Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Journal of **Comparative Effectiveness Research**

Cost–effectiveness of lenalidomide plus low-dose dexamethasone for newly diagnosed multiple myeloma patients ineligible for stem cell transplantation in China

Jin Lu[1] & Wendong Chen*[,2]

[1]Department of Hematology, Peking University People's Hospital, Beijing 100032, China

[2]Toronto Health Economics & Technology Assessment Collaborative, University of Toronto, ON M5G 2C4, Canada

*Author for correspondence: Tel.: +1 647 673 8658; wendong.chen@normin.ca

Aim: To assess the cost–effectiveness of lenalidomide plus low dose dexamethasone (Rd) relative to bortezomib-contained therapy (BCT) for newly diagnosed multiple myeloma patients ineligible for stem cell transplantation (ndMM) in China. **Materials & methods:** A literature review was conducted to identify appropriate evidence for developing a cost–effectiveness model comparing Rd with BCT for lifetime health outcomes and direct medical costs in Chinese ndMM patients. **Results:** The estimated incremental cost–effectiveness ratio per gained quality-adjusted life years for Rd versus BCT was ¥49,793. The chance for Rd to be cost effective, under the cost–effectiveness thresholds of three-times the 2018 Chinese gross domestic goods per capita, was 90.8%. **Conclusion:** The cost–effectiveness of Rd relative to BCT for ndMM in Chinese patients is highly attractive.

First draft submitted: 21 April 2019; Accepted for publication: 10 June 2019; Published online: 24 June 2019

Keywords: bortezomib • China • cost–effectiveness • lenalidomide • newly diagnosed multiple myeloma

Multiple myeloma (MM) is ranked the third highest annual incidence of homological malignance (0.61 per 100,000 persons) in eastern Asia [1]. MM is not a curable disease and is commonly associated with complications such as hypercalcemia, anemia, bone disease and renal insufficiency that substantially impair quality of life and increase medical costs [2]. The 5-year survival rate of MM was about 30% before the development of novel agents [3]. However, novel agents such as bortezomib and lenalidomide have significantly improved the survival prognosis of MM [4]. The 5-year survival rate associated with MM in high-income countries has been almost doubled after the approvals of the novel agents [5,6]. The latest American [7] and European [8] clinical guidelines have recommended bortezomib and lenalidomide for newly diagnosed MM patients, who are ineligible for stem cell transplantation (ndMM) or those with relapsed or refractory multiple myeloma (rrMM).

Even though there are no randomized trials directly comparing the two agents for clinical outcomes in MM patients, the oral administration of lenalidomide could bring MM patients more survival benefits through longer treatment durations. For example, patients could receive lenalidomide in an outpatient setting until disease progression, and bortezomib was usually given in fixed treatment cycles. Additionally, the oral administration of lenalidomide plus low-dose dexamethasone (Rd), the most common treatment regimens for both ndMM and rrMM, could save medical costs for treatment administration when compared with bortezomib-contained therapy (BCT), which is usually given to patients in tertiary care hospital settings. Bortezomib was approved for MM much earlier than lenalidomide in China, and is the mainstay treatment for both ndMM and rrMM. Lenalidomide was approved for rrMM in China in 2013 and for ndMM in 2018. Rd has been found to be cost effective when compared with BCT for rrMM in Chinese patients [9]. To support the reimbursement decision-making and real-world clinical practice related to lenalidomide for ndMM in China, a cost–effectiveness analysis is needed to compare Rd versus BCT for their health outcomes and medical costs associated with Chinese ndMM patients

Future Medicine

Materials & methods

This study constructed a decision analytic model to assess the cost–effectiveness of Rd relative to BCT in Chinese ndMM patients from the perspective of healthcare payers. The specific methods are described below.

Model structure

The constructed decision analytic model contained two treatment scenarios, Rd versus BCT, for the lifetime simulation in the model cohort of Chinese patients with ndMM. To simulate the survival outcomes and direct medical costs associated with the model cohort over the lifetime, the decision analytic model adopted a Markov model design to simulate ndMM and rrMM, respectively. The Markov model simulating ndMM and rrMM included health states for PFS, progressive disease survival (PDS) and death to simulate disease progression and mortality. The model cohort was simulated in the Markov model for ndMM under the two treatment scenarios. The patients with developed PDS from the Markov model for ndMM were further simulated in the Markov model for rrMM until patients were deceased. Based on the latest Chinese clinical guideline, the decision analytic model took Rd and two BCT, bortezomib plus dexamethasone regimen (VD), and bortezomib in combination with cyclophosphamide and dexamethasone (VCD) as the treatments for rrMM. Given the fact that rrMM was unlikely to respond to the treatments used in the previous treatment lines, Rd was selected as the treatment for rrMM in the patients who received BCT for ndMM in the model. Instead, VD and VCD were selected as the treatment for rrMM in the patients who received Rd for ndMM in the model. The cycle length of the Markov model for ndMM and rrMM was set to 1 month for more accurate measurement of outcomes, which included PFS, overall survival (OS), quality-adjusted life years (QALY) and lifetime direct medical costs. The decision analytic model discounted the health benefits and direct medical costs by 3% per annum by following the China Health Economics Evaluation Guideline. The structure of the decision analytic model assessing the cost–effectiveness of Rd relative to BCT for ndMM is illustrated in Figure 1.

Model variable estimation

The main source of the data used to estimate model variables was the relevant published literature that was found through systematic searches in the main English and Chinese bibliographic databases. The literature search time window was set between May 2013 and May 2018. Literature search strategies were developed according to the definitions of the model variables. The model variables for patient age and gender distribution were estimated through a single-arm meta-analysis of the reported age and gender from identified observational studies including Chinese ndMM patients [9–53]. The clinical effectiveness and the distributions of serious adverse events, which were defined as grade 3 or 4 adverse events and associated with Rd and BCT for ndMM and rrMM, were based on the collected data from identified randomized clinical trials [54–59]. The reported median progression-free survival (PFS) and OS associated with Rd and BCT were applied to a survival function formula [$S(t) = e^{-\lambda t}$] to estimate the monthly risk of disease progression and monthly risk of mortality after disease progression. A single-arm meta-analysis approach was used for pooled estimation of the monthly risks of disease progression and mortality associated with the same treatment regimen. The overall therapeutic effect of BCT was estimated by a weighted average calculation of the distribution of specific treatment regimens and their corresponding absolute clinical efficacy. The reported serious adverse events associated with the same treatment in the identified randomized clinical trials were pooled to calculate the distributions that were used to estimate overall medical costs of managing serious adverse events per treatment cycle. The quality of life was rarely measured in Chinese MM patients. The identified studies [60–67] reporting quality of life associated with ndMM and rrMM in other countries were used to estimate the model variable for utility associated with PFS and PDS in ndMM and rrMM patients after the country adjustment, which was conducted by applying the ratio of the quality of life associated with the age- and gender-matched general populations of the study country and China [68–71]. Additionally, the quality of life measured by QLQ-C30 in the quality of life studies was converted to a utility value of EQ-5D using the conversion formula developed by Proskorovsky *et al.* [72]. The bottom-up method was used to estimate the model variables for drug acquisition costs according to drug price, treatment dosage, treatment schedule, treatment duration (treatment cycles) and patient body surface area estimated from the weighted mean of height and weight associated with Chinese ndMM patients in the identified observational studies. The medical costs associated with the management of serious adverse events of Rd and BCT in Chinese ndMM patients were estimated from an expert survey of adverse event management and the unit prices of health resources in a Chinese tier III tertiary care hospital. The medical costs associated with the treatment administration of bortezomib and rrMM were based on the estimations

