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Letter to the editor

Sanctuary site central nervous system relapse-refractory DLBCL responding to nivolumab and lenalidomide

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ABSTRACT

Despite improvement in survival in diffuse large B-cell lymphoma (DLBCL) with the introduction of rituximab, central nervous system (CNS) relapse continues to represent a clinical challenge. In diffuse large B-cell lymphoma (DLBCL), the incidence of CNS relapse is only ~5% in unselected cohorts. Immunotherapy is the treatment that either boosts the patient's own immune system or uses man-made versions of the normal parts of the immune system to kill lymphoma cells or slow their growth. We are presenting a thirty-eight year old man who, presented with neck nodes, axillary nodes, altered sensorium, abnormal body movements, unconsciousness, weight loss and, fever, with a past history of DLBCL in May 2008, treated with 6 cycles of CHOP and completed in November 2008. After 9 years in April 2018, the patient developed similar symptoms and treated with salvage chemotherapy with R-DHAP which was completed in September 2018. Post-treatment PET-CT showed partial metabolic response and we started external beam radiotherapy to initial bulky disease. After completion of radiotherapy, the patient was very reluctant for any type of therapy and went home. After one month he presented to us with persistent vomiting, abnormal body movements and, altered sensorium. On examination, his Glasgow Coma Scale (GCS) was E2V3M2 and he was admitted in Intensive Care Unit. The patient was managed with mannitol, dexamethasone, antiepileptics, antibiotics and other supportive care medicines. His brain magnetic resonance imaging (MRI) was showing multiple heterogeneously enhancing lesions with surrounding vasogenic oedema and his cerebrospinal fluid analysis was positive for malignant cells. He was managed with triple intrathecal chemotherapy with methotrexate 12 mg, Cytarabine 50 mg, and Hydrocortisone 50 mg along with other supportive care medicines, and after 4–5 days he regained consciousness and he was able to talk and understand verbal commands. In view of improvement in general condition and performance status, we started biweekly triple intra-thecal therapy, and Inj. Nivolumab 3 mg per kg q 2 weekly. From the second cycle, we started Lenalidomide 10 mg once a day for 21 days with 7 days gap along with 2 weekly nivolumab and biweekly triple IT chemotherapy. After one month his CSF analysis was negative for malignant cells. Now he is on regular treatment with weekly IT chemotherapy, 2 weekly nivolumab and 3 weeks on and one week off lenalidomide. After 2 months of treatment, his MRI Brain was showing. At the time of submission of this article, he has completed the fifth cycle of immunotherapy and two cycles of lenalidomide. He was able to manage his daily ADL and able to walk with a stick. The patient tolerated immunotherapy, triple IT therapy and lenalidomide very well without much intolerable side effects. Therefore, we concluded that nivolumab and lenalidomide was well tolerated and exhibited antitumor activity in extensively pretreated patients with relapsed or refractory sanctuary site CNS B- cell lymphomas. Additional studies of Nivolumab and lenalidomide in these diseases are ongoing.

Introduction

In diffuse large B-cell lymphoma (DLBCL), the incidence of CNS relapse is only ~5% in unselected cohorts [1]. However, in certain high-risk groups, such as those with adrenal/kidney involvement, estimates as high as 40% have been reported. Although large-scale studies can demonstrate a reduction in the risk of CNS relapse with the introduction of rituximab for the treatment of DLBCL, the impact is small, likely reflecting the poor CNS penetration of rituximab [2]. With the exception of primary testicular DLBCL, the time to CNS relapse is typically within the first 6–9 months of diagnosis, which may indicate the presence of occult disease at diagnosis. However, patients are not always routinely screened for CNS disease, and in the case of cerebrospinal fluid (CSF) evaluation, diagnostic sensitivity is low. Regardless, the overall consequence of CNS relapse is often devastating, and for most patients, the median overall survival is typically only a few months, highlighting the need to accurately identify at-risk patients, screen for CNS disease, and develop a safe and effective treatment/prophylaxis strategies.

