Rituximab used in three cases with relapsed non-Hodgkin's lymphoma

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Abstract. Relapsed or refractory B-cell non-Hodgkin's lymphoma (B-NHL) patients have a poor prognosis. New treatment modalities have been used to improve survival rates in children with relapsed or refractory B-NHL. CD20 is expressed in >98% of childhood B-NHL and a chimeric anti-CD20 monoclonal antibody, rituximab, is increasingly being used at relapse. The aim of the present study was to determine the efficacy of rituximab on relapsed B-NHL. Three B-NHL cases were treated successfully with a combination of intensive chemotherapy protocol plus rituximab.

Introduction

Lymphomas are the third most common type of cancer identified during childhood and adolescence, with 60% of those being mature B-cell non-Hodgkin's lymphoma (B-NHL). Primary central nervous system malignant lymphomas (PCNSLs) comprise <2% of malignant lymphomas. B-NHL is usually of B-cell origin (1-4). First-line chemotherapy is found to be effective in the majority of children diagnosed with B-NHL. Although long-term cure rates are 75% for high-risk disease (5), relapses occur in ~20% of the patients, almost always within a year from diagnosis (6). Relapsed or refractory B-NHL has a poor prognosis. CD20 is expressed in >98% of childhood B-NHL and increasingly a chimeric anti-CD20 monoclonal antibody, rituximab, is being used at relapse (7,8). Although rituximab is commonly used as a first-line therapy in adults, the effect of rituximab in children with B-NHL has yet to be adequately investigated (9-12). Three B-NHL cases were investigated in this case study to determine the efficacy of rituximab-containing regimens on relapsed B-NHL.

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Case reports

Patient 1. A 16-year-old male was admitted to the Department of Pediatric Oncology complaining of recurrent abdominal pain and distention for the previous 2 months. Physical examination revealed that the abdomen was distended but non-tender, with an immobile, painless and hard mass, 5x8 cm in diameter, located on the right side of the abdomen. Results of bone marrow (BM) examination, hematologic and basic metabolic analysis were normal. Abdominal computed tomography (CT) scan confirmed multiple retroperitoneal lymph nodes and a mass, 6x10x11 cm in a diameter, surrounding the superior mesenteric artery (Fig. 1A). Burkitt lymphoma was diagnosed. Positive CD20, CD10, bcl6 and negative CD30, CD3, CD5 and TdT were reported by immunohistochemical examination. After 4 months of NHL-Berlin-Frankfurt-Muenster (BFM) 95 chemotherapy protocol, the patient noted backache. BM examination revealed diffuse L3 type lymphoblasts. Additionally, the CT scan showed that the size of the intra-abdominal mass did not decrease. The patient received intravenous rituximab (375 mg/m^2/dose/once every 3 weeks) for six doses and Ifosfamide, Carboplatin and Etoposide (ICE). The control CT scan revealed that the size of the mass decreased and central necrosis was evident (Fig. 1B). Although in complete remission at least 12 months following chemotherapy, the patient succumbed due to systemic progression of severe sepsis.

Patient 2. A 14-year-old male presented with a 1-month history of abdominal pain and distension. He noted a 7-pound weight loss during the previous two weeks. On physical examination, the abdomen was distended, although soft and non-tender, with hypoactive bowel sounds and shifting dullness. No organomegaly was noted. Results of BM examination, as well as hematologic and metabolic tests were normal. Abdominal CT scan revealed enlarged multiple lymphadenopathies, of which the largest was 6 cm in diameter, in the mesenteric region and peritoneal surfaces with ascites (Fig. 1C). Flow cytometry showed that the ascites fluid was 90% positive for CD45 and 80% for CD20. Burkitt lymphoma was diagnosed and NHL-BFM 95 chemotherapy protocol was administered. After 6 months of chemotherapy, the abdominal and the maxillary mass gradually decreased. At the end of the chemotherapy, complete remission was achieved (Fig. 1D). One month later,

