International Journal of Gerontology xxx (2017) 1–5

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Original Article

Verification of Survival Predictors in Elderly Patients with Myelodysplastic Syndrome from Outpatient Clinical Practice

Eva Kadlčková [a *], Peter Rohoň [b], Tomáš Fürst [c], Libor Červínek [d], Anna Jonášová [e], Tomáš Šálek [f], Jiří Tesař [g], Yvetta Stavařová [a]

[a] Hematology and Blood Transfusion Department, Tomáš Baťa Hospital in Zlín, Czech Republic, [b] Department of Hemato-Oncology, University Hospital Olomouc, Faculty of Medicine and Dentistry, Palacký University Olomouc, Czech Republic, [c] Department of Mathematical Analysis and Applications of Mathematics, Faculty of Science, Palacký University Olomouc, Czech Republic, [d] Department of Internal Medicine-Hematology and Oncology, Faculty Hospital Brno, Masaryk University, Brno, Czech Republic, [e] 1st Department of Medicine, General University Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic, [f] Department of Clinical Biochemistry, Tomáš Baťa Hospital in Zlín, Czech Republic, [g] Radiological Department, Tomáš Baťa Hospital in Zlín, Czech Republic

ARTICLE INFO

Article history:
Received 22 October 2016
Received in revised form
8 May 2017
Accepted 2 June 2017
Available online xxx

Keywords:
chelation therapy,
myelodysplastic syndrome,
prognostic scoring system,
transfusion

SUMMARY

Background: Myelodysplastic syndrome (MDS) is a clonal disorder affecting older persons. We aimed to analyze the effectiveness of the scoring systems and of the number of received red blood cell (RBC) units in predicting survival.

Methods: The study included an unselected group of 73 patients with MDS who were diagnosed and treated in a single hospital over a period of 12 years. International Prognostic Scoring System (IPSS), revised IPSS (IPSS-R), WHO-Prognostic Scoring System (WPSS), Charlson Age-Comorbidity Index (CACI), and impact of performance status (PS) on overall survival (OS) and event free survival (EFS) were tested. The follow-up of received RBC units was conducted.

Results: The median age at diagnosis was 69.5 years, the median CACI was 3.0. The median survival times of the group were 7.04 and 2.78 years for OS and EFS, respectively. The concordance values of the IPSS, IPSS-R and WPSS are 0.812, 0.892 and 0.889 for OS; 0.785, 0.847 and 0.827 for EFS. The comorbidity index and PS were the only auxiliary criteria when determining the risk and selecting the therapeutic approach in MDS patients. In transfusion-dependent unchelated patients, both OS and EFS were negatively influenced by both higher ferritin levels and the numbers of RBC units; however, the risk does not continue to increase after more than 20 RBC units are administered.

Conclusions: IPSS-R is best suited as a predictor of survival. CACI and PS present auxiliary criteria for determining the risk. Number of received RBC units was detected as a significant predictor of survival.

1. Introduction

Myelodysplastic syndrome is a heterogeneous group of hematopoietic disorders characterized by dysplastic changes in blood cell precursors in bone marrow, (pan) cytopenia in peripheral blood, and by various levels of risk for progression into acute leukemia[1]. MDS develops either de novo or secondarily due to previous chemo- or radiotherapy. Diagnosis is based mainly on microscopically detected significant dysplastic changes, an increased percentage of myeloblasts in a bone marrow smear, and identification of cytogenetic aberrations typical for MDS in patients with persistent or progressive cytopenia[2]. Patient survival varies from several months to many years, depending on the MDS subtype, cytogenetic aberrations and depth of cytopenias[3]. Annual incidence in general population of developed countries is approximately five per 100,000, ranging from approximately 0.1 in patients aged under 40 years to more than 30 in those over 70 years of age and to approximately 50 per 100,000 in the 80+ age category. Thus, MDS represents a serious issue in geriatric hematology[4].

The key to selecting the proper treatment modality is the classification of the patient into a risk group according to IPSS, IPSS-R or

* Corresponding author. Hematology and Blood Transfusion Department, Tomáš Baťa Hospital in Zlín, Havlíčkovo nábřeží 600, 760 01, Zlín, Czech Republic. Fax: +420 577552327.
E-mail address: kadlckova@tiscali.cz (E. Kadlčková).

http://dx.doi.org/10.1016/j.ijge.2017.06.001

WPSS[5–7]. Patient's age and comorbidities play an important role in selecting adequate therapy.

For many years, MDS management was mainly based on two modalities: supportive care including transfusions, and allogeneic stem cell transplantation. Novel drugs routinely used in clinical practice include hypomethylating agents, immunomodulators, or new chelating agents that may affect the natural course of the disease and prolong the survival of MDS patients[8].

