Multiple myeloma (MM) is the second most common hematological malignancy. The introduction of novel agents such as thalidomide, bortezomib, and lenalidomide in more recent years has significantly improved the response rate, progression-free survival (PFS), and overall survival (OS) of MM patients.\(^1,2\) However, alongside these benefits, a significant increased risk of developing secondary primary malignancies (SPMs) has been observed. Until now, there has not been a relevant large study of Chinese MM patients available to study SPMs, and no secondary malignancy after bortezomib treatment alone has been reported.

A total of 1060 consecutive MM patients observed from November 1989 to May 2016 were included in the study. A definitive diagnosis of MM was confirmed in each case by a pathologist. Patients who refused to receive chemotherapy or did not complete one course of chemotherapy were excluded from the study. Baseline characteristics were collected including Durie and Salmon (DS), International Staging System (ISS), and cytogenetics. Real-time quantitative polymerase chain reaction (RT-qPCR) was used to quantify the expression of \(WT1\) gene. Clinical efficacy was evaluated on the basis of the International Myeloma Working Group (IMWG) criteria. Patients were followed up longitudinally, and the data were updated. A SPM was defined as a previously unidentified invasive cancer occurring after the diagnosis of MM. Pathology reports were obtained and reviewed centrally to confirm the diagnosis.

Six (0.57%) patients developed a SPM. The median age of these patients was 64 years (range: 59–73 years), and the median time of SPM emergence from the diagnosis of MM was 40.5 months (range: 6–77 months). Three of the SPM patients developed solid tumors (one gastric cancer, two lung cancer), and the remaining three patients developed acute myeloid leukemia (AML, one M5, two M2). No therapy-related myelodysplastic syndrome (t-MDS) was recorded in the chart review. Four of the SPM patients received either alkylating agents and/or immunomodulators during MM treatment, but the other two patients received only bortezomib plus dexamethasone (BD) therapy before SPM was diagnosed. The incidence of SPM after bortezomib only was 2.99% (2/67). Median OS of the six patients with a diagnosis of SPM was 8.5 months (range: 1–21 months). The characteristics of these SPM patients are shown in Table 1.

We also analyzed \(WT1\) expression in 75 MM patients in our center. Six patients tested positively for \(WT1\) (8.00%), the median expression of the \(WT1\) gene was 0.71% (range: 0.63–0.90%, cutoff: 0.60%).

One of the SPM patients following bortezomib therapy was a 61-year-old woman with lung adenocarcinoma. Further workup confirmed a diagnosis of immunoglobulin G-lambda MM, DS Stage IIIA, and ISS Stage III. Karyotyping revealed hypodiploid karyotype and deletion of 13q with the following details: 41–45,XX,‑2,add(12)(p11),der(13)t(2;13)(p10;q10),del(13q),del(14)(q24),add(19)(p13),add(20)(p13),‑22[CP5]/48,XX,+X,+X,del(11)(p13).[\(^1\)] No mass was found in her lung by radiography. She received four cycles of...
of BD (bortezomib 1.3 mg/m² day [D] 1, 4, 7, 11 and dexamethasone 20 mg D1–4, 7, 11, 21 days/cycle) treatment, and a mass of 2.5 cm in diameter in her left lung was found by computed tomography scan right before autologous stem cell transplantation (ASCT). Surgical pathology confirmed a lung adenocarcinoma and she did not receive further therapy for it. Thalidomide was taken as maintenance therapy. Her myeloma had progressed 21 months after SPM; she refused to take further chemotherapy and died from it. The OS was 27 months.

Another patient was a 73-year-old man diagnosed with lambda-free MM, DS Stage IIIB, and ISS Stage III. WT1 gene expression was 0.75%. Karyotyping revealed a normal karyotype. Previous medical history included hypertension and atherosclerosis for over 10 years. He received nine cycles of BD treatment weekly  (bortezomib 1.3 mg/m² and dexamethasone 40 mg/week, 4 weeks for a cycle) and achieved a very good partial response (VGPR) after three cycles of therapy, and there was no further improvements after nine cycles of BD. He was admitted to the hospital for routine evaluation 14 months later. MM evaluation indicated that he was still in VGPR, but bone marrow cytology examination revealed 75.00% of myeloblasts. Positive peroxidase staining was 91.00%. Totally, 36.40% of bone marrow cells were abnormal myeloid immature cells expressing cluster of differentiation 33 (CD33) and CD117, 15.01% expressed CD33, CD38, human leukocyte antigen-D related, CD11b, CD123, CD64, and CD11c were abnormal monocytes.