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. Approximately 60% of DLBCL patients are cured using standard chemotherapy that includes monoclonal anti-CD20 antibody (rituximab), cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). However, 30–40% of DLBCL patients will develop relapse or have a refractory disease that cannot be cured with the standard R-CHOP therapy, indicating the need for more effective therapies for this patient subset.

The development of rituximab was an early step in the application of immunotherapy for the treatment of lymphoma, as it was the first monoclonal antibody approved by the US-FDA for the patients with

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advanced stage or relapsed low-grade non-Hodgkin lymphoma, in 1997. More recently, a number of innovative immunotherapy approaches have shown promising results in patients with relapsed or refractory DLBCL → numerous ongoing clinical trials.

Immune checkpoint blockade has promising potential in DLBCL therapy. A subgroup of patients with advanced cancers may respond to single-agent immune checkpoint blockade [3]. Promising immunotherapy approaches, such as chimeric antigen receptor (CAR) T cell therapy and therapeutic blockade of immune checkpoints, in particular, cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein 1 pathway (PD-1/PD-L1), have boosted the development of new therapeutic regimens for patients with relapseed/refractory DLBCL. Immune blockade of the PD-1/PD-L1 interaction by monoclonal antibodies can restore the antitumor activity of cytotoxic T cells. Early clinical trials using two anti-PD-1 antibodies (nivolumab and pembrolizumab), and three anti-PD-L1 antibodies (avelumab, durvalumab, and atezolizumab), have shown great promise.

Case vignette

Thirty-eight year old man, non-smoker and non-alcoholic by habits presented with a past history of histopathology and immunohistochemistry proven stage III DLBCL and has been treated with 6 cycles of CHOP (Cyclophosphamide 750 mg/m^2 D1, Doxorubicin 50 mg/m^2 D1, Vincristine 1.4 mg/m^2 and Prednisone 100 mg per orally from D1-D5) from May 2008 to November 2008. Post-treatment images were suggestive of complete response and he was not under regular follow up with the treating Doctor. After 9 years he again developed similar symptoms and he took some Ayurvedic treatment in the initial 3–4 months period of his first relapse from May 2017 to September 2017.

For the first time, he presented in April 2018 to us, with neck nodes, axillary nodes, fever, and weight loss, since last 8 months before coming to the hospital. On examination, there was cervical, axillary and inguinal lymphadenopathy, moderate splenomegaly, and moderate hepatomegaly. He was not able to turn his neck properly because of cervical nodes. He was having right brachial plexopathy with weakness in the C8-T1 nerve root area. His routine investigations revealed hemoglobin of 10.3 gm/dl, the total count of 7400/cu mm and platelet count of 225,000/cu.mm. Erythrocyte sedimentation rate (ESR) was 80 mm at first hour, uric acid was 7.8 mg/dl, creatinine was 0.9 mg/dl, potassium was 5.7 mg/dl, calcium was 9.5 mg/dl, and lactate dehydrogenase was 750 IU/L. Serology for human immunodeficiency virus, hepatitis B and C viruses were negative. Positron Emission Tomography-Computed Tomography scan (PET-CT) showed increased Standard Uptake Value (SUV) and hypermetabolic areas in bilateral cervical, intraparotid, axillary, inguinal, mediastinal, para aortic, intramammary and iliac lymph node regions, liver, spleen, and vertebral bodies with contiguous erosions of the right first rib and C6 to T1 vertebrae due to nodal mass with size of 115X115mm with SUV of 26.92. Bone marrow aspiration and trephine biopsy were not done in view of skeletal involvement. The cerebrospinal fluid analysis was normal.

