The Prognostic Impact of t(14;16) in Multiple Myeloma: A Multicenter Retrospective Study of 213 Patients. Is it time to revise the revised ISS?

Artur Jurczyszyn (1), Sarah Goldman-Mazur (1), Jorge J. Castillo (2), Anna Waszczuk-Gajda (3), Norbert Grząśko (4), Jakub Radocha (5), Max Bittrich (6), K. Martin Kortuem (6), Alessandro Gozzetti (7), Lidia Usnarska-Zubkiewicz (8), Iwona Hus (4), Andrew J. Yee (9), David S. Jayabalan (10), Ruben Niesvizky (10), Julia Kelman (10), Daniel Coriu (11), Laura Rosiñol (12), Łukasz Szukalski (13), Julio Davila (14), Veronica González-Calle (14), Krzysztof Jamroziak (15), Irit Avivi (16), Yael Cohen (16), Anna Suska (1), Aimee Chappell (17), Deepu Madduri (18), Saurabh Chhabra (19), Ariel Kleman (19), Parameswaran Hari (19), Sebastian Grosicki (20), Paweł Robak (21), Massimo Gentile (22), Izabela Kozłowska (23), Stuart L. Goldberg (24) and David H. Vesole (25)

(1) Department of Hematology, Jagiellonian University Medical College, Cracow, Poland; (2) Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; (3) Department of Hematology, Oncology and Internal Diseases, Warsaw Medical University; (4) Department of Haematology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland; (5) 4th Department of Internal Medicine – Haematology, Faculty of Medicine in Hradec Kralove, Charles University, Czech Republic; (6) Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany; (7) Le Scotte Hospital, Siena, Italy; (8) Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland; (9) Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; (10) Weill Cornell Medical College, New York, NY, USA; (11) Department of Hematology, Fundeni Clinical Institute, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania; (12) Department of Hematology, Amyloidosis and Myeloma Unit, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain; (13) Department of Hematology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland; (14) Hospital Universitario de Salamanca, Salamanca, Spain; (15) Institute of Hematology and Transfusion Medicine, Warsaw, Poland; (16) Tel Aviv Medical Center, Tel Aviv, Israel; (17) Medstar Georgetown University Hospital Department of Hematology/Oncology, Washington, NW, USA; (18) Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; (19) Division of Hematology/Oncology Department of Medicine Medical College of Wisconsin, Milwaukee, WI, USA; (20) Medical University of Silesia, Katowice, Poland; (21) Medical University of Lodz, Lodz, Poland; (22) Division of Haematology, Dipartimento di Biotecnologie Cellulari et Ematologia, University La Sapienza, Rome, Italy; (23) Department of Hematology, SPZOZ ZSM in Chorzow, Poland; (24) John Theurer Cancer Center at Hackensack UMC, Hackensack, NJ, and Cota Inc., New York, NY, USA; (25) John Theurer Cancer Center at Hackensack UMC, Hackensack, NJ, USA

INTRODUCTION

Intrinsic genetic abnormalities in malignant plasma cells are one of the strongest predictive factors in multiple myeloma (MM) patients. The presence of t(14;16)(q32;q23) is associated with deregulation of the c-musculoaponeurotic fibrosarcoma (c-MAF) oncogene. Due to the relative rarity of t(14;16) [<5% of newly diagnosed MM], there are no large databases constituting a source of information about the natural history of this abnormality (the largest reported by Palumbo et al.*, *R-ISS for MM: An IMWG Report* included 84 patients).

METHODS

We retrospectively analyzed 213 patients with t(14;16) from 24 clinical centers in Germany, Italy, Spain, Israel, Poland, Romania, Czech Republic and the United States. The diagnosis and clinical responses were based on the International Myeloma Working Group criteria. The t(14;16) was detected by double color fluorescence *in situ* hybridization using bone marrow samples. Baseline characteristics at diagnosis, patient treatment and clinical outcomes were collected using unified forms. The study was approved by institutional review boards. Progression-free survival (PFS) was defined as the period between the date of diagnosis and either the date of the first relapse, or the last observation or death from any cause. Overall survival (OS) was defined as the period between the date of diagnosis and the date of death or last observation. Cox proportional hazard regression analysis was applied to assess risk factors of death. Survival curves were plotted by the Kaplan-Meier method and compared using log-rank and Breslow-Gehan-Wilcoxon tests.

RESULTS

Patient Characteristics

We analyzed a total of 213 patients, mean age 62.1 years (range 32 to 90), including 91 (42.7%) males. Immunoglobulin isotype included IgG (n=98, 46.0%), IgA (n=60, 28.2%) and light chain only in 47 cases (22.1%). ISS stage at diagnosis included: stage I (n=47, 22.1%), stage II (n=81, 38.0%), stage III (n=78, 36.6%) and for R-ISS: stage I (n=10, 4.7%), stage II (n=71, 33.3%) and stage III (n=79, 37.1%). The stage was unknown for the remaining patients. Hypercalcaemia was present in 38 cases (17.8%), anemia (<10g/dL) in 109 (51.2%) and impaired renal function (creatinine clearance <40 mL per minute or serum creatinine >2 mg/dL) in 54 (25.4%) patients. In 104 (48.8%) cases, osteolytic lesions were present.

t(14;16)

The t(14;16) was associated with other aberrations in 134 (62.9%) cases (Table 1.), including 35 (16.4%) patients with del17p.

Treatment Modalities in Patients Positive for t(14;16)

First line treatment for MM with t(14;16) included proteasome inhibitors (PIs) +chemotherapy in 72 patients (36%), PIs + immunomodulators (IMIDs) in 39 patients (20%) and chemotherapy + PIs + IMIDs in 25 patients (13%). Responses to the treatment are presented in Table 2.

