Patient Report

Rituximab-combination chemotherapy achieves a tenth cycle of remission for Burkitt's lymphoma

Running head: Rituximab-combination chemotherapy for Burkitt's lymphoma

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Abstract

A 14-year-old girl with multiple intra-abdominal tumors was diagnosed with stage III Burkitt's lymphoma. She achieved complete remission after multi-drug chemotherapy; however, she relapsed after six courses. Autologous peripheral blood stem cells (PBSC) or allogeneic PBSC harvested from an HLA-identical sibling were insufficient, and her family did not agree to bone marrow collection from the sibling. Although the patient exacerbated nine times (the relapses involved intra-abdominal organs or bone) during the following 4 years and 7 months, treatment with rituximab monotherapy or in combination with ifosphamide, carboplastin, and etoposide, or local irradiation (33.8 to 40.0 Gy) to treat the bone metastases, proved effective, resulting in complete or partial remission. The patient has been in a tenth cycle of remission lasting 1 year and 6 months and did not require transplantation. Thus, a chemotherapy regimen including rituximab might be effective for Burkitt's lymphoma in patients experiencing multiple relapses.

Key words: Burkitt's lymphoma, chemotherapy, relapse, rituximab

Introduction

The advent of intensive multi-drug chemotherapy has led to very high survival rates for pediatric patients with Burkitt's lymphoma[1, 2]. However, the prognosis for relapsed or refractory patients remains poor; the event-free survival of patients undergoing autologous or allogeneic transplantation is less than 30%, and few patients that do not undergo transplantation survive long-term[3]. Recent reports show the efficacy of rituximab-combination chemotherapy as a first-line or salvage therapy for various types of CD20-positive non-Hodgkin's lymphoma, including Burkitt's lymphoma[4-7]. Here, we report a pediatric case of Burkitt's lymphoma for whom rituximab-combination chemotherapy was effective after each exacerbation. The patient is currently in a tenth cycle of remission lasting 1 year and 6 months and has not required transplantation.

Case Report

A 14-year-old girl was admitted to our hospital complaining of worsening abdominal pain, abdominal distension, and dyspnea. Laboratory examination showed marked elevation of LDH (4078 IU/L), uric acid (20.0 mg/dL), and soluble IL-2R (2140 IU/mL). An EBV antibody test suggested previous infection and an HIV antibody test was negative. Abdominal computed tomography (CT) revealed large ovarian tumors and multiple intra-abdominal disseminations with massive ascites (Figure, panel A). Histological examination of the intra-abdominal tumors revealed monotonous infiltration by large lymphoid cells with a high N/C ratio; these cells were positive for CD10, CD20, Bcl-6, and MUM1 (Figure, panel D and data not shown). The MIB-1 labeling index was almost 100% and EBER was negative. Examination of a bone marrow aspirate and a cerebrospinal fluid sample revealed no metastatic disease. Detection of the IgH/c-Myc rearrangement by fluorescence *in situ* hybridization (FISH) led to a diagnosis of group III Burkitt's lymphoma. The patient was then treated with six courses of multi-drug chemotherapy according to the Japanese Pediatric Leukemia/Lymphoma Study Group B-NHL03 Study protocol[2]. All measurable intra-abdominal lesions disappeared after two treatment courses.

During the 4 years and 7 months after the initial chemotherapy protocol the patient experienced nine exacerbations (involving the intra-abdominal organs or bones), which were

confirmed by adnominal MRI or ^{18}F-fluorodeoxyglucose positron emission tomography-CT scans (Figure, panels B and C and Table 1). Histological and/or FISH analysis of biopsy samples confirmed the first, second, and seventh exacerbations (Figure, panels E and F)[8]. After the first exacerbation (involving the ileocecum and left femur), the patient was treated with seven courses of ICE (ifosphamide, 2500 mg/day for 3 days; carboplatin, 450 mg/day for 1 day; and etoposide, 150 mg/day for 3 days), ICE combined with rituximab (375 mg/m^2; R-ICE)[4], or rituximab monotherapy, all of which resulted in partial remission (PR). Insufficient autologous peripheral blood stem cells (PBSC) were harvested after the third round of ICE therapy. Unfortunately, insufficient allogeneic PBSC were harvested from an HLA-identical sibling and her family would not agree to bone marrow collection from the sibling. Therefore, each exacerbation was treated with rituximab (either alone or as part of the R-ICE regimen), combined with local irradiation (33.8–40.0 Gy) to treat the bone metastases. This treatment was effective and resulted in either complete remission (CR) or PR. During treatment with rituximab and/or combination chemotherapy, any severe adverse effects were not observed. To date, the patient is alive and in her tenth cycle of remission, which has lasted for 1 year and 6 months. No transplantation has been performed.