WT1 mutation was highly expressed at 115.6%. FLT3/ITD mutation was positive. No AML1-ETO, BCR/ABL, MLL-AF, MLL-PTD, and EVII mutations were identified. Cytogenetics by G-banding was normal. A  diagnosis of AML-M5 was determined. The patient refused to receive chemotherapy and discharged to take Chinese Traditional Medicine treatment and supportive care. He died of pulmonary alveolar hemorrhage 2 months after the diagnosis of AML. The OS was 16 months.

For MM, the number of long-term survivors is continuously rising, and the risk of secondary malignancies is of great importance. The latency between previous cancer treatment and leukemia development is longer after alkylating agents (3–8 years) and shorter after topoisomerase II inhibitors (2–3 years). The incidence of SPM after MM has been reported to be 3.30–10.40% in Western countries, in which a high incidence of t-MDS/AML and melanoma has been observed. The data from our center are much lower than those of Western data, which might be due to: (1) differences in therapeutic regimen (especially melphalan and lenalidomide); (2) missed diagnosis of MDS after MM; (3) racial differences; and (4) shorter OS. Previous researches have shown that alkylating agents, especially melphalan, have been considered as a positive factor in the cause of SPM. Although there have previously been reports of SPM after bortezomib, all of these cases had received not only bortezomib, but also other medicines such as melphalan, thalidomide, and/or lenalidomide. A previous study revealed that MM itself was

### Table 1: Clinical information in six cases of SPM secondary to MM

| Cases | Age (years)/gender | MM type | MM stage (DS/ISS) | Latency from MM to SPM (months) | Treatment for MM | SPM | OS after SPM (months) |
|-------|--------------------|---------|------------------|--------------------------------|-----------------|-----|-----------------------|
| 1     | 67/female          | IgG-kappa | IIIA/III         | 70                             | Melphalan/prednisone/cyclophosphamide/vindesine × 3 cycles | Gastric cancer | 9                      |
| 2     | 68/female          | IgG-lambda | IIA/I           | 77                             | Melphalan/prednisone/cyclophosphamide/vindesine × 6 cycles | Lung cancer  | 15                     |
| 3     | 61/female          | IgG-lambda | IIIA/III        | 6                              | BD × 4 cycles   | Lung cancer | 21                     |
| 4     | 73/male            | Light chain | IIIB/III      | 14                             | BD × 9 cycles   | AML-M5     | 2                      |
| 5     | 59/male            | IgG-kappa | IIIA/I         | 22                             | TAD × 6 cycles  | AML-M2     | 8                      |
| 6     | 61/female          | IgA-kappa | IIA/I          | 59                             | VAD × 2 cycles  | AML-M2     | 1                      |

SPM: Secondary primary malignancy; MM: Multiple myeloma; DS/ISS: Durie and Salmon/International Staging System; OS: Overall survival; Ig: Immunoglobulin; VAD: Vindesine/epirubicin/dexamethasone; CVAD: Cyclophosphamide/vindesine/epirubicin/dexamethasone; TAD: Thalidomide/epirubicin/dexamethasone; COHP: Cyclophosphamide/vindesine/epirubicin/prednisone; COEP: Cyclophosphamide/vindesine/etoposide/prednisone; CONPT: Cyclophosphamide/vindesine/mitoxantrone/prednisone/thalidomide; BD: Bortezomib plus dexamethasone; DT-PACE: Dexamethasone/thalidomide/cisplatin/epirubicin/cyclophosphamide/etoposide; VBAP: Vindesine/carmustine (BCNU)/epirubicin/prednisone; T: Thalidomide; AML: Acute myeloid leukemia; BCNU: Bis-chloroethylnitrosourea.
more prone to develop into MDS. A 2.4-fold increased risk of MDS was reported in persons with monoclonal gammopathy of undetermined significance who had not received anti-myeloma therapy. We reported two cases of SPM after bortezomib only, one solid tumor and the other AML, and further analyzed the incidence of SPM after bortezomib as 3.00% in our center. However, the causal relationship between the use of bortezomib and the development of SPM is still unclear, and the disease itself as an etiology cannot be excluded either.

We observed WT1 gene expression of the AML patient at the onset of MM and it significantly increased when AML was diagnosed. We suggest that the WT1 gene might be a predictive factor of secondary myeloid neoplasms (s-MNs). The significance of the gene for MM is still not clear. The prognosis of s-MN in general is poor because of therapy resistance, with an overall 5-year survival rate of <10.00%. OS of SPM patients is shorter than patients without SPM.

In conclusion, with the onset of novel agents and widespread use of ASCT, the MM patients’ lifespan had been prolonged. The increased risk of SPM is of great importance and Chinese myeloma patients should be aware of this. Daily clinical workups should take this into consideration, and periodic cytogenetic monitoring is recommended.

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Conflicts of interest
There are no conflicts of interest.

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