Case report

Early relapse of Burkitt lymphoma heralded by a bone marrow necrosis and numb chin syndrome successfully treated with allogeneic stem cell transplantation

Jan Cerny a,*, Katherine Devitt b, Hongbo Yu b, Muthalagu Ramanathan a, Bruce Woda b, Rajneesh Nath a

a Division of Hematology Oncology, Department of Medicine, UMass Memorial Medical Center, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA
b Department of Pathology, UMass Memorial Medical Center, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA

ARTICLE INFO
Article history:
Received 19 April 2014
Received in revised form
26 May 2014
Accepted 3 June 2014
Available online 4 July 2014

Keywords:
Burkitt lymphoma
Salvage
Allogeneic
Bone marrow necrosis
Numb chin syndrome

ABSTRACT

The optimal salvage therapy for patients with relapsed Burkitt lymphoma is unknown. Bone marrow necrosis is an underreported (< 1% of bone marrow failures). Numb chin syndrome is another rare syndrome associated with aggressive malignancies. Survival of these syndromes is dictated by the underlying disease and is usually dismal. Our 35-year-old patient experienced an early relapse of Burkitt lymphoma accompanied by syndromes, achieved second complete remission and underwent allogeneic stem cell transplantation. He remains alive and well > 2 years after the transplant. To our knowledge, this is the longest reported survival of the two syndromes in the setting of BL relapse.

1. Case report

We present a case of a man who initially presented at age of 34 with complaints of cough, malaise, fever and bone pain, thrombocytopenia 35 × 10^9/μL, anemia (hematocrit 23.9%) and leukocytosis 13.7 × 10^9/μL with 16% bands, but no other immature cells. Given his outdoor lifestyle and exposures an extensive infectious disease work up was performed including Lyme disease, Rocky Mountain Spotted Fever, anaplasmosis, babesiosis was negative. With worsening clinical status and LDH of 2730 IU/L the patient had a bone marrow (BM) biopsy performed. The bone marrow was inappraisable, however core biopsy revealed 100% cellularity and blastocytic cells with high nuclear to cytoplasmic ratio, prominent nucleoli, basophile cytoplasm and cytoplasmic vacuoles (see Fig. 1A and B). Interphase fluorescence in situ hybridization (FISH) revealed 72/100 nuclei carried an IGH@-CMYC rearrangement further confirming a high-grade Burkitt lymphoma (BL), no rearrangements were seen using BCL6 and BCL2 probes. Polymerase chain reaction showed IGH monoclonal band. At the same time CT scan showed a 4.2 × 4.9 cm² mass arising from the medial wall of the cecum, involving terminal ileum, an adjacent 5.0 × 3.7 cm² lymphnode mass was seen in the mesentery with extensive soft tissue nodularities in the omentum. His cerebrospinal fluid showed normal protein and glucose, negative cytology (2 specimens × 2–3 mL) and flow (sensitivity 10^-4).

The patient began CODOX-M/IVAC with rituximab [2]. PET and BM after 2 cycles showed complete remission (CR) and this was confirmed 3 and 6 months later after he completed the full treatment course. There was no delay in administration of each cycle (average: 19 days, 16–21). Eight months after therapy completion he developed flu-like symptoms, WBC 9.1 × 10^9/μL, mild anemia and thrombocytopenia 23 × 10^5/μL, uric acid 4.7, LDH 1977 IU/L. CT scans were negative and BM showed relapse (see Fig. 1C and D). The patient complained of submental numbness, CSF sampling was negative × 3 by cytology and flow (2–3 mL each), MRI of the brain with focus on cranial nerves was negative for leptomeningeal involvement, his condition was concluded as numb chin syndrome (NCS). He received EPOCH-R with IT methotrexate 15 mg (on day 1) and IT cytarabine 100 mg (at least 72 h after MTX) [3]. After the first cycle the patient’s marrow showed 80% cellularity and a large area of necrotic tumor cells occupying 60–70% of the total marrow space consistent with bone marrow necrosis (BMN), the remaining 30–40% of marrow comprised of viable tumor cells, which were intermediate in cell size with round nuclei, indistinct nucleoli and scant amount of cytoplasm (see...
Fig. 1E and F). CD20 was strongly positive in both viable and necrotic tumor cells. Subsequent cycles were initiated at the first sign of hematological recovery (plts > 75,000/μL, ANC > 500/μL). Second CR was confirmed after second cycle (PET and BM). Aggressive prophylaxis with antibiotics, antifungals, antivirals, and against pneumocystis together with G-CSF were used. Fourth cycle was delayed by an episode of respiratory infection with parainfluenza 3, which was treated with IVIG (dose 500 mg/kg). After 6 cycles (average 16.6 days, 15–20) the patient underwent 10/10 HLA matched unrelated donor transplant (CMV: R+/D–) with
thiopeta/fludarabine/melphalan, posttransplant cyclophosphamide and sirolimus [4], which was tapered rapidly within 4 months. He remained asymptomatic and GVHD free at one year after his transplant: WBC 6.7 × 10^9/L, HCT 37.9%, and platelets 260 × 10^9/L. BM from the site where necrosis was present at relapse showed 40% cellular marrow with maturing adequate trilineage hematopoiesis and 40% of the biopsy contained a necrotic area with many ghost outlines of intermediate-sized cells, which were positive for CD20, but negative for other markers (see Fig. 1G and H). The patient’s counts and chimerism ( > 97% donor BM and blood) were stable. For profound hypogammaglobulinemia and frequent respiratory infections he has received monthly IVIG. He is currently alive and well 2 years after his transplant. To our knowledge, this is the longest reported survival of BMN in setting of BL relapse.

