Research Article

Prognostic Significance of Blood Transfusion in Newly Diagnosed Multiple Myeloma Patients without Autologous Hematopoietic Stem Cell Transplantation

Liping Fan,1 Danhui Fu,1,2 Jinping Zhang,3 Haobo Huang,1 Qingqing Wang,2 Yamei Ye,2 and Qianling Xie4

1Department of Blood Transfusion, Fujian Medical University Union Hospital, Gulou District, Fuzhou City, Fujian Province 350001, China
2Department of Hematology, Fujian Medical University Union Hospital and Fujian Institute of Hematology, Gulou District, Fuzhou City, Fujian Province 350001, China
3Department of Blood Transfusion, Xiamen University Affiliated Fuzhou Second Hospital, Cangshan District, Fuzhou City, Fujian Province 350001, China
4Department of Anesthesia, Macare Women's Hospital in Quanzhou, Quanzhou City, Fujian Province 362000, China

Correspondence should be addressed to Haobo Huang; huanghaobo1981@163.com

Received 2 January 2017; Revised 16 March 2017; Accepted 4 April 2017; Published 8 May 2017

The aim of this study was to evaluate whether blood transfusions affect overall survival (OS) and progression-free survival (PFS) in newly diagnosed multiple myeloma (MM) patients without hematopoietic stem cell transplantation. A total of 181 patients were enrolled and divided into two groups: 68 patients in the transfused group and 113 patients in the nontransfused group. Statistical analyses showed that there were significant differences in ECOG scoring, Ig isotype, platelet (Plt) counts, hemoglobin (Hb) level, serum creatinine (Scr) level, and \( \beta_2 \)-microglobulin (\( \beta_2 \)-MG) level between the two groups. Univariate analyses showed that higher International Staging System staging, Plt counts < \( 100 \times 10^9 \)/L, Scr level \( \geq 177 \mu \text{mol/L} \), serum \( \beta_2 \)-MG \( \geq 5.5 \mu \text{mol/L} \), serum calcium (Ca) \( \geq 2.75 \text{mmol/L} \), and thalidomide use were associated with both OS and PFS in MM patients. Age \( \geq 60 \) was associated with OS and Ig isotype was associated with PFS in MM patients. Moreover, blood transfusion was associated with PFS but not OS in MM patients. Multivariate analyses showed that blood transfusion was not an independent factor for PFS in MM patients. Our preliminary results suggested that newly diagnosed MM patients may benefit from a liberal blood transfusion strategy, since blood transfusion is not an independent impact factor for survival.

1. Introduction

Blood transfusion is an important therapeutic tool for patients with critical or malignant diseases. In the last several decades, many studies have shown that blood transfusion improves abnormalities in levels of blood components and increases patients’ ability to tolerate therapy, but short-term and long-term adverse effects have also been reported [1]. Several studies showed that components of transfused blood contain several factors that are important for the survival of tumor cells or perturb the recipient’s immune system such as VEGF, PDGF-D, tissue plasminogen activator, TGF-\( \beta \), IL-2, IFN-\( \gamma \), and IL-10 [2]. In clinical studies, the effects of blood transfusion on survival in patients with solid tumors remain controversial [3–7].

In hematological malignancies, few studies have examined the relationship between blood transfusion and short-term or long-term adverse effects [8–10]. Jaime-Pérèz et al. found that, in children with acute lymphoblastic leukemia (ALL), the number of blood products transfused correlated with poor survival, which may also reflect the severity of the disease [10]. In contrast, Alkayed et al. showed that blood transfusion did not correlate with overall survival (OS) or event-free survival (EFS) in children with ALL [8]. To date,
we have not found any studies elucidating the relationship between blood transfusion and survival in patients with multiple myeloma (MM).

In the current study, we reviewed the medical records and follow-up data of newly diagnosed patients with MM in our single center to assess the correlation between blood transfusion on OS and progression-free survival (PFS) of newly diagnosed patients with MM without ASCT.

