Sequential autologous and allogeneic stem cell transplantation for treatment of primary plasma cell leukemia: A case report

WEIJIA FU*, AIJIE HUANG*, YANRONG LUO*, MIAOMIAO LIU, GUSHENG TANG, JIANMIN YANG and XIONG NI

Department of Hematology, Institute of Hematology, Changhai Hospital, Shanghai 200433, P.R. China

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Abstract. Primary plasma cell leukemia (pPCL) is a rare and aggressive form of plasma cell disorder, which accounts for ~70% of all PCL. Survival of pPCL remains poor, and is related with early mortality. There is no standard therapy for patients with pPCL. In the present study, a 26-year-old man who was diagnosed with pPCL was reported. The patient achieved stringent complete remission to the successful treatment of intensive chemotherapy combined with sequential autologous and allogeneic stem cell transplantation (SCT) followed by maintenance therapy with oral administration of ixazomib, thalidomide and dexamethasone (IRD regimen). Development of complex treatment algorithms that combine novel agents, SCT and post-transplantation remission strategies may translate into survival in patients with pPCL.

Introduction

Primary plasma cell leukemia (pPCL) is a rare and aggressive plasma cell disorder (1,2). The prognosis of pPCL is poor. The median overall survival ~12 months based on patients untreated with novel drugs (2). Over the past decade, the use of new agents, such as proteasome inhibitors or immunomodulatory drugs, followed by high-dose melphalan conditioning and autologous stem cell transplantation (ASCT) or allogeneic hematopoietic stem cell transplantation (allo-HSCT), has improved prognosis in younger patients with pPCL. However, the outcome of patients with pPCL has only slightly improved (1,3-12). Due to the low incidence of pPCL, there are no large prospective and randomized trials to support high-level evidence on the timing and role of the SCT, thus making it difficult to evaluate whether ASCT or allo-HSCT is more beneficial for pPCL patients. In the present study, a case of pPCL that was successfully treated with intensive chemotherapy combined with ASCT and sequential allo-HSCT followed by maintenance treatment with ixazomib, thalidomide and dexamethasone (IRD) was reported.

Case report

A 26-year-old man who suffered repeated nosebleeds was admitted to the Changhai Hospital on April, 2020. A complete blood count revealed a white blood cell count of $53.5x10^9$/l (with 14% blasts), hemoglobin level of 68 g/l and platelets count of $22x10^9$/l. The serum immunoglobulin G (IgG) level was 41.5 g/l and an IgG-kappa type-M component was identified by serum immunofixation. The serum free light chain kappa/lambda ratio was 193.202. Peripheral blood smear and bone marrow aspiration revealed 62 and 74% plasmacytes, respectively (Fig. 1A and B). Immunophenotypic analysis using multiparameter flow cytometry revealed a cluster of 60.445% neoplastic plasma cells that were positive for CD38, CD138, CD56 and cKappa, and negative for cLambda, CD19, and CD20. The antibodies were purchased from BD Biosciences. A total of 1 ml freshly isolated whole BM aspirate was collected, of which 400 μl was used to lyse erythrocytes using RBC lysis buffer (cat. no. R1010, Beijing Solarbio Science & Technology Co., Ltd.). After washing once, the mononuclear cells were obtained and stained with monoclonal antibodies for 15 min at room temperature. Following mononuclear cells were washed, collected, and analyzed following the manufacturer's instructions using a FACSAria II instrument (BD Biosciences). The karyotype of the patient was 41-44, XY, -X, del (3) (p21), -4, inv (5) (p11q13), -6, -7, add (8) (p21), +add (8) (p21), -9, -10, -11, -12, del (11) (q23), del (13) (q132q22), -13, -15, -16, -17, +mar [CP4]/46, XY [7] (Fig. 1C). Fluorescence *in situ* hybridization analysis using locus-specific identifier probes was performed with Isis Software (MetaSystems). Hybridized chromosome slides were analysed using an epifluorescence microscope Axio imager A2 (Carl Zeiss AG). The result showed the typical TP53 deletions. (Fig. 1D). The image of positron emission tomography-computed tomography (PET-CT) revealed hypermetabolic activity in the bone marrow (data not shown). Therefore, the patient was diagnosed as having IgG-kappa pPCL.

Correspondence to: Dr Xiong Ni, Department of Hematology, Institute of Hematology, Changhai Hospital, 168 Changhai Road, Shanghai 200433, P.R. China
E-mail: xiongny1998@163.com