Table 1.

Additional cytogenetic abnormality	Number of patients
t(14;20)	4 (1.9%)
del 17p	35 (16.4%)
RB1	1 (0.5%)
trisomy 15	4 (1.9%)
gain 1q21	69 (32.4%)
del 13q14	65 (30.5%)
t (6;14)	6 (2.8%)
t (4;14)	29 (13.6%)
t (11;14)	23 (10.8%)
IgH disruption	43 (20.2%)

Table 2.

Responses	Response after 1. line of treatment n=159
Complete remission	46 (28.9%)
Very Good Partial Remission	47 (29.6%)
Partial Remission	46 (28.9%)
Minimal Response	4 (2.5%)
Stable Disease	7 (4.4%)
Progressive Disease	9 (5.7%)

Survival

Overall response rate was 67%. Median PFS was 31 months (95% CI 28-40.3 months, Figure 1.). Median OS was 88 months (95% CI 49-177 months, Figure 2.). 5-year OS from MM diagnosis was 55% (95% CI 46-63%), and 10-year OS was 44% (95% CI 31-56%). For stage I median PFS was 41 months (95% CI 29-54 months), median OS for stage I was not reached. For stage II median PFS was 92 months (95% CI 22-177 months) and median OS was 62 months (95% CI 38-177 months). For stage III median PFS was 18 months (95% CI 12,4-28 months) and median OS was 32 months (95% CI 18-88 months; Figure 3 and 4; in *Palumbo et al.* study* for stage I R-ISS: median PFS= 66 months , median OS= not reached; for stage II R-ISS median PFS= 42 months , median OS= 83 months and for stage III R-ISS median PFS= 29 months and median OS= 43 months). Patients in ISS stage I had better OS than stage III patients (p<0.001). Patients with additional del17p (double hit myeloma) exhibited worse OS than patients with single t(14;16) mutation (median OS 42 vs. 107 months, p=0.043, Figure 5.). A total of 74 (34.7%) patients died. The causes of death included mostly disease progression in 28 cases (37.8%; 16 patients received ≥4 treatment lines) and infection in patients with progression in 21 cases (28.4%).

Patients treated with combined therapy with IMIDs, PIs ± chemotherapy had better survival than patients treated with IMIDs or PIs alone or chemotherapy alone (p=0.044, Figure 6). Patients after auto-PBSCT (median OS not reached, n=62, 29.1%), especially tandem auto-PBSCT (median OS not reached, n=18, 8.5%) had better OS than patients without transplant (median OS 42.1 months, 95% CI 27-62 months, p<0.0001, Figure 7.).

Figure 1. Progression-free survival

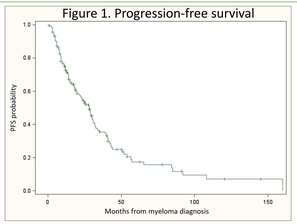


Figure 2. Overall survival

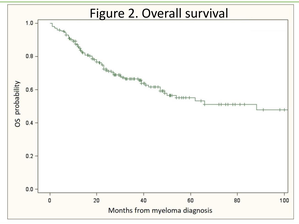


Figure 3. OS according to ISS stage

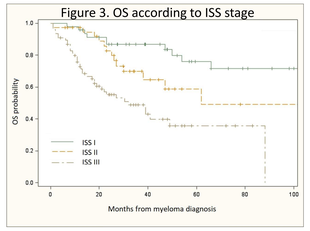


Figure 4. PFS according to ISS stage

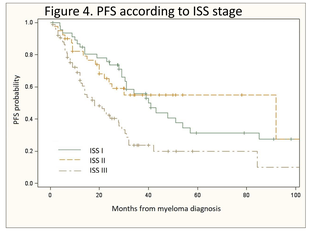


Figure 5. OS according to del17p status

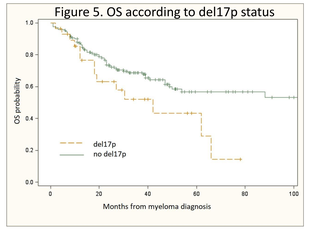


Figure 6. OS according to treatment

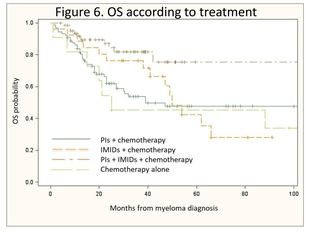
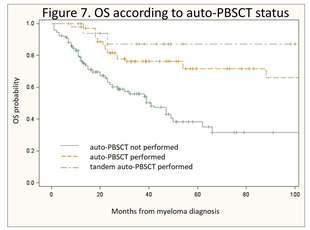


Figure 7. OS according to auto-PBSCT status



CONCLUSION

This is the largest report of myeloma patients with t(14;16). Patients with isolated t(14;16) had better prognosis than those with t(14;16) and del17p. The use of auto-PBSCT, especially in patients who received planned tandem auto-PBSCT, was associated with better survival. Combined therapy with PIs and IMIDs improved OS in t(14;16) patients, which may suggest that this high-risk prognostic feature might be partially overcome by the use of new drug therapies. This study of 213 patients indicates that t(14;16) is not as unfavorable factor as shown in the original IMWG R-ISS analysis (n= 84); this may be the result of higher numbers of patient in our study being treated with combinations of IMiDs and PIs. Regardless, this data suggests that the revised ISS may require updating.

*Palumbo et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015;33:2863-9.