2. Materials and Methods

2.1. Ethics Statement. This study was approved by the ethics committee of Fujian Medical University Union Hospital. As this study was retrospective, written informed consent from patients was not sought.

2.2. Study Design. A total of 181 newly diagnosed patients with MM without ASCT who had complete follow-up data between June 2010 and June 2015 at our hospital were included in this study.

2.3. Acquisition and Definition of Data. In this study, data were collected from the medical records of newly diagnosed patients with MM without ASCT from June 2010 to June 2015 at Fujian Medical University Union Hospital, Fujian, China. Patients who did not receive any therapeutic regimen or received ASCT or those without complete follow-up data were excluded.

Diagnosis and clinical event end points, such as disease progression and relapse, were evaluated by use of the International Myeloma Working Group criteria. OS was measured from the date of diagnosis to the date of death or last follow-up. Death from all causes was included. PFS was measured from the date on which the patient started treatment to the date of disease progression, relapse, or death, whichever came first. Survival time was measured until 31 December 2015.

Patients that received more than 2 units of packed red blood cells (RBC) and/or more than 1 unit of apheresis platelets (Plt) and/or more than 15 mL/kg of fresh frozen plasma (FFP) during induction, consolidation, and maintenance therapy were categorized as blood transfusion group. All blood products were leukocyte-reduced (leukocyte number < 5 × 10⁵). The storage duration of RBC units ranged from 7 days to 21 days. The storage duration of Plt units and FFP was limited to 5 days and one year, respectively. The decisions to transfuse in patients with MM were made based on the treating doctors’ judgment and guided by our hospital's technical manual of clinical blood transfusion [1]. Technical manuals of clinical blood transfusion in our hospital were listed briefly as follows: the RBC transfusion threshold is 60 g/L of hemoglobin, the plasma transfusion threshold is 1.3 times the upper limit of normal or 1.5 times the midpoint of the reference range in standard coagulation screening tests, and the prophylactic Plt transfusion threshold is 10 × 10⁹/L.

2.4. Statistical Analyses. Demographic and clinicopathological characteristics were compared between the blood transfusion group and the no-blood transfusion group using the chi-squared test for categorical variables and independent t-test for continuous variables. The Kaplan-Meier method was used to calculate survival for PFS and OS, and the log-rank test was used to analyze the significance of differences among these survival curves. Cox regression models were performed for multivariate analyses with adjustments for characteristics that might be significant prognostic factors according to the univariate analyses. All statistical analyses were performed using SPSS 19.0 software. Two-sided P values of <0.05 were used as the criterion for statistical significance.

3. Results

3.1. Characteristics of Transfused and Nontransfused Groups. A total of 181 newly diagnosed inpatients with MM without ASCT were included. The median follow-up interval of all patients was 20.03 (range from 0.3 to 66.73) months. During the follow-up period, 79 deaths occurred.

The demographic and clinicopathological characteristics of all patients before treatment are listed in Table 1. Of the 181 inpatients, 68 patients (37.57%) received a blood transfusion and 113 patients (62.43%) did not. Erythropoiesis-stimulating agents (ESAs) were not used in all 181 patients. The transfused patients had higher ECOG scores, lower platelet (Plt) counts, lower hemoglobin (Hb) levels, higher serum creatinine (Scr) levels, and higher serum β₂-microglobulin (β₂-MG) levels than nontransfused patients. There was a significant difference in Ig isotype between transfused and nontransfused patients. In the therapeutic regimens that followed their diagnosis, the patients in the transfused group received more bortezomib than nontransfused patients. There were no significant differences in age, gender, ISS staging, serum albumin (Alb) level, serum lactate dehydrogenase (LDH) level, serum calcium (Ca) level, or thalidomide use between the two groups (Table 1).