Discussion

Due to a very high proliferation rate, patients with Burkitt's lymphoma often develop chemotherapy-resistant clones. Therefore, the event-free survival of patients with relapsed Burkitt's lymphoma ranges from 10–20%, despite the availability of several conventional salvage chemotherapy regimens, no patients survive long-term without an autologous or allogeneic transplantation[3]. Previous studies that used rituximab alone or in combination with chemotherapy to treat relapsed or refractory Burkitt's lymphoma showed a CR + PR of 57–100%[4-7]; a few cases are alive and in remission without transplantation (Table 2)[6, 7]. Interestingly, when the current received R-ICE therapy after each relapse, she achieved either CR or PR, suggesting that this regimen might be effective even for Burkitt's lymphoma patients that have experienced multiple exacerbations. Of concern is the increasing risk of etoposide-related secondary malignancy, and it will be required to develop other rituximab-containing chemotherapy. Furthermore, the addition of 30 Gy local irradiation seems to be effective for controlling bone metastasis, as previously reported[9].

Relapse of rapidly proliferating Burkitt's lymphoma usually occurs within 1 year of the initial diagnosis, whereas a clonally distinct tumor would develop secondarily as a late recurrence[10]. The current patient experienced several early exacerbations within a short period of time; however, the length of the remissions increased after the fifth exacerbation (Table 1).

Analysis of immunoglobulin heavy chain rearrangements identified the same rearrangement in tumor samples taken at the time of the initial diagnosis, first exacerbation, and seventh exacerbation, suggesting the same lymphoma clone contributed to all exacerbations (data not shown). Genome wide analysis of a large series of cases with a similar clinical course would provide new insights into the pathogenesis of Burkitt's lymhoma.

References

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Figure legends

Figure (A–C) Radiographic findings. Abdominal computed tomography (CT) at the time of disease onset revealed huge ovarian tumors and multiple intra-abdominal disseminations with massive ascites **(A)**. ^{18}F-fluorodeoxyglucose positron emission tomography-CT performed at the time of the second and seventh exacerbations showed abnormal uptake in the right scapula **(B)** and pancreatic body **(C)**, respectively. Tumors are indicated by arrows. **(D)** Hematoxylin and eosin staining of a biopsy sample taken at the time of disease onset. **(E)** Immunostaining of a biopsy sample taken after the second exacerbation for CD20. Scale bars = 50 μm in D and E. **(F)** Fluorescence *in situ* hybridization analysis for IgH and c-MYC in a biopsy sample taken after the seventh exacerbation. Arrows show fusion signals.