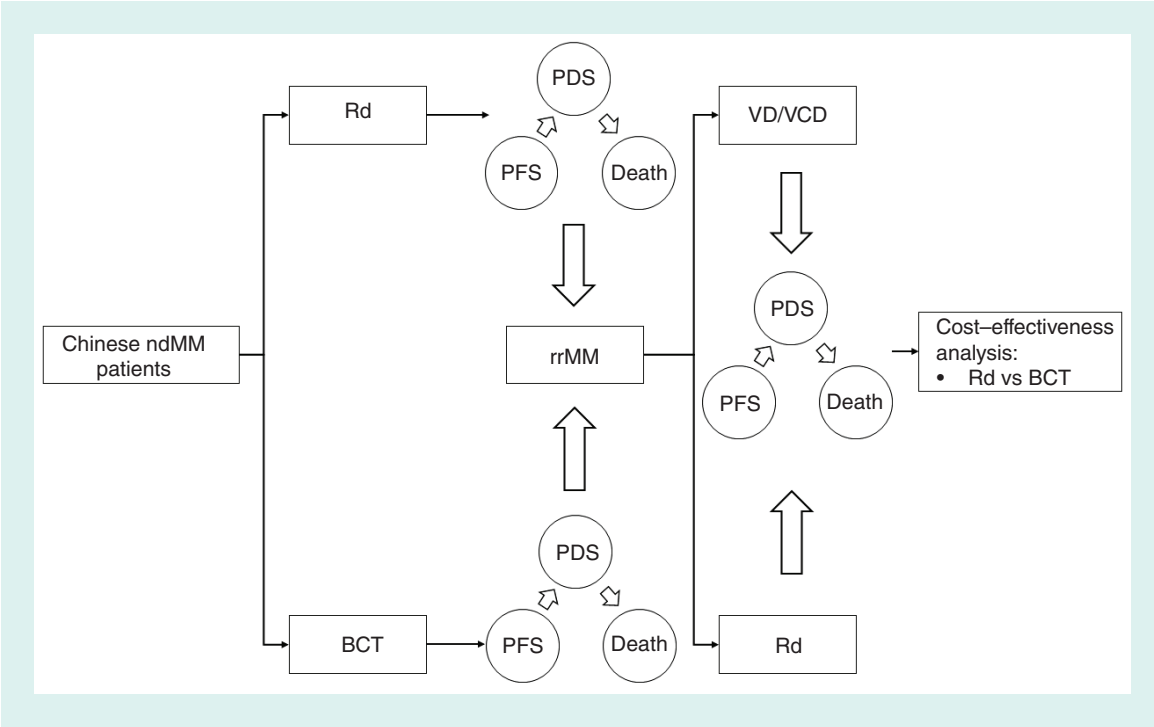

Figure 1. The structure of decision analytic model assessing the cost–effectiveness of lenalidomide plus low dose dexamethasone relative to bortezomib-contained therapy for newly diagnosed multiple myeloma in Chinese patients.

BCT: Bortezomib-contained therapy; ndMM: Newly diagnosed multiple myeloma but ineligible for stem cell transplantation; PDS: progressive disease survival; PFS: progression-free survival; Rd: Lenalidomide plus low dose dexamethasone; rrMM: Relapsed or refractory multiple myeloma; VD: Bortezomib plus dexamethasone; VCD: Combination of bortezomib, cyclophosphamide, and dexamethasone.

from a previous cost–effectiveness analysis assessing Rd relative to two bortezomib-based treatment regimens in Chinese rrMM patients [73]. All costs were adjusted to the Chinese currency in 2018 using Chinese historical annual inflation rate. The estimated model variables are summarized in Table 1.

Cost–effectiveness analysis

The constructed decision analytic model with the estimated model variables was used to conduct the following cost–effectiveness analysis. First, the constructed decision analytic model with the base-case values of the model variables was used to conduct base-case analysis for the point estimation of PFS, OS, quality-adjusted life years (QALY) and the distributions of lifetime medical costs under the two treatment scenarios for Rd versus BCT. The point estimations of QALY and lifetime medical costs associated with two treatment scenarios were used to calculate the incremental cost–effectiveness ratio (ICER) per gained QALY for Rd relative to BCT. The recommended Chinese cost–effectiveness threshold, three-times the 2018 Chinese gross domestic product per capita (GDPPC) per gained QALY [74], was used to interpret the cost–effectiveness of Rd in the base-case analysis. Second, the constructed decision analytic model was used to conduct one-way sensitivity analysis to explore the change of ICER associated with the varying the 95% CI or the +/-25% of the base-case value of each model variable. Finally, the constructed decision analytic model with β distributions of model variables for model cohort demographics and clinical efficacies associated with Rd and BCT for ndMM and rrMM was used to conduct a probabilistic sensitivity analysis through 10,000 Monte Carlo simulations. The generated ICERs from the 10,000 simulations were plotted to estimate the median value and 95% credible interval of ICER for Rd relative to BCT. The cost–effectiveness acceptability curve for Rd relative to BCT was created under the willingness-to-pay per gained QALY from zero to three-times the 2018 Chinese GDPPC.

Table 1. Summary of estimated model variables of the decision analytic model assessing the cost–effectiveness of lenalidomide plus low dose dexamethasone relative to bortezomib-contained therapy in Chinese patients with newly diagnosed multiple myeloma patients ineligible for stem cell transplantation.

Variables	Baseline	95% CI	
		Lower limit	Upper limit
Demographics			
Age (years)	60.2	58.5	61.8
Male (%)	59.4	57.9	60.8
Body surface area (m^2)	1.681		
Treatment cycles			
Rd	15		
VD	9		
PAD	6		
VTD	9		
Treatment efficacy			
HR of the monthly risk of disease progression from PFS to PDS (Rd vs BCT)	0.795	0.499	1.091
Monthly risk of disease progression from PFS to PDS under VD treatment	0.039	0.031	0.047
Monthly risk of disease progression from PFS to PDS under PAD treatment	0.025	0.011	0.048
Monthly risk of disease progression from PFS to PDS under VTD treatment	0.045	0.029	0.055
Quality of life (utility)			
Under Rd treatment	0.641	0.481	0.802
Under BCT treatment	0.558	0.419	0.698
PFS	0.897	0.672	1.121
PDS	0.766	0.575	0.958
Medical costs			
Drug acquisition costs of Rd per treatment cycle	¥21,678		
Drug acquisition costs of VD per treatment cycle	¥23,048		
Drug acquisition costs of PAD per treatment cycle	¥23,124		
Drug acquisition costs of VTD per treatment cycle	¥23,239		
Administration costs of BCT per treatment cycle	¥5278		
Monthly medical costs associated with PFS	¥119		
Medical costs of managing serious adverse event per treatment cycle			
Rd	¥2987		
VD	¥1763		
PAD	¥6582		
VTD	¥1989		

BCT: Bortezomib-contained therapy; HR: Hazard ratio; ndMM: Newly diagnosed multiple myeloma but ineligible for stem cell transplantation; PDS: Progressive disease survival; PAD: Bortezomib combined with adriamycin and dexamethasone; PFS: Progression-free survival; Rd: Lenalidomide plus low dose dexamethasone; rrMM: Relapsed or refractory multiple myeloma; VD: Bortezomib combined with dexamethasone; VTD: Bortezomib combined with thalidomide and dexamethasone.

This study used R statistical software to conduct data analysis regarding the estimations of the model variables from the collected data from the literature review. Microsoft Excel 2013 was used to construct the decision analytic model and perform the cost–effectiveness analysis.

Results

The literature review identified 14 Chinese observational studies reporting up to ten treatment regimens containing bortezomib for ndMM. However, the literature search only identified randomized clinical trials assessing three treatment regimens containing bortezomib: bortezomib plus dexamethasone (VD), the combination of bortezomib, epirubicin, and dexamethasone combination (PAD), and the combination of bortezomib, thalidomide, and dexamethasone (VTD). Thus, the cost–effectiveness analysis created the BCT treatment scenario according to the estimated distributions of VD (29.6%), PAD (30.7%) and VTD (39.7%). The constructed decision analytic model was used to generate the following results.