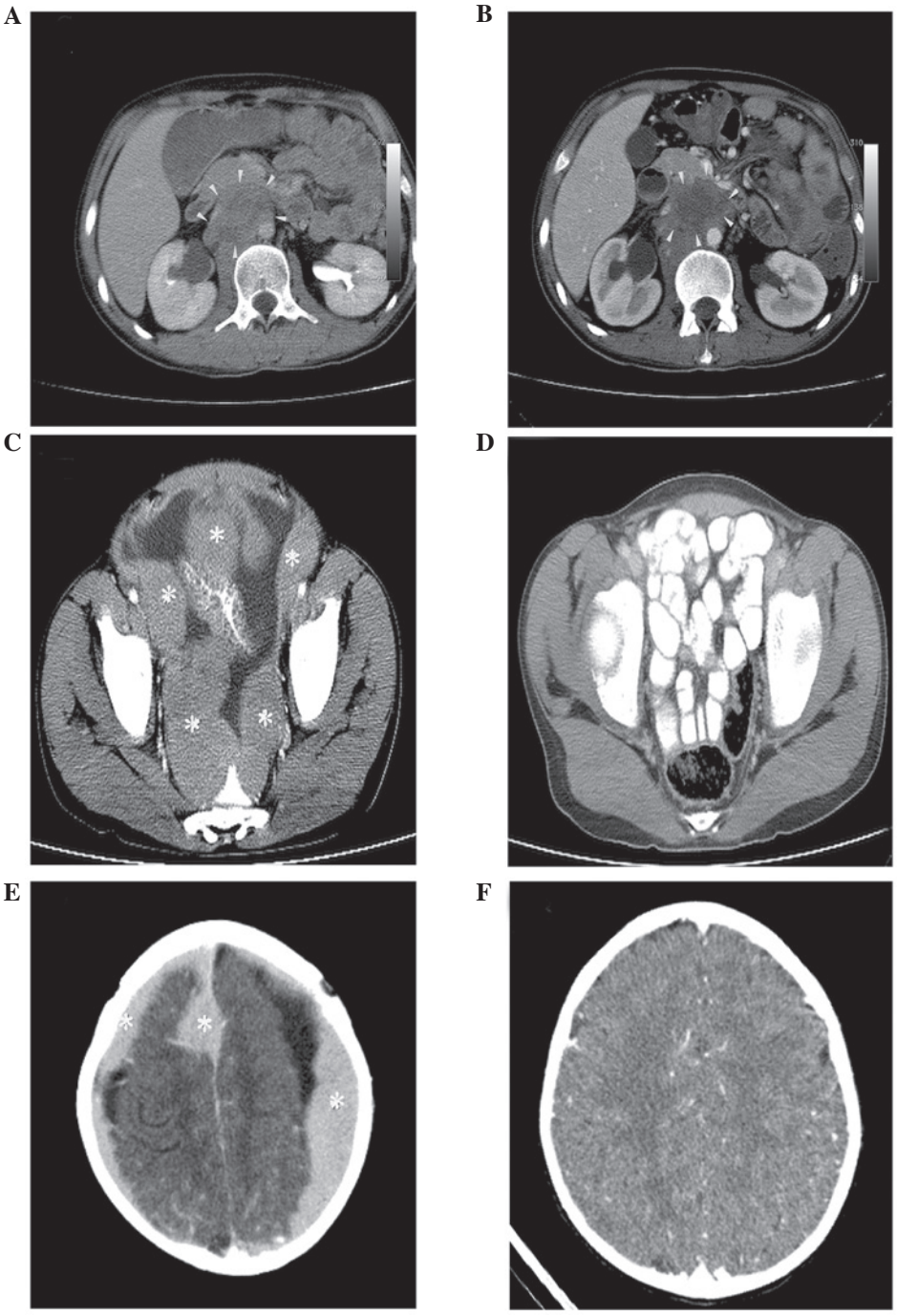

Figure 1. (A) The axial contrast-enhanced computed tomography (CT) scan showed a heterogeneous contrasted solid mass (arrowheads) compatible with conglomerated lymphadenopathies in the abdominal aorta-caval region. (B) Following the completion of chemotherapy, the size of the solid mass decreased and central necrosis developed (arrows). (C) The homogeneous contrast-enhancing solid masses (asterisks) compatible with conglomerated lymphadenopathies located adjacent to the iliac vessels and at the mesenteric fatty tissue were homogeneously shown by the axial contrast-enhanced CT scan. (D) The masses were not evident following treatment at the same level of the CT scan. (E) The homogeneously enhanced mass (asterisks) involving whole dura mater was evident on the axial contrast-enhanced CT scan. (F) Following treatment, no solid mass was observed at the same level of CT scan.

the patient complained of chest pain and a 4x3 cm solid mass on the right 4th rib was detected in the thorax CT scan. Fine-needle aspiration confirmed B-cell lymphoma. ICE and intravenous rituximab (375 mg/m^2/dose/once every 3 weeks) for 6 weeks were given and remission was achieved again. After 2 years of follow-up, the patient is still in complete remission.