Histopathological examination of the cervical lymph node biopsy specimen shows B cells with diffuse growth pattern and large lymphocytes, round in shape, pleomorphic nuclei, medium to large in size. The immunohistochemistry panel of the specimen shows positivity to LCA and B-cell antigens CD19, CD20, CD45, BCL-2 and negativity for CD3, CD5, CD10, MYC and BCL-6 and was diagnosed to have the first relapse of Diffuse Large B Cell Lymphoma. The proliferation rate is extremely high with numerous mitotic figures. Nearly 90% cells expressed proliferation antigen Ki-67, which is recognized by the antibody MIB-1. So overall staging evaluation revealed a relapse stage IV Diffuse large B cell lymphoma.

The patient was managed with supportive care for tumor lysis syndrome and started treatment with low dose COP [cyclophosphamide, oncovin (vincristine) and prednisolone] as reduction or prophase to prevent tumor lysis syndrome. Definitive treatment was done with 6 cycles of R-DHAP (Rituximab 375 mg/m^2 D1, Cisplatin 100 mg/m^2 D1, Cytarabine 2000 mg/m^2 IV 12 hourly on D2, and Dexamethasone 40 mg D1-D4) from April 2018 to September 2018. Post-treatment PET-CT showed a reduction in the number, size and metabolic activity of previously seen areas without any new FDG avid lesions suggesting partial metabolic response and was planned for external beam radiotherapy to initial bulky disease and the same was started.

After completion of radiotherapy, we planned for oral Ibrutinib in view of his poor performance status but the patient was very reluctant for any type of therapy and went home. After one month he presented to us with persistent vomiting, abnormal body movements, and altered sensorium. On examination, his vitals were stable, and his Glasgow Coma Scale (GCS) was E2V3M2 and was admitted in the Intensive Care Unit. He was managed with mannitol, dexamethasone, antiepileptics, antibiotics and other supportive care medicines. His routine blood investigations and electrolytes were within normal limits. His brain magnetic resonance imaging was showing and his cerebrospinal fluid analysis was positive for malignant cells.

He was managed with triple intrathecal chemotherapy with methotrexate 12 mg, Cytarabine 50 mg, and Hydrocortisone 50 mg along with other supportive care medicines. After 4–5 days he regained consciousness and he was able to talk and understand verbal commands. In view of improvement in general condition and poor performance status, we started biweekly triple intra-thecal chemotherapy till CSF is negative for malignant cells and immunotherapy with Inj. Nivolumab 3 mg per kg q 2 weekly. After completion of first cycle nivolumab, he was able to walk with support and was able to talk with some tremors in the left upper limb. From the second cycle, we started Lenalidomide 10 mg once a day for 21 days with 7 days gap along with 2 weekly nivolumab and biweekly triple IT chemotherapy. After one month his CSF analysis was negative for malignant cells. Now he is on regular treatment with weekly IT chemotherapy, 2 weekly nivolumab and 3 week on and one week off lenalidomide. After 2 months of treatment, his MRI Brain was showing near complete response. At the time of submission of this article, he has completed fifth cycle of immunotherapy and two cycles of lenalidomide. He was able to manage his daily activities of daily living (ADL) and able to walk with a stick. The patient tolerated immunotherapy, triple IT therapyand lenalidomide very well without much intolerable side effects. Now he is continuing the same dose and schedule of nivolumab and lenalidomide and weekly triple IT for 6 weeks followed by 6 cycles of monthly IT. We planned for a total of 2 years of post-remission Nivolumab immunotherapy and lenalidomide till progression of the disease.

Discussion

Patients with relapsed or refractory aggressive B-cell Non-Hodgkin lymphoma (B-NHL) have a poor outcome. Lymphomas were one of the first cancers to show sensitivity to manipulations of the immune system. Nivolumab targeting the PD-1 receptor has shown promising results in several malignancies like melanoma, renal and lung carcinoma and Hodgkin lymphoma. Data for aggressive B-NHL are just emerging. The programmed death-1 (PD-1) pathway is an immune checkpoint to attenuate T-cell–mediated immune responses and may be exploited by tumors to avoid immune surveillance. Immune blockade of the PD-1/PD-L1 interaction by monoclonal antibodies can restore the antitumor activity of cytotoxic T cells [4].

