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Case Report Open Access

Complete Remission of Progressive SLE after High-dose Chemotherapy and Autologous Hematopoietic Cell Transplantation for Relapsed Non-seminomatous Germ Cell Tumor

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Abstract

Objective: High dose chemotherapy and hematopoietic stem cell support remains a curative and accepted treatment option for relapsed or non-responsive germ cell tumors, and has been applied experimentally to control severe life-threatening autoimmune diseases.

Case Report: In the present study, we report on a patient with systemic lupus erythematosous nephritis, not controllable with monthly cyclophosphamide pulses followed by immunosuppressive treatment with mycophenolate mofetil, developing a non-seminomatous germ cell tumor that had relapsed after standard chemotherapy and surgery. The patient received salvage chemotherapy with paclitaxel-ifosfamide-cisplatin (TIP) with G-CSF support for three cycles and hematopoietic stem cells were mobilized and harvested with leukapheresis after the first TIP cycle. This was followed by high-dose chemotherapy with carboplatin-etoposide-cyclophosphamide supported by autologous hematopoietic cell transplantation, based on its indication for the relapsed germ-cell tumor, leading to a complete remission of both the neoplastic and autoimmune disease that is sustained for more than 4 years after high-dose chemotherapy.

Conclusion: Prolonged control of his relapsed germ cell tumor and systemic lupus erythematosous was attained with high dose chemotherapy and hematopoietic stem cell support. An extensive literature review is provided besides a detailed discussion of the above case.

Keywords: Germ cell tumor; High dose chemotherapy; Hematopoietic cell transplantation; Systemic lupus erythematosous

Introduction

Over the last 30 years, the outcome of patients with advanced germ cell tumors (GCTs) has been favorable compared to that of other solid tumors, with more than 70-80% of patients experiencing long term disease free survival (DFS) [1]. However, patients experiencing an incomplete response (IR) or relapse after previous CR after first-line therapy, in general, have a dismal prognosis. Treatment programs exploring high-dose chemotherapy (HDC) and hematopoietic stem cell (HSC) support, either in the form of autologous bone marrow transplantation (ABMT) or HSCs derived from peripheral blood after appropriate mobilization, have been developed since the 1980s in an attempt to circumvent drug resistance, considered as the ultimate cause of treatment failure in GCTs [2].

In recent years, there has been increasing interest in treating severe and organ damaging autoimmune diseases, such as progressive systemic sclerosis (PSS), multiple sclerosis (MS), or systemic lupus erythematosous (SLE), with lympho- or myelo-ablative chemotherapy and either allogeneic, syngeneic or more commonly autologous HSCT. Successful recovery of immune system to a pre-autoimmune state with ablation of autoimmune cell clones and resultant prolonged control of disease activity has been observed [3].

Herein we report on a unique patient with active SLE glomerulonephritis and relapsed non-seminomatous GCT (NSGCT) treated with salvage chemotherapy, HSC collection, followed by myeloablative HDC and HSCT that, eventually led to prolonged ongoing control of both his autoimmune and malignant disease.

Case Report

A 22-year old man with a recent history of SLE was initially evaluated at "Laiko" General Hospital. His disease was expressed as arthritis, pericarditis and diffuse, segmental proliferative and sclerosing lupus nephritis class IV (A/C) according to ISN/RPS 2004 [4]. He was positive for antinuclear antibodies (ANA) at a titre of 1:1250 with a fine speckled pattern, positive for anti-dsDNA [135 binding units (bu); cut off 7 bu) and anti-phospholipid antibodies. His 24-hour urine protein was 1.6 g and his urinalysis was positive for red blood cell casts and red blood cells of glomerular origin. He was subjected to 6 cycles of monthly pulses of cyclophosphamide (CTX): 1 $g \cdot m^{-2}$, between November 2008 and February 2009 and then mycophenolate mofetil (MMF; Cellcept), 2 g po daily. Despite intensive immunosuppression the disease remained active with anti-