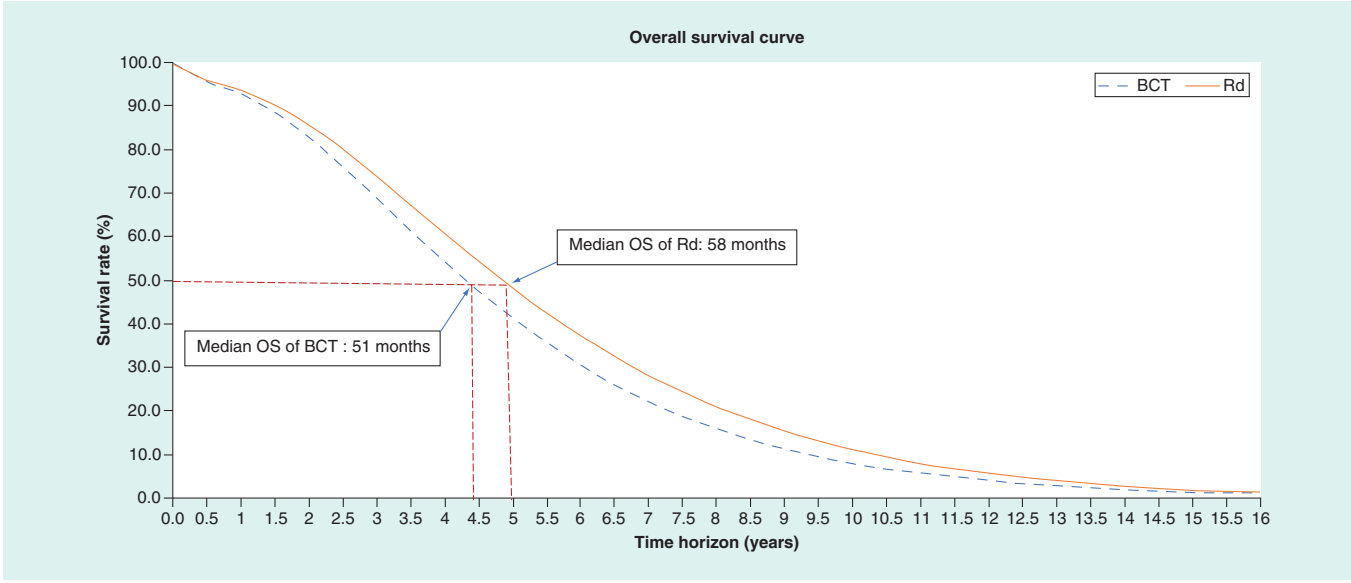

Figure 2. Overall survival curves associated with lenalidomide plus low dose dexamethasone and bortezomib-contained therapy over lifetime simulation in Chinese patients with newly diagnosed multiple myeloma but ineligible for stem cell transplantation.
BCT: Bortezomib-contained therapy; ndMM: Newly diagnosed multiple myeloma but ineligible for stem cell transplantation; OS: Overall survival; Rd: Lenalidomide plus low dose dexamethasone.

Estimated health outcomes associated with Rd & BCT for ndMM over the lifetime simulation

The lifetime simulation of the constructed decision analytic model without discounting projected that Rd was associated with 0.597 years (5.496 vs 4.899 years) than BCT in Chinese ndMM patients. Further comparisons of the survival types associated with the two treatment scenarios indicated that the gained PFS associated with Rd for ndMM accounted for 72.2% of the gained OS associated with Rd. Based on the plotted OS curves associated with the two treatment scenarios (Figure 2), Rd was associated with higher median OS (58 vs 51 months) and also 5-year survival rate (48.6 vs 41.2%) compared with BCT in the Chinese ndMM patients. When taking into account the quality of life associated with the model health states, the Rd treatment was associated with more QALY than the BCT treatment scenario over the lifetime simulation of Chinese ndMM patients (3.384 QALY vs 2.966 QALY, QALY gain: 0.418). Because PFS had a higher quality of life than PDS, the gained QALY through PFS associated with Rd accounted more for all gained QALY (76.3%) when compared with the proportion of gained PFS in the gained OS under the Rd treatment scenario. The health outcomes associated with the two treatment scenarios over the lifetime model simulation are summarized in Table 2.

Estimated lifetime direct medical costs associated with Rd & BCT for ndMM over the lifetime simulation

The lifetime simulation of the constructed decision analytic model without discounting projected that the Rd treatment scenario was associated with ¥19,031 more lifetime medical costs than the BCT treatment scenario (¥483,787 vs ¥464,756, ¥1 = US $0.15 as of December 2018). The comparisons of the distributions of lifetime direct medical costs by the classified categories indicated that the Rd treatment scenario saved ¥35,599 for treatment administration, ¥12,225 for the management of serious adverse events and ¥35,940 for the management of rrMM. However, these saved costs associated with the Rd treatment scenario could not fully offset the increased drug acquisition costs of Rd over BCT (¥258,305 vs ¥156,127). The distribution of undiscounted lifetime medical costs associated with the two treatment scenarios is summarized in Table 2.

Base-case analysis

With discounting the QALY and direct medical costs in the constructed decision analytic model, the base-case analysis estimated that the Rd treatment scenario was associated with more gained QALY (3.032 QALY vs 2.679 QALY, difference: 0.354 QALY) and also higher lifetime direct medical costs (¥455,527 vs ¥437,920, difference: ¥17,607). The calculated point estimation of ICER per gain QALY for Rd relative to BCT was ¥49,793, which

Table 2. Summary of the undiscounted health outcomes and lifetime direct medical costs associated with lenalidomide plus low dose dexamethasone and bortezomib-contained therapy over lifetime simulation in Chinese newly diagnosed multiple myeloma but ineligible for stem cell transplantation patients.

Treatment scenario	Rd	BCT	Difference
Survival outcomes			
PFS of ndMM (years)	2.747	2.316	0.431
PFS of rrMM (years)	1.066	0.900	0.166
PDS of rrMM (years)	1.683	1.683	0.000
Overall survival (years)	5.496	4.899	0.597
QALY outcomes			
PFS of ndMM	1.790	1.471	0.287
PFS of rrMM	0.671	0.568	0.082
PDS of rrMM	0.923	0.926	-0.015
Total QALY	3.384	2.966	0.418
Lifetime medical costs			
Drug acquisition costs	¥258,305	¥156,127	¥102,178
Treatment administration	¥0	¥35,599	¥-35,599
Management of serious adverse events	¥8446	¥20,671	¥-12,225
Management of PFS	¥3932	¥3316	¥617
Management of rrMM	¥213,103	¥249,044	¥-35,940
Total lifetime medical costs	¥483,787	¥464,756	¥19,031

BCT: Bortezomib-contained therapy; PDS: Progressive disease survival; PFS: Progression-free survival; QALY: Quality-adjusted life years; Rd: Lenalidomide plus low dose dexamethasone; rrMM: Relapsed or refractory multiple myeloma.

is slightly lower than the 2018 Chinese GDPPC (¥64,644). Thus, the cost–effectiveness of Rd relative to BCT for ndMM in Chinese patients was found to be highly attractive according to the cost–effectiveness threshold recommended by WHO.

