Long-term survival in a patient with refractory B-cell lymphoma unclassified (diffuse large B-cell lymphoma/classical Hodgkin lymphoma) treated with rituximab in combination with IGEV: A case report

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Received January 12, 2016; Revised September 21, 2016; Accepted December 10, 2016; Published Online December 27, 2016

Case Report

Abstract

Although most lymphoid neoplasms can be classified into distinct entities, there is a small subset with overlapping features which are difficult to classify. Here, we report a case of a patient with “unclassifiable” B-cell lymphoma (BCLU)-diffuse large B-cell lymphoma (DLBCL)/classical Hodgkin lymphoma (cHL), refractory to traditional chemotherapy, high-dose chemotherapy and autologous stem cell transplant who achieved a sustained response to combined rituximab and ifosfamide, gemcitabine, vinorelbine, and prednisone (R-IGEV) chemotherapy. The outcome of this case suggests that R-IGEV may be a valuable treatment option for patients with BCLU – DLBCL/cHL composite lymphoma that should be further explored.

Keywords: Composite, Lymphoma, Rituximab, Unclassified, Ifosfamide, Gemcitabine

Introduction

The vast majority of lymphoid neoplasms can be classified into distinct entities based on morphological, immunophenotypic and molecular genetic alterations. However, there remains a small subset of lymphoid neoplasms that have overlapping features between two different types of lymphoid neoplasms and remain difficult to classify. These entities have been previously labeled as “composite” lymphomas or “grey zone” lymphomas. The updated 2008 World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues has created two new provisional categories of “unclassifiable” B-cell malignancies (BCLU). One of these has features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL) [BCLU – DLBCL/cHL], and the second demonstrates features intermediate between DLBCL and Burkitt lymphoma (BL) [BCLU – DLBCL/BL]. Controversy surrounds whether the two components of the lymphomas are clonally related or distinct clones.

Most BCLU – DLBCL/cHL are typically associated with mediastinal large B-cell lymphoma (MLBCL) and nodular sclerosing Hodgkin lymphoma (NSHL). BCLU – DLBCL/cHL cases with extramediastinal or extranodal disease are exceedingly rare. A recent review of the literature identified only 9 cases. The natural history of this entity and prognosis remain undefined and no definitive treatment guidelines exist either at initial diagnosis or at relapse posing a conundrum for the treating physician.

The IGEV (ifosfamide, gemcitabine, vinorelbine, and prednisone) regimen is often used as a salvage regimen prior to high dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) in patients with relapsed/refractory Hodgkin lymphoma (HL). The reported complete response rate is 53.8%, the partial response rate is 27.5%, and the overall response rate is 81.3%. Nearly all patients treated with IGEV have undergone subsequent HDC and ASCT, and the natural history of relapsed/refractory HL patients treated with IGEV without a subsequent consolidation with HDC and ASCT is unknown. Long-term survival after failure of HDC-ASCT with conventional salvage chemotherapy is

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Moreover, we could not find any data utilizing this regimen as a salvage after failure of HDC and ASCT. Also, we were not able to find any reports of the use of the IGEV combination in patients with DLBCL although the individual components of this combination have clear cut single agent activity. Rituximab has been studied in heavily pretreated HL patients with a demonstrated single agent activity of 22%. It is presumed to act by depleting B cells in the microenvironment since Reed Sternberg (RS) cells are not known to express CD20.

Chemoimmunotherapy with rituximab-containing combinations is now considered to be standard of care in initial treatment of DLBCL and has also been used in the vast majority of relapsed/refractory patients. Although, gemcitabine, which is an important component of the IGEV regimen, has been combined with rituximab in patients with relapsed/refractory HL with a demonstrated response rate of 38%, the combination of rituximab with IGEV has not been previously reported to the best of our knowledge. Here, we report a case of a patient with BCLU-DLBCL/cHL, refractory to traditional chemotherapy, HDC and ASCT who achieved a sustained response to combined rituximab and IGEV chemotherapy. The patient has maintained a complete response for over six years as of this writing. To our knowledge this is the first application of the R-IGEV (rituximab, ifosfamide, gemcitabine, vinorelbine, and prednisone) combined chemotherapy regimen. The outcome of this case suggests that R-IGEV may be a valuable treatment option for patients with BCLU – DLBCL/cHL composite lymphoma that should be further explored.

