Original Study

Revised International Staging System Applied to Real World Multiple Myeloma Patients

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Abstract

Recently, the Revised International Staging System (RISS) was introduced for clinical use and is being adopted by the International Myeloma Working Group. The RISS was developed using data from patients enrolled in clinical trials. To assess the effect of RISS in real world patients, we studied 381 patients with newly diagnosed multiple myeloma and confirmed the role of RISS in unselected nonclinical trial patients.

Background: A variety of validated prognostic markers for multiple myeloma has been described to help inform clinical practice. Recently, a robust system has been introduced for clinical use and is being adopted by the International Myeloma Working Group Revised International Staging System (RISS). The RISS was developed using data from patients enrolled in clinical trials. Consequently, its utility is less clear in unselected patients with myeloma. **Materials and Methods:** All consecutive patients newly diagnosed with multiple myeloma treated and followed up at Tom Baker Cancer Center from January 2004 to October 2015 were included in the present study. A total of 381 consecutive patients were identified and retrospectively classified as having RISS I, II, and III. **Results:** RISS I exhibited a median overall survival and progression-free survival of not reached and 38.9 months compared with 77.9 and 26.9 months and 29.9 and 15.3 months for RISS II and III, respectively. These results correlated well with those seen in the International Staging System (ISS). Multivariate analysis showed that age $>$ 65 years, ISS stage III, abnormal lactate dehydrogenase and high-risk chromosomal abnormalities by fluorescence in situ hybridization [t(4:14), deletion 17p, and t(14;16)] are independent prognostic factors for overall survival and progression-free survival, and β_2-microglobulin $\geq$ 5.5 mg/L, C-reactive protein $>$ 20 mg/L, and creatinine $>$ 200 μmol/L are not. **Conclusion:** We have confirmed the role of RISS in unselected nonclinical trial patients and suggest that increased serum lactate dehydrogenase and high-risk cytogenetics are very robust prognosticators when combined with the ISS.

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Introduction

Multiple myeloma (MM) is a very heterogeneous disease with a wide variation in survival.[1] It has been recognized that the prognosis is related to both patient factors and tumor variables.[2] The most widely applied prognostic system in myeloma is the International Staging System (ISS), which segregates patients into 3 different groups according to the levels of serum albumin and β_2-microglobulin.[3] The combination of these 2 factors provided the simplest and most powerful and reproducible stage classification.[3] Since then, attempts have been made to improve this system by identifying intrinsic tumor genetic characteristics associated with short survival.[4,5] In particular, interphase fluorescence in situ hybridization (iFISH) cytogenetics identifying deletion 17p [del(17p)], t(4;14), and t(14;16) has demonstrated independent prognostic value and has been widely adopted in many clinical centers. Moreover, these tumor biologic abnormalities have implications for risk-adapted management in patients with MM, justifying the use of novel approaches such as consolidation and/or maintenance in patients with poor prognosis cytogenetics.[6] In addition, other prognostic factors associated with very-high-risk MM have been identified, including the presence of plasma cell leukemia, high plasma cell labeling index, increased β_2-microglobulin (>5.5 mg/L), age, response to therapy and, serum lactate dehydrogenase (LDH).[7-10]

More recently, the Revised International Staging System (RISS) improved on the prognostic value of ISS by combining the variables

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in the ISS with the chromosomal abnormalities (CA) detected by iFISH after CD138 plasma cell purification and serum LDH in those with newly diagnosed multiple myeloma (NDMM).[11] In brief, 4445 patients with NDMM enrolled in 11 international, multicenter clinical trials from 2005 to 2012 were included. The RISS allows for a simple, reliable, and powerful risk stratification of NDMM patients treated with novel agents.[11] As a result, the RISS was recommended for use in future clinical studies by the International Myeloma Working Group. However, the utility of the RISS remains less clear if used in routine clinical practice, where most patients are not enrolled in clinical trials.

Therefore, we evaluated the effect of this novel staging system in the real world setting by assessing NDMM patients treated at our institution who had not been enrolled in any upfront clinical trial from 2004 to 2015. Importantly, most of our patients were treated with novel agent combinations.