CNS relapse in the Rituximab era, the best evidence comes from the RICOVER-60 trial, which evaluated 1112 patients with aggressive B-cell lymphoma (primarily DLBCL [81.6%]) and reported a 2-year incidence of CNS disease of 6.9% using cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) administered every 2 weeks compared with 4.1% using rituximab plus cyclophosphamide, doxorubicin,

vincristine, and prednisone (R-CHOP) [5]. A recent meta-analysis of 4859 patients treated with R-CHOP (-like) on 7 prospective trials demonstrated an overall CNS recurrence risk of ~5% in rituximab-treated patients [1].

PD-1–blocking antibodies (nivolumab and pembrolizumab) produced durable objective responses and improved overall survival (OS) in patients with solid tumors and hematologic malignancies, including HL [6,7]. Nivolumab therapy resulted in ORRs of 36% and 40% among patients with DLBCL and FL, respectively. With continued nivolumab therapy, the depth of objective responses may improve as demonstrated by one patient with DLBCL with an initial PR (at 16 weeks) that converted to a CR (at 72 weeks) with extended treatment. Response durations exceeded 1 year for two (one each with FL and DLBCL) of three patients who achieved a CR and ≥6 months for patients with FL who achieved a PR [8].

Currently there is very scarce information is available in the literature regarding the use of Nivolumab and Lenalidomide combination in the treatment of relapse refractory DLBCL and other Non-Hodgkin's lymphomas, but one Phase I/II trial which is going on at the Ohio State University Comprehensive Cancer center "Nivolumab and Lenalidomide in Treating Patients With Relapsed or Refractory Non-Hodgkin or Hodgkin Lymphoma" will address the issue [9].

More recently, frequent PDL1/2 copy-number alterations and increased PDL1/2 protein expression were demonstrated in primary CNS lymphoma and testicular DLBCL, leading to a strong rationale for PD1 inhibitors in these immune sanctuary sites [10,11]. A case series of 5 patients with relapsed/refractory primary CNS lymphoma (n = 4) or testicular DLBCL (n = 1) treated with nivolumab demonstrated responses in all patients, 3 of whom have remained in a durable remission for over 1 year [12]. A phase 2 study evaluating nivolumab is ongoing in these disease settings (#NCT02857426). Other uses of Nivolumab in Head and Neck malignancies are Squamous cell carcinoma of head and neck after progression to platin based therapies (SCCHN) [13], Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma.

Conclusion

Cancer immunotherapy that harnesses the host immune system in novel ways to kill tumor cells is emerging. Immunotherapy offers promising opportunities with the potential to induce sustained remissions and is expected to become a "game changer" for the treatment of patients with cancer. Nivolumab was well tolerated and exhibited antitumor activity in extensively pretreated patients with relapsed or refractory B-cell lymphomas. Additional studies of Nivolumab in these diseases are ongoing. The exploration of novel agents that cross the blood-brain barrier or, in the case of PD1 inhibitors, target the mechanism of immune evasion requires further study in high-risk patients.

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None.

Conflicts of interest

None.

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Irappa V. Madabhavi[a,*], Swaroop Revannasiddaiah[b], Malay S. Sarkar[c], Mitul G. Modi[d]
[a] *Department of Medical and Pediatric Oncology, Kerudi Cancer Hospital, Bagalkot, Karnataka, India*
[b] *Department of Medical Oncology, M S Ramaiah Medical College, Bangalore, Karnataka, India*
[c] *Department of Pulmonary Medicine, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India*
[d] *Department of Pathology, Gujarat Cancer Research Institute, Gujarat, Ahmedabad, India*
E-mail address: irappamadabhavi@gmail.com (I.V. Madabhavi).

[*] Corresponding author at: Department of medical and pediatric oncology, Gujarat Cancer Research Institute, Gujarat, Ahmedabad, India.