Case presentation

A 62-year-old man presented in September 2008 with a three-week history of unexplained episodes of abdominal pain. He reported no weight loss, night sweats or other unusual symptoms, and his only concurrent diagnosis was restless leg syndrome. An initial computed tomography (CT) scan of the abdomen and pelvis revealed extensive retroperitoneal periaortic lymphadenopathy and positron emission tomography (PET) imaging showed hypermetabolic adenopathy in the neck, chest, abdomen and pelvis (Figure 1).

Needle core biopsy of retroperitoneal lymph node tissue showed large atypical cells with features of classic RS cells as well as RS variants. Immunostaining was found to be positive for CD30 and dimly positive for CD15 but negative for CD45, CD3 and CD20, supporting the diagnosis of HL (Figure 2A).
**Figure 2C:** Large atypical cells negative for CD45 with surrounding positive small lymphocytes (CD45, X400).

**Figure 2D:** Several large cells present which appear negative for CD20 with surrounding positive small B cells (CD20, X400).

**Figure 3:** PET/CT after 2 cycles of ABVD.

**Figure 4:** PET/CT demonstrating recurrence after ABVD.

**Figure 5:** PET/CT demonstrating response to ICE prior to SCT.
Combination chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was initiated and after two cycles, the patient experienced resolution of the pain in his abdomen. PET imaging indicated a complete response (Figure 3). ABVD was continued for six cycles and less than three months after the final treatment cycle, the patient’s symptoms of abdominal pain returned. A PET demonstrated evidence of recurrent lymphoma in the form of enlarged hypermetabolic lymph nodes in the retroperitoneum (Figure 4). At this point in time, the patient was referred to a tertiary referral center for consideration of HDC and ASCT. His initial pathology was reviewed and was consistent with the findings of the first reading; CD3 was determined to be negative and CD30 positive. Several stains, however, were interpreted differently by the outside group. CD15 was reported to be negative, CD45 equivocal, and the reviewers commented that the CD20 immunostaining did not appear to have stained properly but was thought to be negative. Despite these subjective differences, the initial diagnosis of HL was ultimately confirmed by the second pathology group.

The patient returned to our institution and was then treated with two cycles of combination ifosfamide, carboplatin and etoposide (ICE) to which he responded (Figure 5). He went on to receive high-dose cyclophosphamide followed by stem cell collection, then BEAM (carmustine, etoposide, cytosine arabinoside, and melphalan) conditioning and ASCT. At his first follow-up visit after transplant, a hypodense lesion in the right lobe of the liver was noted on surveillance CT. This mass, in hindsight, had been present before transplant but had grown from 1.3 cm to 4.5 cm at this visit (Figure 6). CT-guided core needle biopsy of the lesion revealed involvement by a B-cell lineage malignancy with overlap features between cHL and DLBCL. Some cells were binucleate and had features consistent with RS cells of cHL while others were mononucleate and resembled the centroblasts or immunoblasts seen in DLBCL. These cells were PAX-5 and MUM-1 positive, and some stained positive for CD20. RS cells were expectedly CD30 positive. CD45, which is useful for discriminating between cHL and DLBCL, had an equivocal result. To elaborate further on the discrepancy between this result and the original lymph nodal tissue biopsy, the original tissue was sent to a second tertiary center. The cells were found to be weakly positive for both CD20 and PAX-5, supporting a diagnosis of a composite HL/non-Hodgkin lymphoma even at initial presentation (Figure 7).

**Figure 6:** CT scan of recurrence after SCT.

**Figure 7A:** Liver biopsy showing several large and rare binucleated cells (H&E, X400).

**Figure 7B:** Liver biopsy with rare large, atypical cells positive for CD30 (CD30, X400).

**Figure 7C:** Liver biopsy with rare large, atypical cells positive for CD20 (CD20, X400).
Figure 7D: Original retroperitoneal lymph node showing several large atypical cells staining weakly with CD20 and surrounding small reactive B cells staining strongly (CD20, X400 performed at Mayo Clinic).

