antibodies. Alemtuzumab, an antiCD52 antibody that can be used with the CHOP standard chemotherapy protocol produced an OS of 75.1% (26.8% percent of the cohort was diagnosed with AITL (14). Another valid option for our patients that have CD30 positive TFH lymphomas (30% of AITL are also CD30+) would be to associate to the chemotherapy protocol Brentuximab, an antiCD30 monoclonal antibody.

New studies focus nowadays to bring CAR (Chimeric Antigen Receptor) T cell therapy for the patients with T cell Lymphomas. Since CART cell therapy has been successfully used to treat patients with B-Cell Lymphomas, the next logical step would be to bring this treatment for the more aggressive T-Cell Malignancies. AntiCD4 CARTs are currently being studied, phase I studies investigating the clinical response (15)

Conclusions

Peripheral T-Cell Lymphomas with a Follicular T Helper phenotype are malignant haematological pathologies known for their inherent treatment resistance, posing significant challenges in achieving favourable outcomes. For many patients, standard chemotherapy protocols prove inadequate, necessitating the exploration of novel therapeutic approaches that take into account the genetic aberrations associated with these lymphomas. Unfortunately, the current treatment options approved in the European Union are insufficient in significantly improving the survival of PTCL with FTH phenotype, especially in the relapsed/ refractory setting.

Additional larger trials, combining novel agents and existing medications are needed to establish a clear benefit of these combinations for nTHFLs.

T-Cell Lymphomas remain intricate and insufficiently studied pathologies. PTCL and in particular nTHFLs,

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could benefit greatly from comprehensive genetic studies and innovative clinical trials aimed at enhancing patients' survival and overall quality of life.

Conflict of interests.
The authors declare none: Alina Marina Dimcea and Miruna Elena Tarnovan have contributed equally to the writing of the manuscript.

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