dsDNA levels raising to 230 bu, reduced C3 and C4 levels (61 and 10 mg·dL-1, respectively), while 24h urine protein raised to 3.0 g. However, arthritis and pericarditis resolved after CTX. While on immunosuppression, he noticed a left testicular mass and a left inguinal orchidectomy was performed in April 2009. A histological diagnosis of a NSGCT with elements of embryonal carcinoma and no teratoma component was made. Staging revealed large para-aortic lymph nodes 6.5 × 5.5 cm and β-hCG=115 mIU/mL, AFP=3.3 ng/ml, and LDH=nl (<250IU laboratory upper limit). At that time, he received 6 cycles of bleomycin-etoposide-carboplatin (BEC) until normalization of his serum β-hCG, between May and August 2009; with a radiological (by CT scan) partial response (PR) and β-hCG normalization after the second cycle of BEC. Carboplatin was chosen instead of cisplatin by his treating oncologists due to the history of glomerulonephritis and potential renal function impairment over time. A CT scan of the abdomen revealed residual retroperitoneal lymph node masses (3.0 × 2.5 cm) and the patient was subjected to an exploratory laparotomy and retroperitoneal lymph node dissection in September 2009 (Figure 1). Histology revealed residual elements of metastatic embryonal carcinoma with extensive areas of necrosis. One month later, a new CT scan of the abdomen demonstrated a new nodular pulmonary lesion of approximately 1cm diameter located at the right lower lobe, a hypodense mass at the aortic bifurcation, sized 2.3 × 3.5 cm, and a raising β-hCG=25 mIU/ml. He was then referred to "Metaxa" Cancer Hospital and received salvage chemotherapy with the combination of TIP; paclitaxel 200 mg/m^2 on d1, ifosfamide 2 g/m^2/d-d1-3, cisplatin 33mg/m^2/d-d1-3 supported by granulocyte-colony stimulating factor (G-CSF) for three cycles, from November 2009 until January 2010. Following the first cycle of TIP+G-CSF, a successful collection of 8.5 × 10^6 CD34/kg of body weight (BW) HSCs through large volume leukapheresis was performed, which were cryopreserved and stored in liquid nitrogen. After 3 cycles of TIP, a complete resolution of his radiological abnormalities (by CT scan) and β-hCG normalization were achieved, thus leading to a CR. At the end of January 2010, the patient subsequently underwent HDC with CarbopEC; CTX 1.5 g/m^2/d, etoposide 400 mg/m^2/d, and carboplatin at an area under the concentration x time curve (AUC) = 6/d, all administered from day (-6) to day (-3). On day 0, 4.25 × 10^6 CD34/kg of BW HSCs were infused and G-CSF 480IU/day was started on day +1. Palifermin [Kepivance®; human recombinant keratinocyte growth factor (KGF)] was administered i.v. at 60 μg/kg/d × 3 days up to 24hrs before the initiation of HDC and re-started at the same dose and schedule on day +1 for the prevention of mucositis. The patient developed grade 4 neutropenia that resolved with an ANC>500/μl on day +10, grade 4 thrombocytopenia that recovered with an untransfused PLT>20000/μl on day +30, grade 2 mucositis, and grade 3 late onset hemorrhagic cystitis (after day +15). During his hospitalization he received irradiated blood products (packed red blood cells, single-donor platelet units, and fresh-frozen plasma), broad-spectrum antibiotics for febrile episodes, antifungals and γ-globulin. On day +32, new CT scans demonstrated CR. Regarding his SLE autoantibody detection revealed: ANA positive at a titer of 1:160 with a fine speckled pattern (Hep-2 cells as substrate), anti-dsDNA negative, antibodies to extractable nuclear antigens negative, while the complement levels raised to normal and were: C3=126 mg·dL^{-1}, C4=27 mg·dL^{-1}. The patient was discharged and followed-up regularly. Prophylaxis for *P.Carinii* pneumonia and herpes simplex virus with co-trimoxazole and acyclovir, respectively, was provided for 3 months after HSCT. So far the patient is in remission of both SLE and GCT 50 months after HSCT, off any immunosuppressive treatment.