3.2. Univariate and Multivariate Analyses. Univariate analyses showed that, in all 181 patients without ASCT, patients with age ≥ 60, higher ISS staging, Plt counts < 100 × 10⁹/L, Scr level ≥ 177 μmol/L, serum β₂-MG ≥ 5.5 μmol/L, or serum Ca ≥ 2.75 mmol/L had shorter OS than others in the cohort. Patients who received thalidomide had longer OS. Blood transfusion was not associated with OS in patients with MM (Table 2, Figure 1(a)).

With respect to PFS in all 181 patients without ASCT, patients with higher ISS staging, Plt counts < 100 × 10⁹/L, Scr level ≥ 177 μmol/L, serum β₂-MG ≥ 5.5 μmol/L, and serum Ca ≥ 2.75 mmol/L and those who received a blood transfusion had shorter PFS. Patients who were treated with thalidomide had longer PFS. Additionally, Ig isotype was associated with PFS (Table 2, Figure 1(b)).

Multivariate analyses showed that age ≥ 60, Plt counts < 100 × 10⁹/L, serum Ca ≥ 2.75 mmol/L, and thalidomide treatment were independent prognostic factors for OS in patients with MM. Moreover, Ig isotype and thalidomide application were independent prognostic factors for PFS in patients with MM (Table 3).
Table 1: Demographic and clinicopathological characteristics of MM patients before treatment.

| Characteristic   | Transfused (n = 68) (%) | Nontransfused (n = 113) (%) | P      |
|------------------|-------------------------|----------------------------|--------|
| Age              |                         |                            |        |
| ≥60              | 40 (58.8)               | 60 (53.1)                  | 0.537  |
| <60              | 28 (41.2)               | 53 (46.9)                  |        |
| Gender           |                         |                            |        |
| Male             | 38 (55.9)               | 76 (67.3)                  | 0.153  |
| Female           | 30 (44.1)               | 37 (32.7)                  |        |
| Ig isotype       |                         |                            |        |
| IgG              | 40 (58.8)               | 57 (50.4)                  |        |
| IgA              | 18 (26.5)               | 29 (25.7)                  | 0.208  |
| Light chain      |                         |                            |        |
| Others           | 0 (0)                   | 6 (5.3)                    |        |
| ISS staging      |                         |                            |        |
| I               | 5 (7.4)                 | 26 (23.0)                  |        |
| II              | 31 (45.6)               | 55 (48.7)                  | 0.006  |
| III             | 32 (47.0)               | 32 (28.3)                  |        |
| ECOG            |                         |                            |        |
| 0–1             | 52 (76.5)               | 101 (89.4)                 | 0.020  |
| 2–4             | 16 (23.5)               | 12 (10.6)                  |        |
| Pt (×10⁹/L)     |                         |                            |        |
| ≥100            | 52 (76.5)               | 104 (92.0)                 | 0.003  |
| <100            | 16 (23.5)               | 9 (8.0)                    |        |
| Hb (g/L)        |                         |                            |        |
| ≥100            | 6 (8.8)                 | 49 (43.4)                  | 0.000  |
| <100            | 62 (91.2)               | 64 (56.6)                  |        |
| Scr (μmol/L)    |                         |                            |        |
| ≥177            | 24 (35.3)               | 15 (13.3)                  | 0.001  |
| <177            | 44 (64.7)               | 98 (86.7)                  |        |
| Serum Alb (g/L) |                         |                            |        |
| ≥35             | 13 (19.1)               | 36 (31.9)                  | 0.062  |
| <35             | 55 (80.9)               | 77 (68.1)                  |        |
| Serum β2-MG (μmol/L) |                   |                            |        |
| ≥5.5            | 32 (47.0)               | 32 (28.3)                  | 0.011  |
| <5.5            | 36 (53.0)               | 81 (71.7)                  |        |
| Serum LDH (IU/L) |                         |                            |        |
| ≥245            | 14 (20.6)               | 14 (12.4)                  | 0.140  |
| <245            | 54 (79.4)               | 99 (87.6)                  |        |
| Serum Ca (mmol/L) |                       |                            |        |
| ≥2.75           | 11 (16.2)               | 10 (8.8)                   | 0.136  |
| <2.75           | 57 (83.8)               | 103 (91.2)                 |        |
| Bortezomib      |                         |                            |        |
| Yes             | 51 (75.0)               | 60 (53.1)                  | 0.003  |
| No              | 17 (25.0)               | 53 (46.9)                  |        |
| Thalidomide     |                         |                            |        |
| Yes             | 54 (79.4)               | 90 (79.6)                  | 0.970  |
| No              | 14 (20.6)               | 23 (20.4)                  |        |