Materials and Methods

Patient Population

All consecutive NDMM patients treated and followed up at Tom Baker Cancer Center (TBCC) from January 2004 to October 2015 were included in the present study. We excluded patients enrolled in clinical trials. Patients were also excluded if they had a concomitant malignant diagnosis or any other plasma cell disorder, such as amyloidosis, at the time MM was diagnosed. The TBCC institutional review board approved the review of these records, which was in accordance with the Declaration of Helsinki.

Data Source

The data required for the retrospective assignment of the RISS stage was collected at patient diagnosis and housed within the TBCC ARIA patient information system. This clinical data system also houses the patient demographic and disease-specific data, the last follow-up date, date of progression, and date of death.

ISS and RISS

ISS stage I is defined as a serum β_2-microglobulin level of < 3.5 mg/L and serum albumin level of ≥ 3.5 mg/dL. ISS stage II includes all patients with neither stage I nor stage III disease. ISS stage III is defined as a serum β_2-microglobulin level of ≥ 5.5 mg/L, irrespective of the serum albumin level.[3] In contrast, the RISS defines RISS I as ISS stage I and standard-risk CA by FISH and normal LDH. RISS II includes all patients with neither RISS I nor RISS III disease. Finally, RISS III includes ISS stage III and either high-risk CA by FISH or high LDH.[11]

The serum LDH level was recorded at baseline and classified as normal or high according to the local laboratory definition of the normal range. High LDH was defined as a serum level greater than the upper limit of normal range. Normal LDH was defined as a serum level less than the upper limit of normal.

Bone marrow plasma cells for FISH were enriched using anti-CD138–coated magnetic MicroBeads in accordance with the manufacturer's instructions. The routine panel included evaluation for t(4;14), del(17p), and t(14;16). A total of 200 bone marrow plasma cell nuclei from each sample was scored. The presence of del(17p), t(4;14), and t(14;16) detected by FISH were considered high-risk CA.

Transplant-Eligible Patients

Stem Cell Mobilization and High-Dose Melphalan. All patients received induction chemotherapy before undergoing autologous stem cell transplantation (ASCT). Standard supportive care with prophylactic antibiotics was provided to all the patients. As part of the ASCT, the stem cells were obtained from the peripheral blood with granulocyte colony-stimulating factor and intravenous cyclophosphamide (2.5 g/m^2). The patients were conditioned, infused, and monitored on an inpatient basis. The patients received high-dose melphalan at 200 mg/m^2 (or adjusted for renal failure, 140 mg/m^2 if creatinine clearance < 30), given intravenously on day -1, and the stem cells were infused on day 0. Pretransplant assessments were performed according to our center guidelines, and data were extracted from the medical records.

Nontransplant-Eligible Patients

Nontransplant-eligible (NTE) patients received bortezomib-containing regimens. Patients were to receive cyclophosphamide, bortezomib, and dexamethasone; bortezomib, melphalan, and prednisone; or bortezomib and dexamethasone.

Response Assessment

The definitions of response and progression were used according to the European Group for Blood and Marrow Transplant modified criteria, and a category of very good partial response was added.[12,13] The response was categorized as a complete response if monoclonal protein had disappeared in the serum and urine by electrophoresis and immunofixation, any soft tissue plasmacytoma had disappeared, $< 5\%$ plasma cells were in the bone marrow, and the free light chain ratio had normalized. A very good partial response was defined as serum and urine M-component detectable by immunofixation but not by electrophoresis or a $\geq 90\%$ reduction in the serum M-component plus urine M-component to < 100 mg in 24 hours. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression or death, and overall survival (OS) was defined from the date of treatment initiation to the date of death from any cause.[13,14]

Endpoints

The primary goal of the present study was to assess the effect of the RISS on clinical outcomes (OS and PFS) for MM patients not enrolled in clinical trials at our medical center. Secondary goals included the comparison of the RISS in both transplant and NTE MM patients.

Statistical Analysis

The effect of RISS was evaluated for transplant-eligible and NTE MM patients. The Cox proportional hazard model was used to perform univariate analysis of possible prognostic variables for OS and PFS after confirming the proportionality of each variable using time-dependent covariates. $P < .05$ was considered statistically significant. The variables included in the univariate analysis were age > 65 years, β_2-microglobulin ≥ 5.5 mg/L, LDH $>$ 235 IU/L (upper normal value), C-reactive protein > 20 mg/L, albumin < 35 g/L, and creatinine > 200 μmol/L. Cox analysis was performed using backward stepwise selection methods. Differences in