2. Discussion

The optimal salvage strategy for BL patients with a partial remission or relapsed disease, is unknown. Combination salvage chemotherapy is usually attempted, but few to no patients with BL achieve a meaningful response regardless of the chemotherapy agents used [1]. Autologous or allogeneic stem cell transplantation (ASCT or AlloSCT) represents a logical next step in consolidation of response; however, published data addressing high-dose therapy in BL are confounded by selection bias and the data is limited to subgroups of retrospective analyses [5–7], and case reports [8]. Chemosensitivity and disease status at the time of transplant determine the outcome. While clinical trial participation is warranted, due to time constrains this is very often not practical for patients and their physicians.

Given the presence of BMN an AlloSCT was chosen for our patient. BMN is a rare and poorly understood complication of aggressive hematological malignancies with dismal survival ranging from 1 to 4 months. Retrospective data associated upto 15% of BMNs with lymphoma [10]. Different sites were used for BM biopsies and we cannot confirm whether BMN was present before salvage therapy. We however confirmed that BMN was persistent at least one year posttransplant proving the point that bone marrow can undergo remodeling, but is a prolonged process [9]. PET scan and MRI were not helpful in identifying the extent of the BMN. Associations with bone marrow fibrosis were seen, but historically these were limited to patients with underlying myeloproliferative neoplasms [9,10]. We did not see any increase reticulin. The finding of persistent BMN represents a therapeutic dilemma. Successful use of rituximab has been previously reported for PTLD related BMN [11]. Rituximab was discussed with the patient, but not used as he remains clinically stable with normal counts and he requires IVIG replacement for frequent respiratory infections.

NCS is a rare syndrome. In case series of NCS 14–47% were associated with of lymphoproliferative disorders [reviewed in [12]]. Survival is usually dictated by the underlying disease and short in the setting of aggressive malignancies. Since NCS may be a manifestation of an underlying malignancy it has to be taken seriously. Though imaging and CSF studies were negative in our patient the specimens collected were not high volume and we treated the patient with prophylactic IT methotrexate and cytarabine. Residual NCS is still present > 2 years since initial presentation. We did not identify the actual etiology, but differential diagnosis includes impingement with lymphoma, BMN, previous exposure to chemotherapy with higher frequency among highly proliferating neoplasms [12].

Conflict of interest

None.

References

[1] Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. Blood 2004; 104:3009–20.
[2] Barnes JA, LaCasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt’s lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859–64.
[3] Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt’s lymphoma. N Engl J Med 2013;369:1915–25.
[4] Nath R, Cerny J, Ramanathan M, et al. High Dose Cyclophosphamide (HDCy) post Stem Cell Transplant (SCT) following High Dose Melphalan (HDMel) based conditioning as a dual strategy for chemotherapy dose intensity and Graft Versus Host Disease (gvhd) prophylaxis in matched and mismatched allogeneic (allo) SCT. Blood 2013;122:4554.
[5] Sweetenham JW, Pearce R, Taghipour G, Blaise D, Gisselbrecht C, Goldstone AH. Adult Burkitt’s and Burkitt-like non-Hodgkin’s lymphoma—outcome for patients treated with high-dose therapy and autologous stem-cell transplantation in first remission or at relapse: results from the European Group for Blood and Marrow Transplantation. J Clin Oncol. 1996;14(9):2465–72.
[6] Peniket A, Ruiz de Elvira M, Taghipour C, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplant 2003;31:667–78.
[7] Maramattom LV, Hari PN, Burns LJ, Carreras J, Arcese W, Cairo MS, et al. Autologous and allogeneic transplantation for Burkitt lymphoma outcomes and changes in utilization: a report from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant 2013;19 (2):173–9.
[8] Ungkanont A, Mongkonsrirakoon W, Jotar S, Srichaikul T. Allogeneic stem cell transplantation in a patient with refractory Burkitt’s lymphoma using non-myeloablative conditioning regimen. Bone Marrow Transplant 2000;26:1351–4.
[9] Paydas S, Ergin M, Baslamisi F, et al. Bone marrow necrosis: clinicopathologic analysis of 20 cases and review of the literature. Am J Hematol 2002;70:300–5.
[10] Janssens AM, Offner FC, Van Hove WZ. Bone marrow necrosis. Cancer 2000;88:1769–80.
[11] Rossi D, Ramponi A, Franceschetti S, et al. Bone marrow necrosis complicating post-transplant lymphoproliferative disorder: resolution with rituximab. Leuk Res 2008;32:829–34.
[12] Evans R, Kirby S, Purdy RA. Numb chin syndrome. Headache: J Head Face Pain 2008;48(10):1526–4610.