Figure

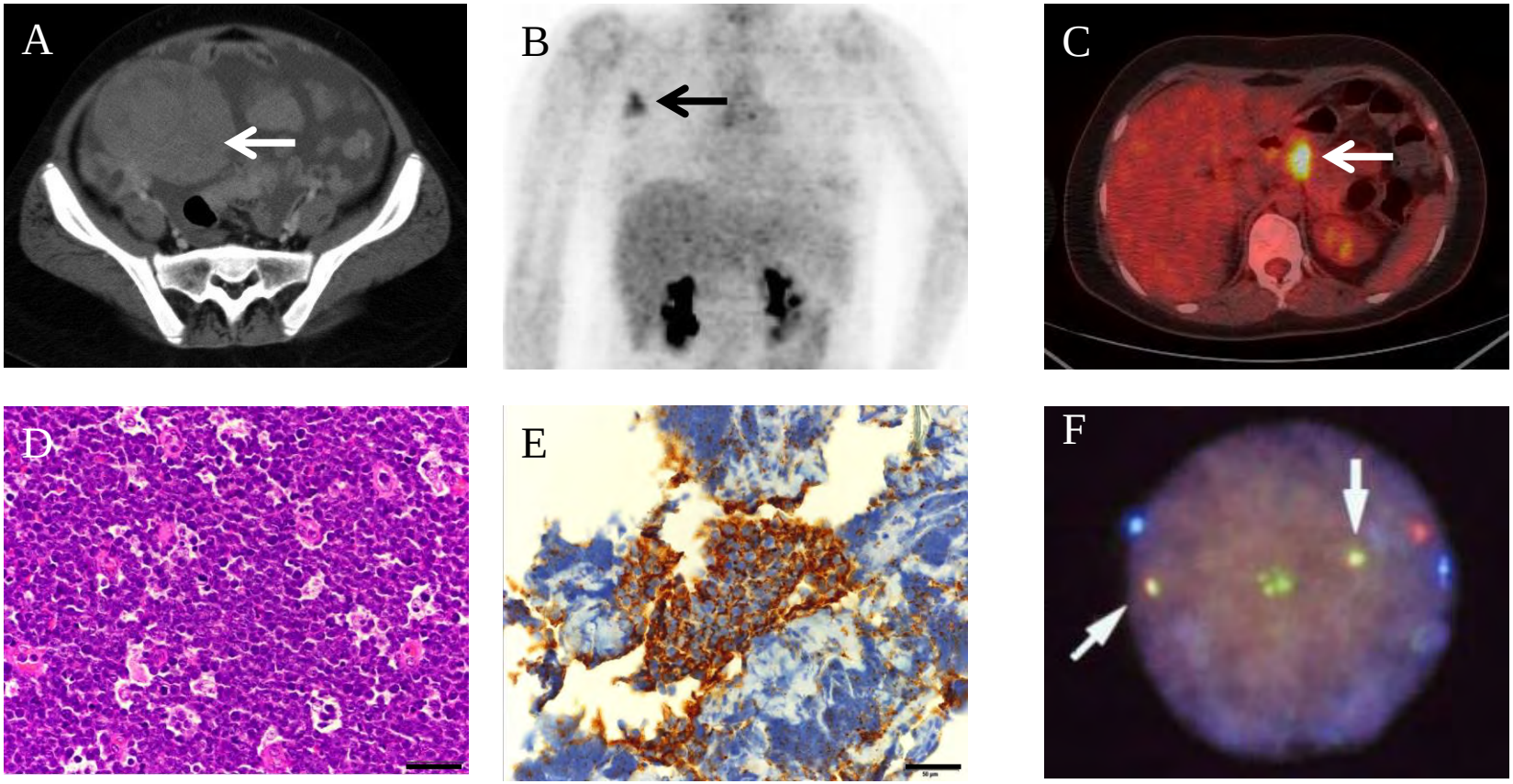

Table 1 Clinical course of the patient

Disease status	Time from disease onset	Duration from the last treatment	Site of exacerbation	Chemotherapy	Radiation therapy	Best response
1st ECB	6 months	1 month	Ileocecum, left femur	R-ICE×1, ICE×3, R×3	No	PR
2nd ECB	1 year	2 months	Right scapula	R×8	No	PR
3rd ECB	1 year 4 months	1 month	Right scapula	R×3	40Gy/20fr	CR
4th ECB	1 year 8 months	1 month	Right ilium	R×1	40Gy/20fr	PR
5th ECB	1 year 10 months	1 month	Bilateral femur	R-ICE×3, R×2	No	CR
6th ECB	2 year 8 months	4 months	Sacrum	No	33.8Gy/13fr	CR
7th ECB	3 year 7 months	7 months	Pancreas body	R-ICE×3, R×2	No	CR
8th ECB	4 year 3 months	2 months	Left iliopsoas muscle	R-ICE×3	No	CR
9th ECB	5 year 1 month	6 months	Left iliopsoas muscle	R-ICE×3	No	CR

ECB, exacerbation; R, rituximab; ICE, ifosfamide+carboplatin+etoposide; PR, partial remission; CR, complete remission.