One-way sensitivity analysis

The performed one-way sensitivity analysis identified that the change of ICER per gained QALY associated with Rd relative to BCT under the uncertainty of model variables ranged from a reduction of ¥113,549 under the number of VTD treatment cycles for ndMM to an increase of ¥301,353 under the 95% CI of the monthly risk of disease progression associated with PAD for ndMM. Among the model variables reducing the ICER per gained QALY associated with Rd, the treatment cycles and monthly risk of disease progression associated with BCT and the quality of life of ndMM patients under Rd treatment could reduce the ICER over ¥50,000. Among the model variables increasing the ICER per gained QALY associated with Rd, the monthly risk of disease progression under VTD regimen and PAD regiments and the treatment cycles of Rd in ndMM patients could increase the ICER per gained QALY for Rd versus BCT by over ¥50,000. The results of the one-way sensitivity analysis are illustrated in Figure 3. Additionally, the price of lenalidomide was expected to be changed in the future, the impact of reducing the price of lenalidomide on the cost–effectiveness was assessed. The cost–effectiveness of Rd relative to BCT for ndMM in Chinese patients was dominant when the price of lenalidomide was reduced by 20% or more (Figure 4).

Probabilistic sensitivity analysis

Based on the plotted distribution of the 10,000 ICERs from the Monte Carlo simulations, the median ICER associated with Rd was ¥32,294 per gained QALY with a 95% credible interval that ranged from -¥473,973 to ¥573,580. If taking one- to three-times the 2018 GDPPC as the cost–effectiveness thresholds, the cost–effectiveness proportions of Rd relative to BCT for ndMM in Chinese patients were 69.1, 84.9 and 90.8%, respectively. The cost–effectiveness acceptability curve associated with the two treatment scenarios under the cost–effectiveness threshold from one- to three-times of 2018 Chinese GDPPC is illustrated in Figure 5.

Discussion

The clinical efficacy of lenalidomide has been well studied for MM in the first-line treatment setting. The additional clinical and economic benefits associated with the oral administration route of lenalidomide were attractive to

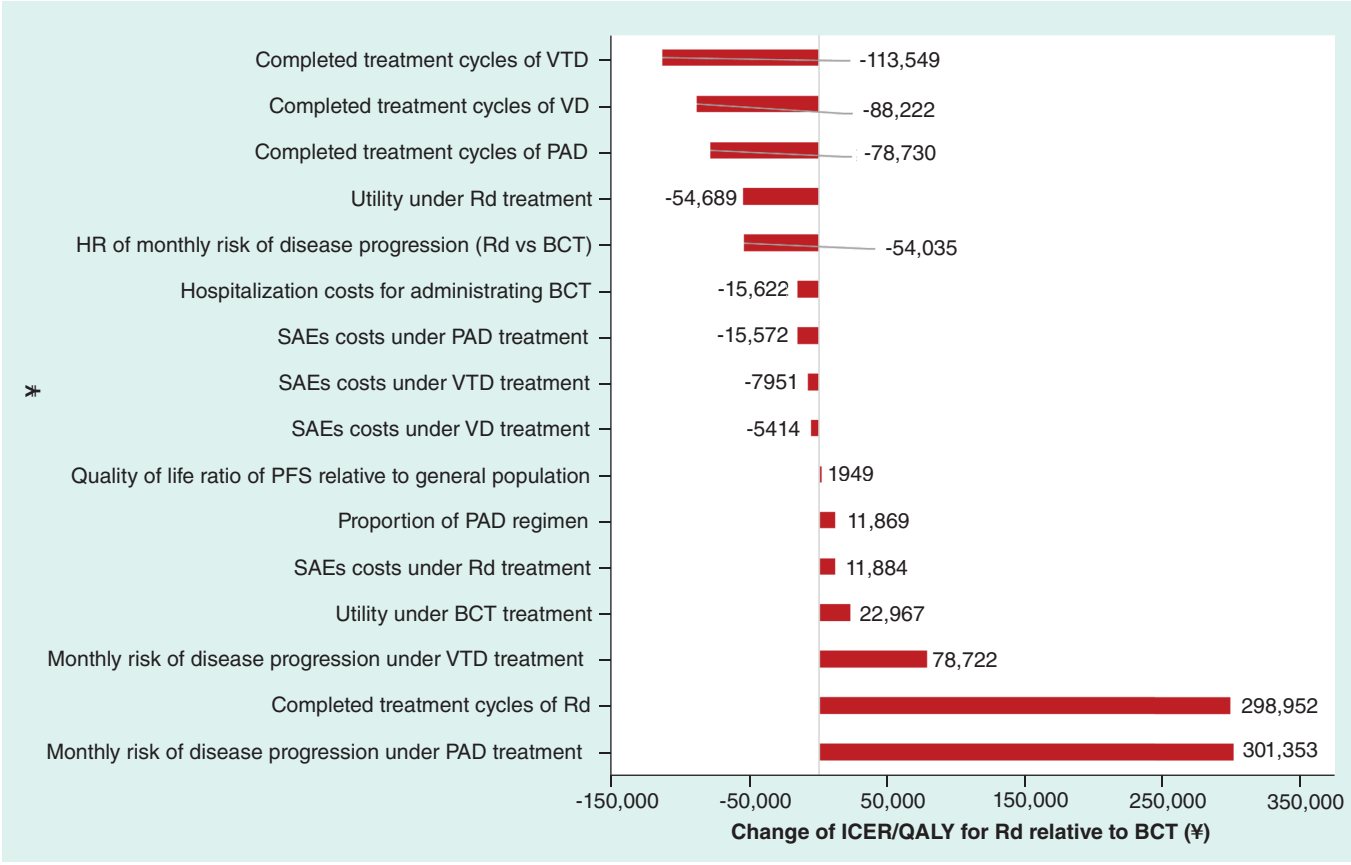

Figure 3. The impact of uncertainty of model variables on the changes of incremental cost–effectiveness ratio per gained quality-adjusted life years for lenalidomide combined with low dose dexamethasone versus bortezomib-contained therapy in Chinese newly diagnosed multiple myeloma patients ineligible for stem cell transplantation patients in the one-way sensitivity analysis.
BCT: Bortezomib-contained therapy; ICER: incremental cost–effectiveness ratio; ndMM: Newly diagnosed multiple myeloma but ineligible for stem cell transplantation; PAD: Bortezomib combined with adriamycin and dexamethasone; PFS: Progression-free survival; PDS: Progressive disease survival; QALY: Quality-adjusted life years; Rd: Lenalidomide combined with low dose dexamethasone; SAE: Serious adverse events; VD: Bortezomib combined with dexamethasone; VTD: Bortezomib combined with thalidomide and dexamethasone.

patients, physicians and reimbursement decision makers. Thus, Rd, the most common lenalidomide-contained treatment combination, has been widely recommended for ndMM in American, European and Chinese clinical guidelines. Since bortezomib was approved for MM much earlier in China, and BCT is the mainstay treatment regimen for ndMM in Chinese patients, BCT was selected as the comparator for Rd in the cost–effectiveness analysis. Based on the fully customized cost–effectiveness analysis for Chinese ndMM patients over a lifetime horizon, this study confirmed the more health benefits (measured by PFS, OS and QALY) and saved medical costs for the treatment administration and serious adverse events management associated with the Rd treatment scenario. However, the saved medical costs could not fully offset the increased drug acquisitions cost of lenalidomide because of its longer treatment duration. Thus, Rd was associated with more gained QALY and higher lifetime direct medical costs than BCT in Chinese ndMM patients, and the cost–effectiveness of Rd was highly attractive by having an ICER closed to the 2018 GDPPC, a third of the recommended cost–effectiveness threshold.