Ig: immunoglobulin; ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group; Pt: platelet; Hb: hemoglobin; Scr: serum creatinine; Alb: albumin; β2-MG: β2-microglobulin; LDH: lactate dehydrogenase; Ca: calcium.

4. Discussion

MM is an incurable plasma cell disease characterized by the proliferation of malignant monoclonal plasma cells in the bone marrow and accounts for 10% of hematological malignancies. This proportion is expected to increase because of the aging population [11]. Inhibition of hematopoietic function in the bone marrow induced by the proliferation of malignant monoclonal plasma cells and treatment with chemotherapy increased the likelihood of requiring a blood transfusion. Therefore, blood transfusion is an important component of MM therapy.

Several studies have shown that stored blood contains factors that may regulate immune cells, leading to immunosuppression, or promote the survival of tumor cells [2]. However, the effect of blood transfusion on the survival of patients with malignant diseases remains controversial [3–8, 10]. In the solid tumor literature, several studies found that red blood cell transfusion is an independent poor prognostic factor for survival in patients with cancer of the digestive, urinary, or respiratory systems [3, 5, 6, 12–15]. However, others reported that blood transfusion does not affect survival in patients with gastric or renal cell cancer [4, 7]. The effects of transfusion are equally unclear in patients with hematological malignancies [8, 10], such as acute lymphoblastic leukemia as above. Prior to this work, there were no reports on the impact of blood transfusion on survival in patients with MM.

Since ASCT may increase the requirement for blood transfusion, we included 181 newly diagnosed patients with MM who had complete follow-up data and who did not undergo...
ASCT. Thirty-two newly diagnosed patients with complete follow-up data were excluded because they underwent ASCT. In the current study, we found that, for patients with MM without ASCT, age ≥ 60, higher ISS staging, Plt counts < 100 × 10^9/L, Scr level ≥ 177 μmol/L, serum β2-MG ≥ 5.5 μmol/L, serum Ca ≥ 2.75 mmol/L, and the use of thalidomide were correlated with OS, whereas blood transfusion was not associated. In contrast, blood transfusion was associated with PFS in patients with MM without ASCT, as were higher ISS staging, Plt counts < 100 × 10^9/L, Scr level ≥ 177 μmol/L, serum β2-MG ≥ 5.5 μmol/L, serum Ca ≥ 2.75 mmol/L, and treatment with thalidomide.

Multivariate analysis showed that blood transfusion is not an independent prognostic factor for PFS in patients with MM without ASCT. After analyzing the characteristics of our cohort, we concluded that, compared with the group of patients who did not require transfusion, higher ISS staging, lower Hb and Plt levels, and renal dysfunction in blood transfusion group led to the requirement for blood transfusion and the lower PFS. Meanwhile, the negative effect of blood transfusion on survival in patients with MM was attenuated by the benefit of bortezomib usage, causing there to be no significant difference in OS between the group that received transfusions and the group that did not. This argument is strengthened by the finding that bortezomib was used at a higher rate in the transfused group than in the nontransfused group, and survival in patients with MM without ASCT is significantly improved by bortezomib [16]. However, lack of data of some important prognostic factors such as fluorescence in situ hybridization (FISH) or cytogenetics in our cohort may influence the results of univariate and multivariate survival analysis. Moreover, hematopoietic failure induced by bortezomib usage may lead to higher transfusion needs, which may influence the analysis of the relationship between blood transfusion and survival in MM patients.