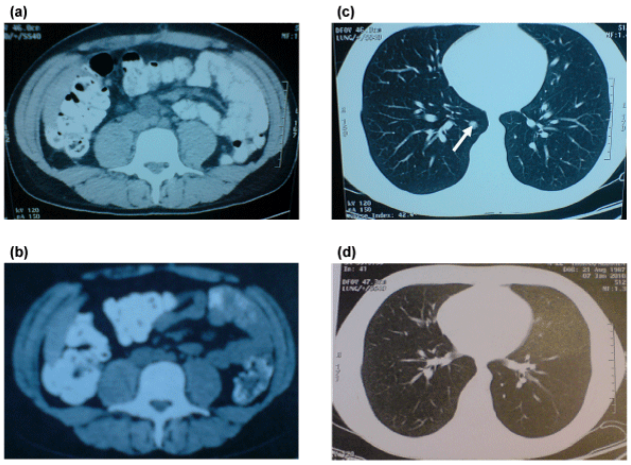

Figure 1: CT scans of patient with relapsed GCT post-retroperitoneal lymph node dissection of active residual carcinoma before [(a), (c)] and after 3 cycles of TIP salvage chemotherapy and before HDC and autologous HSCT [(b), (d)]; CT scan of the abdomen indicating (a) enlarged paraortic hypodense nodule, (b) regression of paraortic mass, and chest CT scan indicating (c) pulmonary nodule in right lower lobe, (d) complete resolution of pulmonary nodule.

Discussion

The present report highlights the curative potential of HDC and HSCT in the treatment of relapsed NSGCT having developed in a patient with pre-existing SLE and associated glomerulonephritis that had been treated with steroids, monthly pulses of CTX followed by MMF. A detailed Medline/EMBase/PubMed based search (under the terms: *systemic lupus erythematosous, germ-cell tumor(s), testicular cancer, high-dose chemotherapy*) revealed that this is the first case reported so far. Moreover, control of both relapsed NSGCT and SLE activity was anticipated by salvage chemotherapy with TIP followed by HDC with CarbopEC and HSCT. SLE in men is rare (1:10, male to female ratio) and generally more severe and more often associated with nephritis. It can be said that progressive SLE was not already controlled by conventional dose CTX, steroids and MMF maintenance, however, significant-almost nephrotic range-proteinuria recessed after salvage TIP chemotherapy, and then C3, C4 and anti-dsDNA levels normalized after HDC and HSCT without any further immunosuppressive medications. The TIP regimen contains ifosfamide, a cyclophosphamide analogue, but at the dose of 6.0 g/m^2 most commonly administered in the salvage setting for GCTs corresponds to an equitoxic dose of 1.7-2.0 g/m^2 of CTX, over two-fold higher than the dose administered to treat major organ involvement in SLE. The CarbopEC HDC regimen, commonly applied in GCTs, is both myeloablative and potentially highly immunosuppressive as it incorporates high doses of CTX and etoposide, cytotoxic agents possessing an immune ablative potential at the doses administered.

A number of single institution or cooperative group studies have evaluated the role of autologous HSCT in the treatment of

autoimmune diseases and progressive life-threatening SLE [5,6]. The premise that myeloablative or lymphoablative conditioning could halt or even reverse organ damage in severe autoimmune diseases stems from early experimental animal work [7,8]. Early clinical translational evidence that HSCT could cure autoimmune diseases, substantiating the above pre-clinical observations, came from rare cases of coincidental hematologic malignancies and autoimmune diseases, where allogeneic bone marrow transplantation led in long-term control of both diseases [9,10]. The proposed mechanisms underlying control of autoimmune diseases by autologous HSCT after myeloablative or lymphodepleting chemotherapy have been; (i) profound lymphopenia in the early post-transplant period followed by rapid B-cell, natural killer (NK) cell and $CD8^+$ T-cell reconstitution in the early post transplant period, with $CD4^+$ T-cells, principally responsive for autoimmune memory, recovering late and incompletely [11,12], (ii) immune resetting via repertoire replacement with regeneration of a new "naïve" and more diverse T-cell repertoire emerging from the thymus in these patients after myeloablation and HSCT [11], and (iii) restoration of immune regulation through normalization of $CD4^+CD25^+FoxP3^+$ T-cell subset (regulatory T-Cells; Tregs) mediating attenuation of immune responses and, tolerance has been proposed as an alternative mechanism underlying clinical remission of autoimmune manifestations post-HSCT [13]. A recent clinical translational report corroborating the above hypotheses described the long-term reconstitution of T- and B-cell subsets in 7 patients with SLE after immunoablative high-dose CTX combined with anti-thymocyte globulin (ATG) followed by autologous HSCT with CD34-enriched HSCs, demonstrating that this approach efficiently depletes naive and memory T and B-cells, including autoreactive populations. Moreover, HSCT reactivated the thymus as evidenced by the post-transplant expansion of $CD31^+CD4^+CD45RA^+$ T-cell subset (recent thymic emigrants), leading to the development of a tolerant, "juvenile" adaptive immune system, which was reflected by long-term, treatment-free clinical remissions [14].