As an immunomodulator developed on the basis of thalidomide, the therapeutic effect of lenalidomide is further enhanced [75]. Because this study could not be found any randomized clinical trials with a common treatment arm for indirect comparison of the clinical efficacies of Rd and BCT, this study had to pool the survival outcomes, including PFS and OS, associated with the treatment arm of Rd and BCT separately to estimate the risk of disease progression and mortality associated with progressive disease using a single-arm meta-analysis approach. Since the patient baseline characteristics associated with ndMM patients in these randomized controlled trials were similar, the method used to estimate the model variables for the clinical efficacies of Rd and BCT should be associated with a minimal bias that could significantly impact the cost–effectiveness analysis. Based on the simulation in the

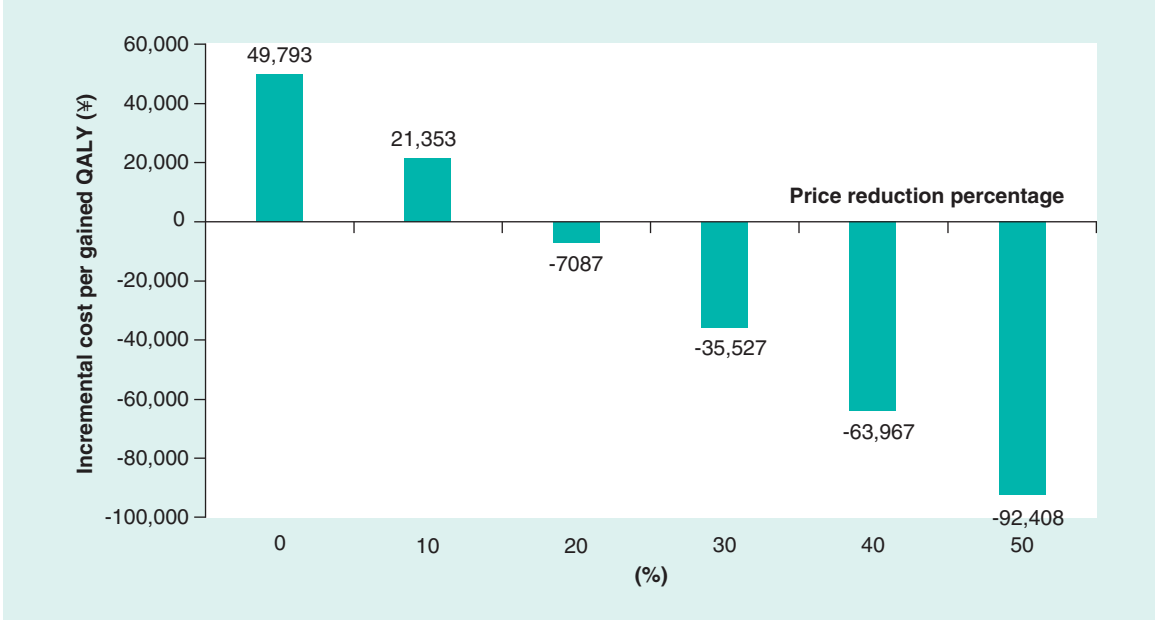

Figure 4. The impact of price change of lenalidomide on the cost–effectiveness of lenalidomide combined with low dose dexamethasone relative to bortezomib-contained therapy for newly diagnosed multiple myeloma patients ineligible for stem cell transplantation in Chinese patients.
BCT: Bortezomib-contained therapy; QALY: Quality-adjusted life years; Rd: Lenalidomide combined with low dose dexamethasone.

cost–effectiveness model, the Rd treatment scenario was associated with a 20% lower risk of disease progression than BCT. This result was highly consistent with a network meta-analysis that reported a hazard ratio of 0.778 for the risk of disease progression between Rd and bortezomib plus dexamethasone [76]. The superior efficacy of Rd for ndMM in the first-line treatment might have opposite effects on the survival of patients who progressed to rrMM in the cost–effectiveness analysis. When ndMM patients failed with the treatment in the first-line setting, these patients were unlikely to have sufficient response to the same treatment in the second-line setting. To factor this clinical scenario, this study did use the treatment-switch strategy for the rrMM treatments in the cost–effectiveness analysis. Thus, the superior effects of Rd over BCT for rrMM could favor the BCT treatment scenario in the cost–effectiveness analysis by increasing the OS of rrMM patients. However, this survival gain of Rd for rrMM was much less than the gained survival of Rd for ndMM in the first-line treatment setting. The Rd treatment scenario was associated with longer survival than the BCT scenario over the lifetime simulation in Chinese patients with ndMM. The estimated 5-year survival rates for Rd and BCT were 48.6 and 41.2%, respectively. The estimations of OS under the two treatment scenarios were comparable with the reported 5-year survival rate (about 50%) in the countries where bortezomib and lenalidomide were widely used and reimbursed for MM [5,6].

The superior efficacy of Rd over BCT also had a substantial impact on the direct medical costs in the cost–effectiveness analysis. Rd was recommended to treat patients until disease progression. Thus, the treatment duration of Rd was much longer than that for BCT, which was usually given to patients for fixed treatment cycles. Thus, estimated drug acquisition costs of Rd increased by 67.4% when compared with BCT in the cost–effectiveness analysis. Lenalidomide and dexamethasone are two oral administration drugs, and Chinese patients received them in outpatient settings. Different from Rd, bortezomib is given to patients in tertiary care hospital settings because of its intravenous administration route and the need for monitoring and managing adverse events. Thus, Rd could save medical costs for treatment administration when compared with BCT. Because the hospital resources, including hospital beds, medical services and utilities, are undercharged in the current Chinese healthcare system [77], the hospital costs in China were far lower than that in high-income countries. Thus, the saved hospital costs for treatment administration in this study had much less impact on the cost–effectiveness than in high-income countries. The Chinese healthcare security authorities are working on the correction of the undercharge of medical utilities and services. With the adjusted costs of medical utilities and services in the future, the oral administration of Rd is expected to save more medical costs and further improve the cost–effectiveness of Rd for ndMM.