Table 2 Clinical information for pediatric patients with refractory/relapsed Burkitt's lymphoma and B-ALL treated with rituximab

Patient No.	Gender/ age	Stage at disease onset	Rituximab therapy	Best response	SCT	Outcome	Ref.
1	M/4	IV	R	CR	Allo	Died in CCR (cGVHD)	5
2	M/6	III	R	PD	No	DOD	5
3	M/3	IV	R	SD	Auto	CCR (48 months)	5
4	F/4	III	R	CR	No	CCR (126 months)	6
5	M/5	III	R	CR	No	CCR (12 months)	6
6	M/16	III	R	CR	No	CCR (30 months)	6
7	F/9	IV	R + TIT	CR	Allo	DOD	5
8	F/4	III	R + NHL BFM 90	CR	No	CCR (24 months)	5
9	M/12	IV	R + NHL BFM 95	CR	Auto	CCR (12 months)	5
10	F/9	IV	R + ICE	PD	No	DOD	4
11	M/5	IV	R + ICE	SD	No	DOD	4
12	F/16	III	R + ICE	PR	No	DOD	4
13	M/5	IV	R + ICE	CR	Auto	CCR (30 months)	4
14	M/14	IV	R + ICE	PR	No	DOD	4
15	M/15	III	R + ICE	PR	Auto	CCR (26 months)	4
16	M/11	III	R + ICE	PD	No	DOD	4
17	M/10	III	R + ICE	PD	No	DOD	4
18	M/20	III	R + ICE	CR	No	AWD (14 months)	4
19	M/9	III	R + ICE	PD	No	DOD	4
20	F/13	IV	R + ICE	CR	Auto	CCR (18 months)	4
21	M/16	IV	R + ICE	CR	Allo	CCR (20 months)	4
22	M/5	IV	R + ICE	PR	No	DOD	4
23	M/14	IV	R + ICE	PR	No	DOD	4
Our case	F/14	III	R + ICE	CR	No	CCR (18 months)	

R, rituximab; TIT, triple intrathecal therapy; BFM, Berlin-Frankfurt-Munster; ICE, ifosfamide+carboplatin+etoposide; PD, progressive disease; SD, stable disease; PR, partial remission; CR, complete remission; Auto, autologous transplantation; Allo, allegeneic transplantation; cGVHD, chronic graft-versus-host disease; CCR, continuous complete remission; DOD, died of disease; AWD, alive with disease.

Patient No.	Gender/age	Stage at the onset	Rituximab therapy	Best response	SCT	Outcome	Ref.
1	M/4	IV	R	CR	Allo	Died in CCR (cGVHD)	1
2	M/6	III	R	PD	No	DOD	1
3	M/3	IV	R	SD	Auto	CCR (48 months)	1
4	F/4	III	R	CR	No	CCR (126 months)	2
5	M/5	III	R	CR	No	CCR (12 months)	2
6	M/16	III	R	CR	No	CCR (30 months)	2
7	F/9	IV	R + TIT	CR	Allo	DOD	1
8	F/4	III	R + NHL BFM 90	CR	No	CCR (24 months)	1
9	M/12	IV	R + NHL BFM 95	CR	Auto	CCR (12 months)	1
10	F/9	IV	R + ICE	PD	No	DOD	3
11	M/5	IV	R + ICE	SD	No	DOD	3
12	F/16	III	R + ICE	PR	No	DOD	3
13	M/5	IV	R + ICE	CR	Auto	CCR (30 months)	3
14	M/14	IV	R + ICE	PR	No	DOD	3
15	M/15	III	R + ICE	PR	Auto	CCR (26 months)	3
16	M/11	III	R + ICE	PD	No	DOD	3
17	M/10	III	R + ICE	PD	No	DOD	3
18	M/20	III	R + ICE	CR	No	AWD (14 months)	3
19	M/9	III	R + ICE	PD	No	DOD	3
20	F/13	IV	R + ICE	CR	Auto	CCR (18 months)	3
21	M/16	IV	R + ICE	CR	Allo	CCR (20 months)	3
22	M/5	IV	R + ICE	PR	No	DOD	3
23	M/14	IV	R + ICE	PR	No	DOD	3
Our case	F/14	III	R + ICE	CR	No	CCR (?? months)	