*Contributed equally

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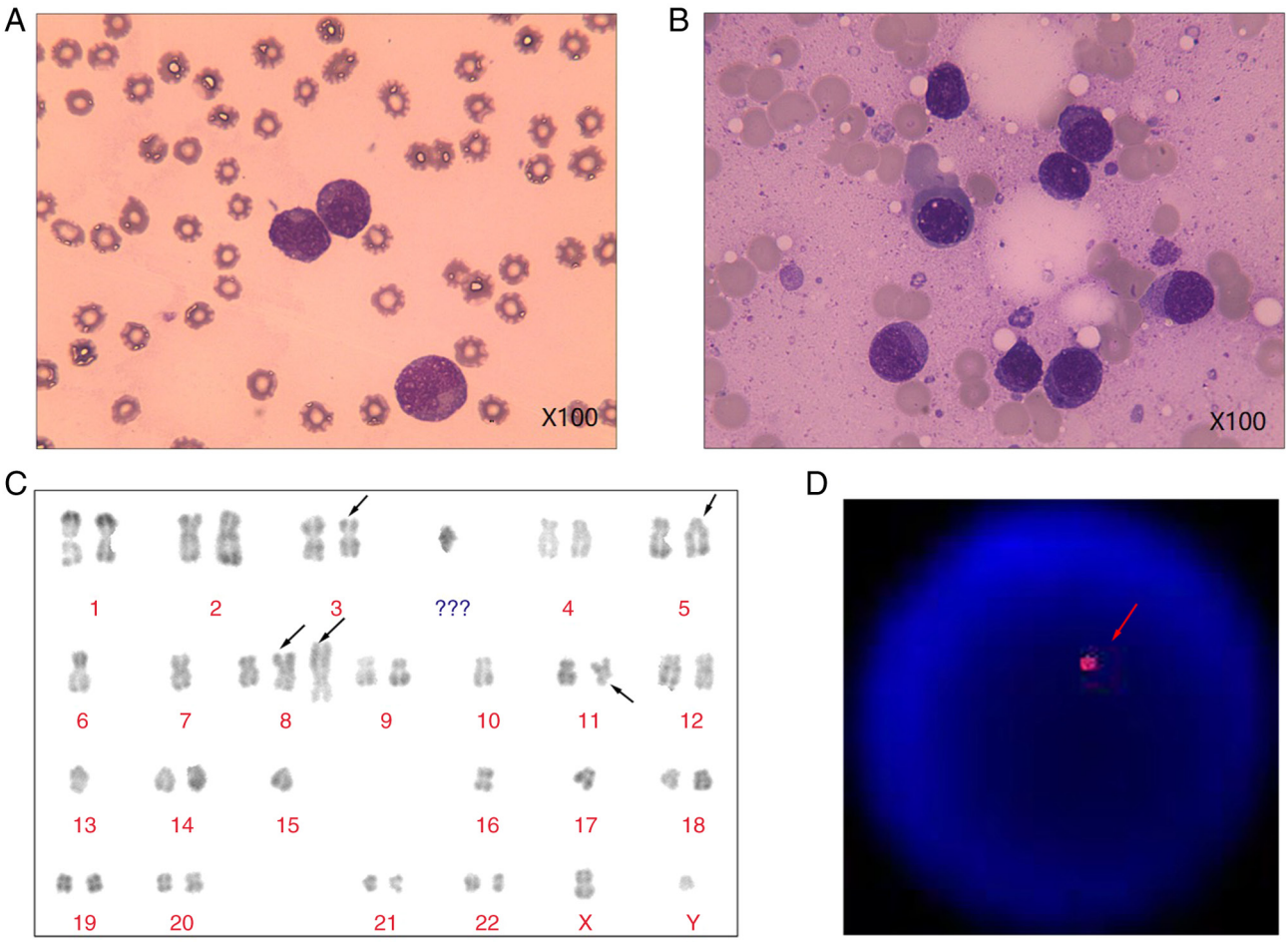

Figure 1. Results of laboratory investigations. (A) Peripheral blood smear. Magnification, x100. (B) Bone marrow morphology. Magnification, x100. (C) R-Banded karyogram at diagnosis. Black arrows indicate the chromosomal abnormalities. (D) Fluorescence *in situ* hybridization analysis at diagnosis. In normal cells, two red signals (P53 probe) are observed. The red arrow indicates the abnormality (only one red signal).

The patient received four cycles of the VTD-PACE regimen (bortezomib, thalidomide, dexamethasone and 4 days of continuous infusions of cisplatin, doxorubicin, cyclophosphamide and etoposide) and were well-tolerated. After the end of chemotherapy sessions, previous laboratory-assessed abnormalities were obviously subsided, and consisted with the very good partial response revealed by the positivity of serum immunofixation. Next, high-dose melphalan (100 mg/m^2 for two consecutive days) was administered along with ASCT, and in so doing, stringent complete remission (sCR) was achieved. For the cure of pPCL, the patient underwent matched, unrelated allo-HSCT, along with myeloablative conditioning with the FAB regimen (fludarabine, cytarabine and busulfan) at the time of six months after ASCT. The numbers of infused mononuclear cells and CD34$^+$ cells were 6.83x10^8/kg and 3.10x10^6/kg, respectively. A post-transplant cyclophosphamide-based regimen was administered to prevent acute graft-vs.-host disease (aGVHD). Neutrophil and platelet were engrafted at 14 days after allo-HSCT. The patient developed grade I skin aGVHD 35 days after allo-HSCT and responded well to steroid treatment. IRD regimen was used (ixazomib, thalidomide and dexamethasone) as a maintenance therapy, which was planned to last 1 year.

The follow-up ended on November 1, 2022 (19 months after allo-HSCT) and the patient remained in sCR. The present study was performed in accordance with the ethical standards formulated of the Helsinki Declaration, and informed consent was obtained from the patient and his family.

