Table 1. The response rate to the first- and second-line therapies.

	CR (%)	PR N (%)	NR N (%)	N
First line				
Steroids	48(32.9)	53(36.3)	45(30.8)	146
IVIG	3(30)	6(60)	1(10)	10
TCM	8(14.0)	19(33.3)	30(52.7)	57
S+T*	12(13.0)	35(38.0)	45(49.0)	92
Others**	4(21.1)	3(15.8)	12(63.1)	19
Total	75(23.1)	116(35.8)	133(41.1)	324
Second line				
Steroids	11(30.6)	13(36.1)	12(33.3)	36
IVIG	1(14.3)	5 (71.4)	1(14.3)	7
TCM	11(21.2)	12(23.1)	29(55.7)	52
S+T*	10(30.3)	12(36.4)	11(33.3)	33
Immunosuppressants	5(17.9)	11(39.3)	12(42.8)	28
Splenectomy	46(76.7)	3(5.0)	11(18.3)	60
Total	84(39.0))	56(25.6)	76(35.4)	216

S+T, steroids plus TCM; Others, vitamin C or any non-regulatory therapy.

and between steroid treatment and steroids plus TCM ($p<0.01$). However, there was not a significant difference between TCM and treatment with steroids plus TCM ($p>0.05$). Two hundred and sixteen of the regularly followed patients received second-line therapy because of a lack of improvement in response to the first-line therapy or because of a relapse after remission. Among these, CR rate obtained with open splenectomy (76.7%) was significantly higher than that with any other modality ($p<0.01$). Steroids as a second therapy was not significantly more effective (CR plus PR) than immunosuppressive therapy or steroids plus TCM ($p>0.05$) therapy. As anticipated, TCM therapy was the least effective of the treatments described above ($p<0.05$) compared to each other treatment. In addition, we note that the effect of steroids as second-line therapy was similar to that of steroids used as first-line therapy ($p>0.50$).

In conclusion, the data from our series revealed that the clinical characteristics of Chinese children with chronic ITP are similar to those of a European cohort of patients reported by Khune *et al.*[6] Steroid therapy is effective for chronic ITP whether used first- or second-line. TCM was much less effective than steroids.

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Key words: idiopathic thrombocytopenic purpura, children, steroids, splenectomy

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Stem Cell Transplantation

Bortezomib treatment followed by a second non-myeloablative allogeneic stem cell transplant in two previously autografted patients with multiple myeloma relapse

We report two cases of multiple myeloma relapse and progression following a combination of autologous stem cell transplantation and non-myeloablative allogeneic stem cell transplantation. After failure of donor lymphocyte infusions and thalidomide salvage therapy, the patients were treated successfully with bortezomib and eventually underwent a second non-myeloablative allogeneic stem cell transplantation.

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Patient #1. A 55-year old man was diagnosed with κ light chain multiple myeloma in stage IIIA in March 2001. Serum lactate dehydrogenase levels were elevated at diagnosis. After autologous stem cell transplantation (autoSCT) with melphalan 200 mg/m^2 in August 2001, he then underwent non-myeloablative allogeneic stem cell transplantation (alloSCT) with peripheral blood stem cells (PBSC) from his HLA-identical sister in November 2001 following conditioning with 2 Gy total body irradiation (TBI). Graft-versus-host-disease (GVHD) prophylaxis consisted of mycophenolate mofetil and cyclosporine A, discontinued on days +27 and +131, respectively. A study of chimerism showed full donor hematopoiesis at day +63. Complete remission (CR) was achieved after the establishment of limited chronic GVHD with cholestatic abnormalities of liver function tests requiring cyclosporine A treatment. Relapse occurred on day +567 and was unsuccessfully managed with cyclosporine A discontinuation and 2 donor lymphocyte infusions given on days +619 (1×10^7 CD3$^+$ cells/kg) and +645 (3.2×10^7 CD3$^+$ cells/kg). Thalidomide 100 mg once daily was started on day +763 but was discontinued one month later because of intolerable toxicity.