Blood transfusion is an important therapeutic method for patients with MM who are receiving chemotherapy. Hypoxia induced by severe anemia may decrease patients’ tolerance to chemotherapy, influence the cytotoxic effect of some drugs such as cyclophosphamide and doxorubicin, and reduce the sensitivity of tumor cells to chemotherapeutics [17]. Meanwhile, protein in plasma may act as a drug carrier and may also influence the metabolism and cytotoxicity of drugs in vivo [18, 19]. Currently, the guidelines regarding thresholds for blood transfusion, including RBC, differ by country. In China, the RBC transfusion threshold is 60 g/L of hemoglobin in nonsurgical patients and 70 g/L of hemoglobin in surgical patients. However, in the United States, a threshold of 70 to 80 g/L of hemoglobin is recommended for patients without underlying cardiac disease, and a threshold of 80 g/L of hemoglobin or less is recommended for patients with underlying cardiac disease [1]. In American and Chinese guidelines, the patient’s clinical situation and response to anemia should be taken into account in the decision-making process.

### Table 2: Univariate analysis of the correlation between demographic and clinicopathological characteristics and survival time in patients with MM.

| Characteristics | n | OS (mean) | PFS (mean) |
|-----------------|---|-----------|------------|
| Age | ≥60 | 100 | 20.355 | 16.935 |
| | <60 | 81 | 28.233 | 20.102 |
| Gender | Male | 114 | 23.614 | 18.836 |
| | Female | 67 | 24.333 | 17.897 |
| Ig isotype | Light chain | 31 | 21.914 | 18.971 |
| | Others | 6 | 51.645 | 33.772 |
| ISS staging | II | 86 | 28.490 | 21.231 |
| | III | 64 | 15.161 | 11.796 |
| | IV | 1 | 29.096 | 22.806 |
| ECOG | 0-1 | 153 | 25.098 | 18.830 |
| | 2-4 | 28 | 17.230 | 14.531 |
| Plt (×10^9/L) | ≥100 | 156 | 25.251 | 19.403 |
| | <100 | 25 | 15.327 | 10.440 |
| Hb (g/L) | ≥100 | 55 | 22.732 | 21.187 |
| | <100 | 126 | 26.311 | 16.846 |
| Scr (μmol/L) | ≥177 | 39 | 13.888 | 10.382 |
| | <177 | 142 | 26.625 | 20.302 |
| Serum Alb (g/L) | ≥35 | 49 | 25.292 | 20.049 |
| | <35 | 132 | 23.357 | 17.465 |
| Serum β2-MG (μmol/L) | ≥5.5 | 64 | 15.161 | 11.796 |
| | <5.5 | 117 | 28.650 | 21.648 |
| Serum LDH (IU/L) | ≥245 | 28 | 18.717 | 14.700 |
| | <245 | 153 | 24.826 | 18.799 |
| Serum Ca (mmol/L) | ≥2.75 | 21 | 13.268 | 11.910 |
| | <2.75 | 160 | 25.273 | 18.986 |
| Bortezomib | Yes | 111 | 24.816 | 18.957 |
| | No | 70 | 22.398 | 16.909 |
| Thalidomide | Yes | 144 | 26.712 | 20.368 |
| | No | 37 | 12.860 | 9.590 |
| Blood transfusion | Yes | 68 | 22.376 | 14.998 |
| | No | 113 | 24.786 | 20.070 |

### Table 3: Multivariate analysis of the correlation between demographic and clinicopathological characteristics and survival time in patients with MM.

| Covariates | Overall survival | Progression-free survival |
|------------|-----------------|---------------------------|
| | 95% CI for HR | P | 95% CI for HR | P |
| Age | 1.005–1.038 | 0.011 | N/A | N/A |
| Ig isotype | N/A | N/A | 0.659–0.957 | 0.015 |
| ISS staging | 0.697–1.661 | 0.740 | 0.694–1.648 | 0.761 |
| Plt (×10^9/L) | 0.369–0.939 | 0.026 | 0.409–1.084 | 0.102 |
| Scr (μmol/L) | 0.977–2.453 | 0.063 | 0.975–2.501 | 0.063 |
| β2-MG (μmol/L) | 0.665–2.524 | 0.447 | 0.849–3.244 | 0.138 |
| Ca (mmol/L) | 1.172–3.389 | 0.011 | 0.838–2.729 | 0.205 |
| Thalidomide | 0.277–0.612 | 0.000 | 0.286–0.641 | 0.000 |
| Blood transfusion | N/A | N/A | 0.735–1.453 | 0.849 |