Discussion

pPCL is a rare, aggressive plasma cell disorder, for which there are no established therapeutic regimens. Although the availability of novel agents and increasing use of SCT strategies have resulted in improved outcomes, long-term survival remains poor (2,4-6,11).

Jurczyszyn *et al* (7) reported that pPCL patients who underwent upfront ASCT (n=55) had a superior median overall survival (OS) than those (n=98) who did not receive ASCT (35 months vs. 13 months, P<0.001). Another retrospective study suggested that allo-HSCT was more beneficial for PCL patients. The results demonstrated that the median progression-free survival (PFS) was 6 months in the ASCT group (n=9) compared with 18 months in the allo-HSCT group (n=7), and the median OS was 19 months and 40 months, respectively (10). However, results from the Center for International Blood and Marrow Transplant Research (CIBMTR) exhibited superior outcomes with upfront ASCT over allo-HSCT for patients with pPCL (3-year OS: 64 vs. 39%; 3-year relapse: 61 vs. 38%). Although

Table I. Published data on patients with pPCL who underwent ASCT or Allo-HSCT.

Year	Number of patients underwent SCT	Treatment	Survival	(Refs.)
2011	23	ASCT (n=17); Allo-HSCT (n=2); tandem auto/allo-HSCT (n=4)	Total transplanted patients: median OS was 38.1 months	(3)
2012	147	ASCT (n=97)	3 years PFS was 34%; 3 years OS was 64%; 3 years relapse was 61%; 3 years NRM was 5%	(4)
		Allo-HSCT (n=50)	3 years PFS was 20%; 3 years OS was 39%; 3 years relapse was 38%; 3 years NRM was 41%	
2016	26	Allo-HSCT (n=1)	NA	(5)
		ASCT (n=2)	NA	
2018	23	ASCT	Median PFS was 5.5 months; median OS was 18.1 months	(6)
2018	55	ASCT	Median OS was 35 months	(7)
2018	19	ASCT (n=13); Allo-HSCT (n=1); Tandem auto/allo-HSCT (n=4); tandem auto/auto-HSCT (n=1)	Total transplanted patients: median OS was 35.5 months	(8)
2019	28	ASCT	Median PFS was 25 months; median OS was 36 months	(9)
2020	16	ASCT (n=9)	Median PFS was 6 months; median OS was 19 months	(10)
		Allo-HSCT (n=7)	Median PFS was 18 months; median OS was 40 months	
2020	348	ASCT (n=277)	4 years PFS was 17%; 4 years OS was 28%; 4 years relapse was 76%; 4 years NRM was 7%	(11)
		Allo-HSCT (n= 71)	4 years PFS was 19%; 4 years OS was 31%; 4 years relapse was 69%; 4 years NRM was 12%	

pPCL, Primary plasma cell leukemi; ASCT, autologous stem cell transplantation; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; SCT, stem cell transplantation; OS, overall survival; PFS, progression-free survival; NRM, non-relapse mortality.

relapse rates were lower with allo-HSCT, treatment-related mortality was significantly higher, ultimately resulting in the lack of a survival benefit (4). In addition, other results from the CIBMTR comparing ASCT and allo-HSCT showed that the survival outcomes were comparable (11).

Due to a lack of multicenter clinical trial-based evidence, it is not clear whether ASCT or allo-HSCT should be pursued (Table I) (3-12). Thus, developing complex treatment algorithms that combine novel agents, SCT and post-transplantation remission strategies should be considered. A recent study confirmed the safety and efficacy of sequential ASCT-allo-HSCT in relapsed Hodgkin lymphoma (13). Similarly, in multiple myeloma patients, sequential ASCT-allo-HSCT demonstrated PFS and OS at 5 years of 41 and 80%, respectively, with a non-relapse mortality of 12% (14). In patients with pPCL, who have a higher risk of relapse after ASCT than patients with Hodgkin lymphoma or multiple myeloma, allo-HSCT could be used as a potential consolidation strategy after ASCT to improve clinical outcomes. Thus, to improve the survival of the young individual with pPCL in the present report, after initial induction of VTD-PACE treatment, sequential ASCT-allo-HSCT followed by maintenance therapy with IRD were administered. The patient maintained sCR for more than 19 months after allo-HSCT.

In conclusion, the present case report demonstrated the early use of novel agents and an upfront sequential ASCT and allo-HSCT approach with encouraging results in pPCL, which could achieve a deeper response and improve prognosis. Further mechanistic studies are required to investigate this phenomenon.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WF, AH and YL collected, verified and interpreted the patient information and drafted the manuscript. ML and GT performed laboratory analysis. JY and XN designed the research, interpreted the data and critically reviewed and revised the manuscript. WF and XN confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the guidelines of the Declaration of Helsinki, and granted an exemption from requiring ethics approval by the Ethics Committee of Changhai Hospital (Shanghai, China).

Patient consent for publication

Informed consent regarding the publication of clinical data was obtained from the patient and his family.

Competing interests

The authors declare that they have no competing interests.

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