Thereafter four courses of bortezomib 1.3 mg/m^2 once daily on days 1, 4, 8 and 11 every 21 days were given at days +800, +827,+849 and +869. A second CR was demonstrated on day +900. The patient then underwent a second non-myeloablative alloSCT with PBSC from the same donor on day +920 after conditioning with fludarabine 30 mg/m^2 for 3 days, melphalan 100 mg/m^2 and 2 Gy TBI. Immunosuppressive treatment with mycophenolate mofetil and cyclosporine A was discontinued on days +947 and +1050, respectively. Thereafter a short course of cyclosporine A plus steroid treatment was started for intestinal and liver GVHD. CR was shown on day +1150; the same day, a study revealed full donor chimerism. The patient is currently alive and well, without evidence of disease recurrence at day +1221 after the first alloSCT and day +272 after the second alloSCT.

Patient #2. A 54-year old woman was diagnosed in August 2002 as having non-secretory multiple myeloma in stage IIIA and elevated serum lactate dehydrogenase levels. She underwent autoSCT in November 2002 followed by alloSCT with PBSC from her HLA-identical sister in February 2003. Conditioning regimens were the same as those used in patient 1. Chimeric data showed full donor chimerism on day +99. No response was observed after the combination of autoSCT and alloSCT; following discontinuation of immunosuppressive treatment, limited chronic GVHD with localized scleroderma and hepatic dysfunction was observed. Salvage treatment with thalidomide 100 mg once daily was then started on day +307 because of progression; one month later the plasma cell infiltrate was 90%. Four courses of bortezomib, using the same schedule as that for patient #1, were given on days +400, +420, +436, and +462. CR was achieved on day +490. Thalidomide was discontinued on day +534. She underwent a second non-myeloablative alloSCT from the same donor on day +540 after the same conditioning as that of patient 1. Cyclosporine A was then tapered by day +581. Full donor chimerism was shown on day +609; CR was shown on day +695. She is now well and alive, without evidence of disease recurrence at day +772 from the first alloSCT and at day +232 from the second alloSCT.

In recent years, the combination of autoSCT and non-myeloablative alloSCT in patients with multiple myeloma has been shown to induce a CR rate ranging from 57 to 73% with an acceptable toxicity.[1,2] However, relapse or progression occurs in a significant proportion of patients and their management with thalidomide or thalidomide and donor lymphocyte infusion remains still unsatisfying with CR in only 22% of cases.[3,4] Bortezomib, a novel proteasome inhibitor, has been shown to induce a response rate of 35% (including some CR) with an acceptable toxicity profile in pretreated multiple myeloma patients after failure of high dose chemotherapy and thalidomide.[5]

A case of successful bortezomib treatment of extramedullary relapse in a recipient of a combined autoSCT and non-myeloablative alloSCT was recently reported.[6] Our patients both had elevated serum lactate dehydrogenase levels at diagnosis, recently reported as a high-risk factor predicting poor response to high dose chemotherapy in patients treated with combined autoSCT and non-myeloablative alloSCT.[7,8] Bortezomib treatment showed a good toxicity profile in our patients without causing thombocytopenia, intestinal side effects, synergistic toxicity with thalidomide or worsening of chronic GVHD. No significant improvement in GVHD symptoms was observed during or immediately after bortezomib treatment; however limited scleroderma improved in patient 2 following the second non-myeloablative alloSCT. Timely application of second non-myeloablative alloSCT after bortezomib treatment was feasible and well tolerated. The toxicity of the previous combination of autoSCT and non-myeloablative alloSCT was very mild, allowing safe application of a further non-myeloablative alloSCT after a more intensive conditioning regimen including a second course of 2 Gy TBI. The contribution of low-dose thalidomide to the response in patient 2 is uncertain. This report suggests that bortezomib treatment followed by second non-myeloablative alloSCT is a safe and effective approach to relapse and progression in patients with high-risk multiple myeloma.

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Key words: bortezomib, multiple myeloma, relapse, progression.

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