A number of studies applied CD34-enrichment by positive selection in order to drastically reduce the numbers of immune cell subsets infused with the hematopoietic graft [14-16], as well as ATG in some studies in order to deplete residual and graft-derived T-cells [16]. However, it remains unknown whether selected HSCs and addition of ATG are superior to unselected HSCT. In other words, it is still debatable whether an almost complete lymphoablation is preferable to autoimmune cell "debulking" induced by current multidrug HDC regimens. The patient in the present report received a standard HDC regimen (CarbopEC), commonly applied in GCTs, rescued by unselected HSCs, as infusion of purified $CD34^+$ HSCs after HDC in malignancies has not resulted in any clinical advantage, and has been associated with more prolonged post-transplant cytopenias.

In the present report, PET scanning was not applied in the evaluation of response either in the initial phase or after salvage therapy (TIPx3→CarbopEC) at relapse. The role of PET scanning is still debatable in guiding treatment decisions after first-line or salvage therapy (including HDC+HSCT) in NSGCTs. PET does not reliably distinguish mature teratoma from benign residual mass, and thus resection of residual masses is required [17]. In one study [17], 3/15 patients developed relapsed GCT after chemotherapy. Initial PET scans were normal in two patients and equivocal in one. Repeat scans done at the time of clear disease relapse confirmed positive serum tumor marker. In another study, PET correctly identified relapse in 2/5 patients who had received high-dose salvage therapy and HSCT [18].

High-dose chemotherapy (HDC) and HSCT has not so far demonstrated any advantage over standard chemotherapy either as consolidation in first-line setting in intermediate/high risk disease [19] or in the salvage setting in first relapse or IR [20]. However, in a recent large single-centre retrospective study examining the effect of 2 cycles of high-dose carboplatin/etoposide, it was anticipated that there should be little or no debate on the use of HDC for patients with GCTs refractory to platinum-based chemotherapy or that is not cured by a cisplatin-ifosfamide salvage regimen, as 45% of patients with progressive metastatic disease, tumors refractory to platinum, and third-line or later therapy experienced prolonged DFS [21]. Moreover, novel approaches that incorporate new active agents in the salvage regimen (TIP) or in the HDC regimen, such as paclitaxel as in the patient under discussion, have yielded very promising results [22,23]. While data from prospective phase III studies are not convincing [24], a recent meta-analysis of trials evaluating HDC *vs* standard salvage chemotherapy indicated that HDC+autologous HSCT confers a statistically significant difference regarding PFS and OS [25] in all prognostic risk categories as defined by the revised Lorch-Beyer score [26]. In this line of evidence and given that TIP represents the most widely accepted salvage regimen, the recently launched international TIGER trial tries to address whether dose-dense Paclitaxel-Ifosfamide (TI) + G-CSF × 2 cycles (every 2 weeks) with intervening HSC collection to support sequentially 3 HDC cycles of timely-spaced Carboplatin-Etoposide is superior to 4 standard cycles of TIP [27].

Conclusion

The patient reported herein achieved a complete response to 3 cycles of TIP salvage followed by consolidation with CarbopEC HDC and HSCT, which led to continuous remission of his NSGCT, as well as control his severe SLE, remaining off any immunosuppressive disease modifying agent. Therefore, the present case illustrates in a clear manner that the indication of HDC and HSCT in a certain patient with relapsed GCT could be useful in the control of both the neoplastic and severe autoimmune disease.

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