Patient 3. A previously healthy 4.5-year-old girl was admitted with a 1-month history of headache and seizures. Her physical examination was normal. BM examination, routine blood chemistry and hematologic parameters had no abnormality. The CT revealed multiple homogeneously enhancing dural mass lesions (Fig. 1E). There was no evidence of lymphoma in any other anatomic location. After partial excision, immunohistochemistry revealed highly expressed HLA-DR, CD19, CD20, CD38 and CD79a. B-NHL was diagnosed. The patient was administered intensive chemotherapy with NHL-BFM 95 chemotherapy protocol. However, at the fourth month of

treatment, right maxillary swelling was identified. The mass, 4x3x5 cm, was evident on maxillofacial MRI scan. Diffuse L3 type lymphoblasts were observed with fine needle aspiration. Two doses of rituximab (375 mg/m^2/dose/once every 3 weeks) were given. The control CT scan revealed that the cranial tumor completely regressed (Fig. 1F). However, the patient's status deteriorated gradually due to sepsis. Consequently acute respiratory distress syndrome and multi-organ failure developed. The patient ultimately succumbed one year after the initiation of chemotherapy of causes unrelated to central nervous system lymphoma (CNSL).

Discussion

Although an improvement in the treatment outcome for children with high-grade B-cell lymphomas has been noted, the prognosis of relapsed or refractory B-cell lymphomas is poor (10). Rituximab has shown good clinical activity in the treatment of CD20-positive B-cell lymphomas. It has also been reported that rituximab provides the opportunity for combining to chemotherapy combinations and increasing the overall and disease-free survival (11-15). Our first case received rituximab in addition to ICE after relapsed B-NHL was diagnosed. One month after completion of the chemotherapy, the tumor size was found to have markedly decreased and there were no blasts in BM. This case supports a potential role of rituximab in children with established relapsed or refractory B-NHL.

The Children's Oncology Group reported that the toxicity of combination with ICE and rituximab was acceptable in children with recurrent or refractory B-NHL (10). Rituximab in combination with ICE was well tolerated and proved to be effective, with no major side effects. The abdominal mass completely recovered with NHL-BFM 95 chemotherapy protocol in the second case. Following rapid detection of a new mass on the patient's right 4th rib, rituximab in combination with ICE was administered and complete remission was achieved. The patient remains in complete remission after 2 years of completing combined therapy. Taken together, for patients who do not achieve complete remission or relapse following reinduction chemotherapy, rituximab combined with intensive chemotherapy could provide a beneficial role in the treatment of B-NHL. Although the number of patients in this study was limited, the follow-up of a larger group of patients could aid in determining the benefits of rituximab in children with B-NHL.

Large-group studies have reported that <1% of PCNSLs, either B- or T-cell, occur in patients under 18 years of age (4,11,16,17). Due to the insufficient number of prospective studies, it is not easy to determine the best therapeutic option for this rare tumor (18). Rituximab was found to be effective in adults with secondary CNSLs (19). When no remission was achieved, the cranial tumor almost completely recovered with rituximab in our case. Although we obtained a remission in only one patient, better understanding of rituximab in pediatric PCNSLs should be emphasized with large-scale studies. PCNSLs tended to occur more frequently in immunodeficient children (17,18). Our case was not immunosuppressive. Therefore, the proper time to apply rituximab is while being unresponsive to current pediatric protocols in relapsed/refractory B-NHL.

This case series has demonstrated that early treatment with rituximab alone or combined with intensive chemotherapy could play a significant role in improving the outcome of relapsed B-cell lymphomas in the pediatric age group. Nevertheless, the identification of clinical efficacy and safety of rituximab as a monotheraphy or combination chemotherapy should be investigated in a large pediatric series.

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