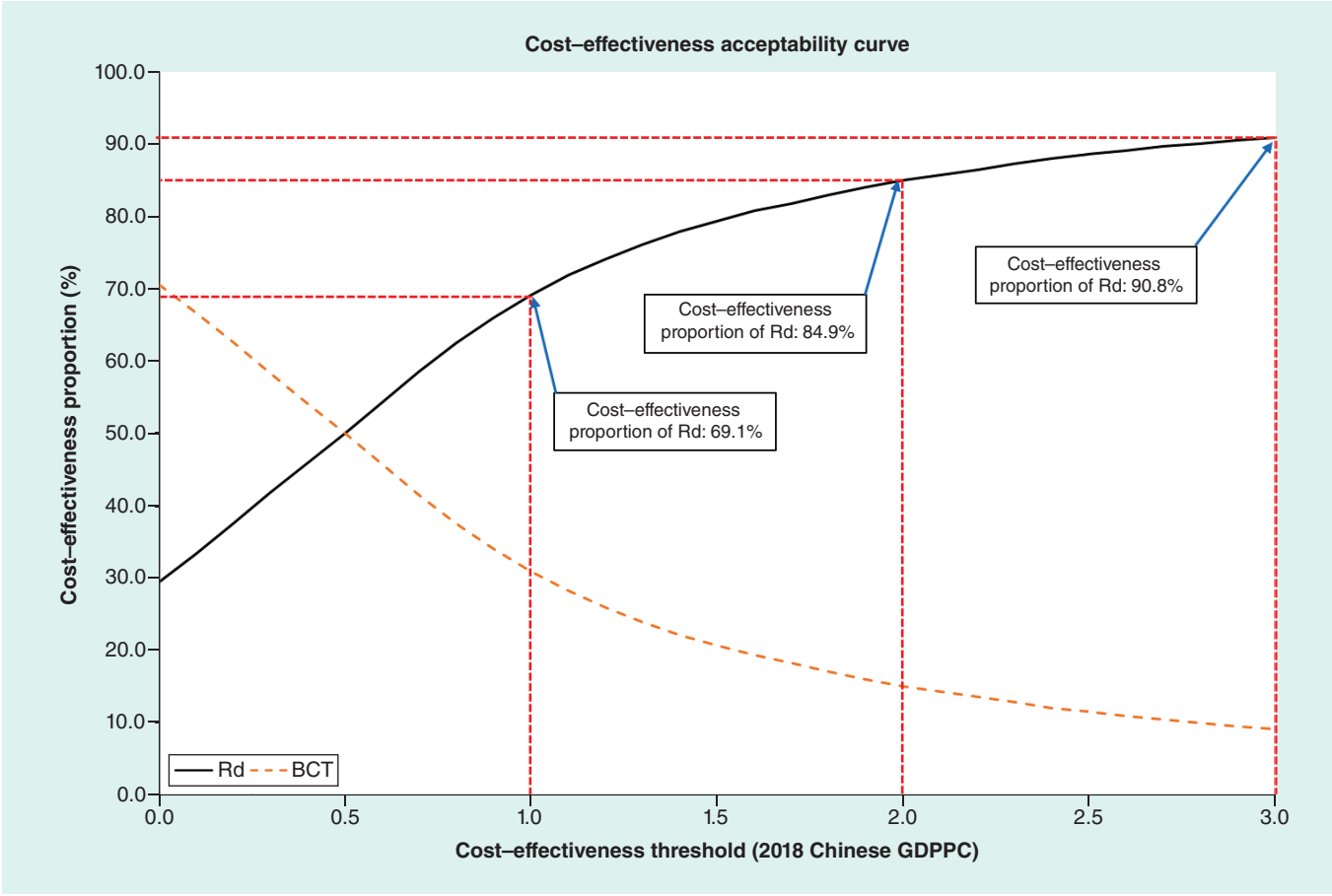

Figure 5. Cost–effectiveness acceptability curves associated with lenalidomide combined with low dose dexamethasone versus bortezomib-contained therapy for newly diagnosed multiple myeloma but ineligible for stem cell transplantation in Chinese patients under the willingness-to-pay of zero to three-times of 2018 Chinese gross domestic product per capita.
BCT: Bortezomib-contained therapy; GDPPC: Gross domestic product per capita; ndMM: Newly diagnosed multiple myeloma but ineligible for stem cell transplantation; Rd: Lenalidomide combined with low dose dexamethasone.

The point estimation of ICER per gained QALY for Rd relative to BCT in the base-case analysis was slightly lower than the 2018 Chinese GDPPC. According to the cost–effectiveness threshold recommendation of the Chinese health economic evaluation guideline, Rd is deemed to be highly cost effective for ndMM in Chinese patients when compared with BCT. However, the one-way sensitivity analysis observed very wide ranges of ICER associated with Rd under the uncertainty of model variables, such as treatment cycles and treatment effects associated with the two treatment scenarios. Since these model variables were estimated from randomized clinical trials, which were mainly conducted in high-income countries, the selection bias associated with study patients in those randomized clinical trials and the lack of treatment effects in Chinese patients indicated a need for future research to confirm these model variables in real-world ndMM patients in China. Even though the cost–effectiveness proportion of Rd was greater than 50% under the cost–effectiveness threshold of the 2018 Chinese GDPPC, the lack of distributions of key model variables for quality of life and medical costs suggested that real-world studies are needed to clarify the uncertainty associated with these model variables and confirm the cost–effectiveness of Rd relative to BCT for ndMM in Chinese patients. Additionally, the current reimbursement negotiation in China usually requires substantially lower drug prices, which could substantially impact the cost–effectiveness. Our one-way sensitivity analysis suggested that the cost–effectiveness of Rd was highly sensitive to the price of lenalidomide. Reducing the price of lenalidomide by 20% or more could make Rd dominate BCT.

This study was associated with several limitations that require caution when interpreting the findings of this cost–effectiveness analysis. First, the literature review identified over ten treatment regimens that contained bortezomib for ndMM. However, this study only identified randomized clinical trials assessing three BCT. Thus, future

real-world studies assessing the clinical effectiveness of BCT for ndMM are needed to further clarify the cost–effectiveness of Rd relative to other BCT treatments for ndMM in Chinese patients. Second, this study only assessed the cost–effectiveness of Rd relative to BCT for ndMM in Chinese patients. The approved and coming new novel agents are likely to impact the treatment landscape for MM in China. Thus, this study should be only limited to the interpretation of the cost–effectiveness of Rd relative to BCT, but not for any other new treatment regimens. Third, this study did not identify Chinese studies directly measuring the quality of life. The model utility variables were estimated from the quality of life studies that were conducted in high-income countries. Even though the utility model variables were adapted into Chinese patients after the adjustment, direct utility measurement in Chinese ndMM patients is still needed under the fact that the cost–effectiveness is sensitive to the utility. Fourth, this study assumed that the treatment in the ndMM setting was switched in the rrMM setting for better treatment response. However, Rd could be still used in the rrMM setting because the fragile patients were unlikely to tolerate BCT. Future real-world studies are needed to further clarify the patient treatment journey for more robust cost–effectiveness assessment. Finally, this study used bottom-up cost methods to estimate model variables for most medical costs (except the medical costs associated with rrMM). The real-world medical costs associated with drug acquisition costs, adverse events management, treatment administration of BCT and the management of PFS should be clarified for more accurate cost–effectiveness assessment.

Conclusion

In the context of overcoming the lack of data, this study made a rational use of existing literature evidence, combined with expert advice and reasonable model assumptions, to construct a cost–effectiveness model that simulated the lifetime health outcomes and medical costs of Rd and BCT in Chinese ndMM patients. The cost–effectiveness of Rd relative to BCT (including VD, PAD and VTD) was highly attractive with a point estimation of ICER per gained QALY slightly lower than the 2018 Chinese GDPPC. Considering the uncertainty and limitations associated with the estimations of model variables, real-world research is strongly needed to verify the model variables and confirm the attractive cost–effectiveness of Rd relative to BCT in Chinese ndMM patients.

Summary points

- Based on the existing clinical evidence, lenalidomide plus low dose dexamethasone (Rd) could be more effective than bortezomib-contained therapy (BCT) for ineligible for stem cell transplantation (ndMM) by gaining longer progression-free survival that was associated with a better quality of life.
- The oral administration of Rd could save medical costs for the administration when compared with BCT that was usually administrated in Chinese hospital settings. However, the saved medical costs for the administration associated with Rd could not completely offset the increased drug acquisition costs of longer Rd treatment and disease management costs associated with the extended survival.
- Relative to BCT, Rd could gain more health benefits and also increase medical costs in Chinese ndMM patients. The cost–effectiveness of Rd was highly attractive by having an ICER per gained QALY lower than the 2018 Chinese gross domestic products per capita.
- One-way sensitivity analyses suggested that the cost–effectiveness of Rd for ndMM was mainly driven by drug acquisition costs, treatment cycles and treatment efficacy associated with Rd and BCT.
- The uncertainty associated with the cost–effectiveness of Rd relative to BCT for ndMM in Chinese patients was modest as Rd was associated with 90.1% chance to be cost effective under the identified uncertainty of model variables.
- Future real-world studies are still needed to verify the model variables to confirm the robustness of the cost–effectiveness of Rd relative to BCT for ndMM in Chinese patients.

Author contributions

J Lu formulated research idea and developed the study protocol. W Chen constructed the model structure, identified the data sources for the estimations of model variables and conducted the cost–effectiveness analysis. J Lu and W Chen were fully involved with the development of this manuscript. The two authors critically reviewed the manuscript and approved the submission of this manuscript.