ISS: International Staging System; Scr: serum creatinine; β2-MG: β2-microglobulin; Ca: calcium; HR: hazard ratio; CI: confidence interval; N/A: not available.
decision to transfuse RBC. Similar problems exist with transfusion of other blood products. In our study, though blood transfusion was associated with decreased PFS in patients with MM, it was not an independent negative factor for PFS and OS. Due to the lack of much important data, such as FISH or cytogenetics, relevant to MM patients’ prognosis in our cohort, effect of bortezomib on survival and blood transfusion, and the indefinite effects of blood transfusion on survival in patients with tumors [3–7], we think that a prospective study including MM patients who have sufficient data of clinical characteristics and more comparable therapy is needed to evaluate the effects of blood transfusion on MM patients, in order to develop a liberal or restricted transfusion strategy used for decisions about blood transfusion in patients with MM.

In recent years, some studies showed that usage of ESAs could increase the hemoglobin level of MM patients with good tolerance during chemotherapy and might lead to the reduction of RBC transfusion [20, 21]. So, ESAs are recommended as an adjunct to transfusions or alternative in MM therapy to increase the patients’ tolerance to chemotherapy and decrease the consumption of blood products.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Acknowledgments**

This study was funded by the Joint Funds for the Innovation of Science and Technology of Fujian Province (Fuzhou, China; Grant no. 2016Y9027), Qihang Foundation of Fujian Medical University (Fuzhou, China; Grant no. 2016QH035), the Natural Science Foundation of Fujian Province (Fuzhou, China; Grants nos. 2016J01461 and 2017J01334), and the Medical Elite Cultivation Program of Fujian Province (Fuzhou, China; Grant no. 2015-ZQN-JC-18).

**References**

[1] K. F. Mark, J. G. Brenda, D. H. Christopher, and M. W. Connie, Technical Manual, 18th Edition, AABB, Bethesda, Md, USA, 2014.

[2] J. P. Cata, H. Wang, V. Gottumukkala, J. Reuben, and D. I. Sessler, "Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions," *British Journal of Anaesthesia*, vol. 110, no. 5, pp. 690–701, 2013.

[3] M. Elmi, A. Mahar, D. Kagedan et al., "The impact of blood transfusion on perioperative outcomes following gastric cancer resection: an analysis of the American College of Surgeons National Surgical Quality Improvement Program database," *Canadian Journal of Surgery*, vol. 59, no. 5, pp. 322–329, 2016.

[4] Y. H. Park, Y.-J. Kim, S. H. Kang et al., "Association between perioperative blood transfusion and oncologic outcomes after curative surgery for renal cell carcinoma," *Journal of Cancer*, vol. 7, no. 8, pp. 965–972, 2016.

[5] M. H. Squires, D. A. Kooby, G. A. Poultsides et al., "Effect of perioperative transfusion on recurrence and survival after gastric cancer resection: a 7-institution analysis of 765 patients from the US gastric cancer collaborative," *Journal of the American College of Surgeons*, vol. 221, no. 3, article 7935, pp. 767–777, 2015.
[6] W. Sui, I. C. Onyeji, J. T. Matulay et al., “Perioperative blood transfusion predicts short-term morbidity after nephrectomy,” Canadian Journal of Urology, vol. 23, no. 4, pp. 8348–8355, 2016.

[7] H.-Y. Zhou, W. Yu, J. Wang, J. Zhang, W.-J. Wang, and Z.-Q. Hu, “Association of perioperative allogeneic blood transfusions and prognosis of patients with gastric cancer after curative gastrectomy,” American Journal of Surgery, vol. 208, no. 1, pp. 80–87, 2014.