Figure 7E: A few large cells with weak nuclear staining with PAX5 and surrounding small B cells staining strongly (PAX5, X400 performed at Mayo Clinic).

A chemotherapy regimen with activity in both relapsed cHL and DLBCL was necessary, so R-IGEV was selected. The patient started treatment in April 2010 using standard doses of rituximab 375 mg/m² and IGEV as reported by Santoro et al. given every 3 weeks. Significant neutropenia was anticipated so a single dose of pegfilgrastim was administered at the completion of each treatment cycle. Despite this intervention, transient neutropenia did occur after each cycle. These episodes generally resolved within two weeks of treatment, but increased in both severity and duration as treatment cycles continued. Despite considerable neutropenia, no infection was identified throughout the course of chemotherapy; however, the patient did receive prophylactic antibiotics. During the first treatment cycle, the patient developed grade 4 thrombocytopenia requiring platelet transfusions. This pattern of thrombocytopenia with precipitous drops in platelet count reoccurred with each treatment cycle, and platelet recovery time grew increasingly prolonged with each successive cycle. The doses of ifosfamide, gemcitabine, and vinorelbine were reduced in the fourth and fifth cycles in an attempt to dampen this effect, but thrombocytopenia ultimately limited therapy despite this attenuation. After the fifth of a planned six treatment cycles, profound thrombocytopenia persisted and platelet count did not return to a treatable level for 38 days. A sixth cycle of R-IGEV was never administered. Anemia related to chemotherapy also occurred after each of the five cycles and the patient generally required packed red blood cells with each cycle.

CT scan of the chest, abdomen, and pelvis after two cycles of R-IGEV showed marked improvement. The size of the hepatic lesion was reduced from 4.5 cm to 3.6 cm, and lymphadenopathy was visibly resolving. These physical indicators of disease status continued to improve with additional R-IGEV cycles.

Figure 8: CT 2 years post R-IGEV.

The patient has maintained a complete response for over six years since his final treatment cycle. His blood counts have recovered. The lymphadenopathy has entirely resolved and the hepatic lesion is no longer appreciable. (Figure 8)

Discussion

Patients with both cHL and DLBCL who are refractory or relapse soon after HDC and ASCT have a poor prognosis. Anti-CD30 monoclonal antibodies are generally well-tolerated but have limited, albeit some, single-agent activity in heavily pretreated patients with Hodgkin lymphoma. More recently anti-CD30 antibodies conjugated to monomethyl auristatin E, a potent anti-tubulin agent, revealed an 86% tumor shrinkage rate and 50% objective response rate. Allogeneic stem cell transplant, both myeloablative and reduced-intensity conditioning (RIC), has also been investigated as salvage therapy after failed ASCT. There is significant transplant-related mortality, and patients are heavily pre-selected.
Our patient was offered a RIC allotransplant but refused. He verbalized a strong desire to be treated locally with some form of conventional therapy.

While the therapeutic validity of the R-IGEV regimen cannot be confirmed from a single report, five cycles of this novel combination elicited a sustained, possibly curative response in this patient with a composite hematologic malignancy. Ambiguous histologic results at baseline made it difficult to determine if DLBCL existed at the time of presentation. Based on the clinical course and subsequent pathology review, it is our suspicion that both cHL and DLBCL were present originally versus sequential development of a second lymphoma following the initiation of chemotherapy. Regardless of the origin, the eventual presentation of a combined diagnosis of DLBCL and relapsed cHL after ASCT theoretically made R-IGEV an ideal combination of agents in this unique clinical scenario. This theoretical potential translated into a positive clinical outcome. The achievement of a sustained response seems to indicate efficacy but the hematologic toxicity observed here seems greater than would be expected with IGEV alone. We cannot completely exclude the possibility the addition of rituximab to any of his previous chemotherapeutic regimens would have resulted in a similar positive outcome. Hematologic toxicity may have been augmented by the patient’s previous ASCT or the concurrent use of rituximab.

**Conclusion**

The outcome of this case supports the efficacy of R-IGEV, a new combination chemotherapy regimen, in the treatment of BCLU – DLCBCL/cHL. To the best of our knowledge, this is the first report of the use of IGEV and rituximab in combination.

**Conflict of interest**

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**