Financial & competing interests disclosure

This study was funded by BeiGene. W Chen owns a consulting firm that receives industry funds for health outcomes and economics research. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

1. Ferlay J, Soerjomataram I, Ervik M *et al.* GLOBOCAN 2012 v1. 0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11. 2013. International Agency for Research on Cancer Website (2014). http://globocan.iarc.fr
2. Gen CY, Chen WM. Supporting treatments on newly diagnosed MM patients with complications. *Leukemia Lymphoma* 12, 707–709 (2010).
3. Mai YJ, Li Y, Zou DH *et al.* Treatment response analysis of 206 patients with multiple myeloma. *Chinese J. Hematol.* 26(4), 193–196 (2005).
4. Kumar SK, Rajkumar SV, Dispenzieri A *et al.* Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 111(5), 2516–2520 (2008).
5. Palumbo A, Bringhen S, Larocca A *et al.* Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. *J. Clin. Oncol.* 32(7), 634–640 (2014).
6. Srivastava G, Rana V, Lacy MQ *et al.* Long-term outcome with lenalidomide and dexamethasone therapy for newly diagnosed multiple myeloma. *Leukemia* 27(10), 2062 (2013).
7. Moreau P, San Miguel J, Sonneveld P *et al.* Multiple myeloma: ESMO clinical practice guidelines. *Ann. Oncol.* 28(Suppl. 4), iv52–iv61 (2017).
8. Kumar SK, Callander NS, Alsina M *et al.* Multiple myeloma, version 3.2017, NCCN clinical practice guidelines in oncology. *JNCCN* 15(2), 230–269 (2017).
9. Chen HM. *The Clinical Significance of Serum Ferritin Levels in the Newly Diagnosed Multiple Myeloma*. Nanchang University, China (2016).
10. Cheng Y. *Clinical Significance of Absolute Lymphocyte Count in Newly Diagnosed Patients with Multiple Myeloma, 2015*. Ningxia Medical University, China (2015).
11. Deng P, Zhou YL, Wei YL *et al.* Prognostic Impact of 1q21 amplification in newly diagnosed multiple myeloma patients receiving bortezomib-based first-line treatment. *J. Exp. Hematol.* 6, 1696–1701 (2017).
12. Feng XY, Deng SH, An G *et al.* Clinical characteristics and survival of newly diagnosed multiple myeloma patients under 40 years old from single center and literature review. *Chinese J. Hematol.* 11, 933–936 (2015).
13. Gao SJ, Sun YH, Zhao HG. Clinical characteristics and chemotherapy efficacy in patients with newly diagnosed multiple myeloma: observation of 176 cases. *J. Leukemia Lymphoma* 9, 539–542 (2016).
14. Gu Y, Yuan YH, Shi QL *et al.* Efficacy and safety of CTD and PCD regimens in treatment of patients with newly diagnosed multiple myeloma. *Chinese J. Hematol.* 4, 279–284 (2017).
15. Guo SQ, Zhi YQ, Jin X *et al.* Efficacy comparision of thalidomide for 132 cases of newly diagnosed multiple myeloma with or without extramedullary disease. *J. Leukemia Lymphoma* 1, 53–56 (2013).
16. Li F, Xu Y, An G *et al.* The prognostic impact of 1p21 deletion on newly diagnosed multiple myeloma patients receiving thalidomide-based first-line treatment. *Chinese J. Hematol.* 10, 862–867 (2013).
17. Li H, Li Q, Cao Z *et al.* Peripheral blood absolute lymphocyte count, absolute monocyte count and their ratio in prognosis prediction of newly diagnosed multiple myeloma. *Tumor* 8, 865–872 (2017).
18. Li H, Li Q, Xu WG *et al.* Prognosis analysis of 68 newly diagnosed multiple myeloma patients 18F-FDG PET/CT. *Chinese J. Cancer Prev. Treat.* 2, 124–129 (2017).
19. Lu P, Song R, Wu LX *et al.* Analysis of auxiliary diagnostic test in 175 patients with multiple myeloma. *Int. J. Lab. Med.* 20, 3011–3012 (2015).
20. Wang QQ. *The Clinical Features and Prognostic Factors of 320 Newly Diagnosed Multiple Myeloma Cases*. Fujian Medical University, China (2016).
21. Yuan T, Guo SQ, Zhi YQ *et al.* Efficacy of radiotherapy for newly diagnosed multiple myeloma with extramedullary disease. *Chinese J. Clin. Oncol.* 13, 845–848 (2014).
22. Zhang JJ, Li Y. Clinical characteristics and efficacy analysis of newly diagnosed multiple myeloma patients with renal insufficiency. *J. China Med. Uni.* 6, 494–498 (2016).

23. Zhang PY, Chen YX, Cao XM *et al.* Observation of the treatment effects associated with bortezomib-contained therapy and its impact on IL-6 and iron-protein in newly diagnosed patients with multiple myeloma. *Shaanxi Med. J.* 11, 1511–1514 (2016).
24. Zou J, Sun LH, Meng YH *et al.* Efficacy and safety of modified PAD regimen in the treatment of primary multiple myeloma. *Chinese J. Clin. Med.* 6, 782–784 (2016).
25. Zheng YS, Yao YZ, Chen T *et al.* The efficacy observation of treatment of T-VAD Regimen in 68 cases of primary multiple myeloma. *Clin. Res. Practice* 5, 3–5 (2017).
26. Yang X, Wang XF, Lin ZH *et al.* The treatment effects of VCD and VDD in Chinese senior patients with newly diagnosed multiple myeloma. *Med. J. Commun.* 5, 497–499, 502 (2015).
27. Yang HH. Clinical characteristics and treatment effects in newly diagnosed multiple myeloma patients. *Cancer Res. Clin.* 5, 348–350 (2013).
28. Yan S, Fu ZZ, Ling M *et al.* Efficacy and prognosis of PAD combination therapy for fifty-six previously untreated patients with multiple myeloma. *Chinese J. Hematol.* 6, 520–522 (2016).
29. Zhang XJ, Zou SH, Li F *et al.* Efficacy and safety of PAD and VAD combined with thalidomide in the treatment of newly diagnosed multiple myeloma. *Chinese J. Clin. Med.* 5, 670–672 (2013).
30. Zhang YP, Wang XF. Treatment effects of VCD and VD in 51 patients with newly diagnosed multiple myeloma. *Chongqing Med.* 20, 2832–2834 (2016).
31. Zhou YN, Chen ZX, Zhang R *et al.* PDD regimen for the treatment of patients with initially diagnosed multiple myeloma. *Chinese J. Hemorheol.* 3, 373–375, 397 (2014).
32. Bao L, Huang XJ. Effect of weekly administration of bortezomib in chemotherapy regimen in treating newly diagnosed multiple myeloma. *China Med.* 2, 246–250 (2016).
33. Zeng TM, He HY, Shi HT *et al.* Response and prognosis of patients with multiple myeloma induced by PAD/TAD. *Nat. Med. J. China* 10, 731–735 (2015).
34. Dong LH, Yang PC, Dai CB. Treatment effects of bortezomib plus thalidomide and DEX in 30 patients with newly diagnosed multiple myeloma. *Herald Med.* 6, 746–748 (2015).
35. Dong YH, Xu FH, Zhao LJ. Contained-bortezomib BDT, BCD or BAD chemotherapy for newly diagnosed multiple myeloma. *Pract. J. Med. Pharm.* 4, 298–301 (2016).
36. Li MY, Zhou F, Liu JH. Clinical features of 124 patients with newly diagnosed multiple myeloma and their curative effect. *Clin. J. Med. Officers* 7, 711–713 (2013).
37. Liu ZS. Application of routine biochemical tests in patients with newly diagnosed multiple myeloma. *Contemp. Med.* 18, 65–66 (2013).
38. Wang ZF, Liu F, Li JH *et al.* Low-dose thalidomide combined with MP in the treatment of 32 multiple myeloma cases. *J. Modern Oncol.* 8, 1850–1851 (2013).
39. Sun C, Wang J, Guo HF *et al.* Influence of chromosome abnormality on therapeutic efficacy and prognosis of newly diagnosed multiple myeloma treated with bortezomib. *J. Exp. Hematol.* 1, 142–146 (2017).
40. Zhu XF, Wang AY, Cai XY. Efficacy and safety of pegylated liposomal doxorubicin in the treatment of newly diagnosed multiple myeloma. *Anhui Med. Pharm. J.* 2, 371–373 (2015).
41. Hong P. *Clinical Significance of Serum Free Light Chain Test in the First Onset of Multiple Myeloma*. Zhejiang University, China (2013).
42. Wang PF, Li YC, Xu Y *et al.* Role of whole-body diffusion weighted imaging (WB-DWI) in the diagnosis and monitoring of newly diagnosed multiple myeloma. *Chinese J. Hematol.* 2, 129–133 (2017).
43. Yu HY. *Efficacy and Safety of Bortezomib-Based Induction Treatment for Multiple Myeloma*. Jiangxi Medical College, Nanchang University, China (2017).
44. Lu YH. *Efficacy and Safety of Bortezomib-Based Combination Therapy in the Treatment of Newly Diagnosed Multiple Myeloma*. Fujian Medical University, China (2014).
45. Wu PQ, Jing L, Li XM. cost–effectiveness analysis of two chemotherapy regimens in the treatment of initially diagnosed multiple myeloma. *China Pharm.* 23, 3169–3172 (2015).
46. Gao S, Zhu B, Bai YX. Clinical analysis and treatment response of newly diagnosed multiple myeloma patients with renal insufficiency. *Food Drug* 6, 403–406, 407 (2015).
47. Li Q, Wu ZD, Zeng WQ *et al.* Clinical analysis of blood calcium in patients with newly diagnosed multiple myeloma. *Zhejiang Clin. Med. J.* 10, 1723–1724 (2015).
48. Chen Y. *The Clinical Analysis of Serum Calcium Levels of Newly Diagnosed Mutiple Myeloma Patients*. Chongqing Medical University, China (2013).
49. Zheng FY, Zhang XL, Wang CL. Association of peripheral ALC with clinical features and prognosis in newly diagnosed multiple myeloma patients. *J. Prac. Oncol.* 4, 352–355 (2017).