[8] K. Alkayed, A. A. Hmood, and F. Madanat, “Prognostic effect of blood transfusion in children with acute lymphoblastic leukemia,” Blood Research, vol. 48, no. 2, pp. 133–138, 2013.

[9] Y. Gu, L. J. Estcourt, M. Trivella, S. Hopewell, and P. Vyas, “Comparison of a restrictive versus liberal red cell transfusion policy for patients with myelodysplasia, aplastic anemia, and other congenital bone marrow failure disorders,” Cochrane Database of Systematic Reviews, vol. 3, 2015.

[10] J. C. Jaime-Pérez, P. R. Colunga-Pedraza, and D. Gómez-Almaguer, “Is the number of blood products transfused associated with lower survival in children with acute lymphoblastic leukemia?” Pediatric Blood and Cancer, vol. 57, no. 2, pp. 217–223, 2011.

[11] J. Liu, J. Lu, W. Chen, Y. Huo, X. Huang, and J. Hou, “Clinical features and treatment outcome in newly diagnosed Chinese patients with multiple myeloma: results of a multicenter analysis,” Blood Cancer Journal, vol. 4, no. 8, article e239, 2014.

[12] C. T. Aquina, N. Blumberg, A. Z. Becerra et al., “Association among blood transfusion, sepsis, and decreased long-term survival after colon cancer resection,” Annals of Surgery, 2016.

[13] D. Reim, A. N. Strobl, C. Buchner et al., “Perioperative transfusion of leukocyte depleted blood products in gastric cancer patients negatively influences oncologic outcome: a retrospective propensity score weighted analysis on 610 curatively resected gastric cancer patients,” Medicine, vol. 95, no. 29, Article ID e4322, 2016.

[14] M. Rink, A. Soave, R. Dahlem et al., “Impact of perioperative allogeneic blood transfusion on survival after radical nephroureterectomy for upper tract urothelial carcinoma,” Clinical Genitourinary Cancer, vol. 14, no. 1, pp. 96–104, 2016.

[15] T. Wang, L. Luo, H. Huang et al., “Perioperative blood transfusion is associated with worse clinical outcomes in resected lung cancer,” Annals of Thoracic Surgery, vol. 97, no. 5, pp. 1827–1837, 2014.

[16] C. T. Kouroukis, F. G. Baldassarre, A. E. Haynes, K. Imrie, D. E. Reece, and M. C. Cheung, “Bortezomib in multiple Myeloma: a practice guideline,” Clinical Oncology, vol. 26, no. 2, pp. 110–119, 2014.

[17] K. Ghattass, R. Assah, M. El-Sabban, and H. Gali-Muhtasib, “Targeting hypoxia for sensitization of tumors to radio- and chemotherapy,” Current Cancer Drug Targets, vol. 13, no. 6, pp. 670–685, 2013.

[18] F. Liu, J. Mu, and B. Xing, “Recent advances on the development of pharmacotherapeutic agents on the basis of human serum albumin,” Current Pharmaceutical Design, vol. 21, no. 14, pp. 1866–1888, 2015.

[19] D. Sleep, “Albumin and its application in drug delivery,” Expert Opinion on Drug Delivery, vol. 12, no. 5, pp. 793–812, 2015.

[20] J. Kurtz, P. Soubeyran, M. Michallet, E. Luporsi, and H. Albrand, “Biosimilar epoetin for the management of chemotherapy-induced anemia in elderly patients,” OncoTargets and Therapy, vol. 9, pp. 6689–6693, 2016.

[21] C. Losem, M. Koenigsmann, and C. Rudolph, “Biosimilar Retacrit® (epoetin zeta) in the treatment of chemotherapy-induced symptomatic anemia in hematology and oncology in Germany (ORHEO)—non-interventional study,” OncoTargets and Therapy, vol. 10, pp. 1295–1305, 2017.