50. Chen R, Zhang X, Gao C *et al.* Treatment and prognostic factors for survival in newly diagnosed multiple myeloma patients with bortezomib and dexamethasone regimen: a single Chinese center retrospective study. *Cancer Manag. Res.* 9, 373–380 (2017).
51. Geng C, Liu N, Yang G *et al.* Retrospective analysis of 264 multiple myeloma patients. *Oncol. Lett.* 5(2), 707–713 (2013).
52. Lu J, Lu J, Chen W *et al.* Clinical features and treatment outcome in newly diagnosed Chinese patients with multiple myeloma: results of a multicenter analysis. *Blood Cancer J.* 4, e239–e239 (2014).
53. An N, Li X, Shen M *et al.* Analysis of clinical features, treatment response, and prognosis among 61 elderly newly diagnosed multiple myeloma patients: a single-center report. *World J. Surg. Oncol.* 13(1), 1–6 (2015).
54. Niesvizky R, Flinn IW, Rifkin R *et al.* Efficacy and safety of three bortezomib-based combinations in elderly, newly diagnosed multiple myeloma patients: results from all randomized patients in the community-based, Phase IIIb UPFRONT study. *Blood* 118(21), 478 (2011).
55. Xu SF, Bai H, Wang CB *et al.* Comparison of efficacy and safety between Bortezomib based therapy and routine chem-otherapy regimen on patients with newly diagnosed multiple myeloma. *J. Modern Oncol.* 11, 1585–1588 (2015).
56. Benboubker L, Dimopoulos MA, Dispenzieri A *et al.* Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N. Engl. J. Med.* 371(10), 906–917 (2014).
57. Durie BGM, Hoering A, Abidi MH *et al.* Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, Phase III trial. *Lancet* 389(10068), 519–527 (2017).
58. Gay F, Rajkumar SV, Jayabalan DS *et al.* Clarithromycin (Biaxin)-lenalidomide-low-dose dexamethasone (BIRD) versus lenalidomide-low-dose dexamethasone (RD) as initial therapy for newly diagnosed multiple myeloma. *Blood* 114(22), 2868 (2009).
59. Magarotto V, Bringhen S, Offidani M *et al.* Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. *Blood* 127(9), 1102–1108 (2016).
60. Acaster S, Gaugris S, Velikova G *et al.* Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer* 21(2), 599–607 (2013).
61. Ramsenthaler C, Osborne TR, Gao W *et al.* The impact of disease-related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study. *BMC Cancer* 16(1), 427 (2016).
62. Gries K, Fastenau J, Chen Y *et al.* Health-related quality of life in patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation: results from the ALCYONE trial. Presented at: *2018 ASCO Annual Meeting*, Chicago, IL, USA, 1–5 June 2018.
63. Delforge M, Dhawan R, Robinson D *et al.* Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs MP: results from the VISTA trial. *Eur. J. Haematol.* 89(1), 16–27 (2012).
64. Delforge M, Minuk L, Eisenmann JC *et al.* Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. *Haematologica* 100(6), 826–833 (2015).
65. Verelst S, Termorshuizen F, Uyl-De Groot C *et al.* Effect of thalidomide with melphalan and prednisone on health-related quality of life (HRQOL) in elderly patients with newly diagnosed multiple myeloma: a prospective analysis in a randomized trial (HOVON 49). *Haematologica* 96, S135 (2011).
66. Robinson D Jr, Orlowski RZ, Stokes M *et al.* Economic burden of relapsed or refractory multiple myeloma: results from an international trial. *Eur. J. Haematol.* 99(2), 119–132 (2017).
67. Fonseca R, Panjabi S, Campioni M *et al.* Economic evaluation of carfilzomib+lenalidomide+dexamethasone (krd) vs lenalidomide+dexamethasone (rd) in relapsed or refractory multiple myeloma (r/rmm). *Haematologica* 101, 526 (2016).
68. Luo N, Johnson JA, Shaw JW, Feeny D, Coons SJ. Self-reported health status of the general adult US population as assessed by the EQ-5D and Health Utilities Index. *Med. Care* 43(11), 1078–1086 (2005).
69. Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D.* Discussion Paper 172, Centre for Health Economics, The University of York, UK (1999).
70. Versteegh MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value Health* 19(4), 343–352 (2016).
71. Sun S, Chen J, Johannesson M *et al.* Population health status in China: EQ-5D results, by age, sex and socio-economic status, from the National Health Services Survey 2008. *Qual. Life Res.* 20(3), 309–320 (2011).
72. Proskorovsky I, Lewis P, Williams CD *et al.* Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual. Life Out.* 12(1), 35 (2014).
73. Hu SL, Lu J, Feng YF *et al.* cost–effectiveness analysis of lenalidomide combined with low-dose dexamethasone in the treatment of relapsed or refractory multiple myeloma. *China Health Insurance* 9, 51–57 (2017).
74. China guidelines for pharmacoeconomic evaluations. www.ispor.org/workpaper/ispor_comments/China
75. Kumar S, Rajkumar SV. Thalidomide and lenalidomide in the treatment of multiple myeloma. *Eur. J. Cancer* 42(11), 1612–1622 (2006).

76. van Beurden-Tan CH, Franken MG, Blommestein HM, Uyl-de Groot CA, Sonneveld P. Systematic literature review and network meta-analysis of treatment outcomes in relapsed and/or refractory multiple myeloma. *J. Clin. Oncol.* 35(12), 1312–1319 (2017).

77. Zhang H, Hu H, Wu C, Yu H, Dong H. Impact of China's public hospital reform on healthcare expenditures and utilization: a case study in ZJ Province. *PLoS ONE* 10(11), e0143130 (2015).