The objectives of the study were to provide a picture of the diagnosis and treatment of an unselected group of MDS patients cared for in the Zlín hospital in the setting of daily hematology practice over a long-term period (2002−2015) and to compare the results with the literature data. Frequently, data in literature is influenced by selection of certain patient groups (e.g. allogeneic transplantation, administration of hypomethylating agents), stemming from the fact that highly specialized hematology centers typically care for patients requiring curative or intensified therapy while those suitable for palliative therapy continue to be cared for in local hematology centers. Therefore, we aimed to determine which of the three prognostic indices is best for predicting OS and EFS. As MDS is mainly an old age disease usually accompanied by multiple comorbidities, we wanted to determine whether or not CACI[9] is a stronger predictor of OS and EFS than the prognostic indices.

Transfusion of blood products remains the basis of MDS treatment even at the present time. Therefore, special attention is paid to the follow-up of the number of RBC units and serum ferritin levels in the subgroup with RBC transfusion-dependent patients.

2. Material and methods

Between January 1, 2002 and June 30, 2015, a total of 73 patients with MDS and chronic myelomonocytic leukemia (CMML) were diagnosed and treated in the outpatient center of the Hematology and Blood Transfusion Department of Tomáš Baťa Hospital in Zlín, often in collaboration with centers in Brno, Olomouc and Prague. The reason for including patients with CMML is a historical one since the older French-American-British (FAB) classification categorized the condition as belonging to the MDS groups of diseases[1]. All patients came from the Zlín District with a population of approximately 200,000 inhabitants. Patient data has been kept in both the Zlín center and the MyDyS Registry 2.0 of the Czech MDS Group, a part of the Czech Medical Association of J. E. Purkyně.

Data selected for statistical analyses comprise sex, age at diagnosis, date of diagnosis and date of death or the last visit, 2008 WHO classification MDS subtype, risk groups according to the IPSS[5], IPSS-R[6] and WPSS[7], presence/absence of cytogenetic aberrations, karyotype according to the IPSS and IPSS-R[5,6], presence/absence of bone marrow fibrosis in a bone marrow trephine biopsy sample, presence/absence of secondary MDS, date of progression, transfusion dependence according to the WPSS[7], total RBC and platelet transfusions, performance status[10], comorbidities expressed as the CACI[9], treatment modalities used, and presence/absence of progression as of 30 June 2015[11], Diagnoses were made based on assessing peripheral blood smears, panoptic staining of sternal puncture samples (May-Grünwald, Giemsa-Romanowski)[12], sternal puncture samples stained to evaluate iron (Perls' reaction)[13], classical karyotyping, and identification of cytogenetic aberrations typical for MDS in bone marrow using fluorescence in situ hybridization. For some patients, cytogenetic examination and trephine biopsy results are missing as they were not performed at all or valid samples were not obtained.

In 37 patients dependent on RBC transfusions, the follow-up was at 3, 6, 12 and 24 months and then at yearly intervals, starting from the onset of transfusion dependence. The parameters followed were: ferritin and received RBC units. The data was related to those obtained at the time of diagnosis. Among the subjects, a small cohort of four patients was selected who underwent magnetic resonance imaging (MRI) of the heart using the T2* approach and MRI of the liver.

The patients mainly received outpatient treatment modalities, ranging from a watch and wait approach, transfusions with chelation, to erythropoiesis-stimulating protein (ESP) support, vitamins, immunosuppressants, low-dose chemotherapy (hydroxyurea, low-dose cytarabine), to immunomodulatory therapy with lenalidomide and administration of the hypomethylating agent 5-azacytidine (5-AZA), in cooperation with the centers in Brno, Olomouc and Prague.

Chelating agents were administered to low-risk transfusion-dependent patients with ferritin levels of at least 1000 μg/L. In the first years, only parenteral deferoxamine was used; later, patients included in a study carried out by the Czech MDS Group received deferiprone[14]; in the second part of the study period, deferasirox was administered. To reduce or completely eliminate their dependence on transfusions, low-risk patients received ESPs, either alone or in combination with granulocyte colony-stimulating factor. Immunosuppressive therapy with prednisone and/or cyclosporine A was instituted in patients with hypoplastic MDS confirmed by trephine biopsy. Combination chemotherapy (7 + 3) and allogeneic stem cell transplantations were carried out in the referral university hospitals.

All participants signed an informed consent form. This study was approved by the medical ethics committee of the Tomáš Baťa Hospital in Zlín, Czech Republic.

2.1. Statistical methods

Overall survival is defined as the time from diagnosis to death from any cause (event) or the last visit (censoring). Event-free survival is defined as the time from diagnosis to disease progression (a higher degree of cytopenia, higher number of blasts in the bone marrow, progression in the FAB classification) or death from any cause (event) or the last visit (censoring)[11]. The impact of individual prognostic factors on OS and EFS was assessed by the Cox proportional hazard model. Concordance was used to determine the predictive power of the prognostic indices IPSS, WPSS and IPSS-R. Concordance measures the probability of agreement between survival times in a randomly selected pair of patients and their scores. Agreement means that a patient with a shorter survival time also has a less favorable score. Concordance always ranges from 0.5 (if the score has no predictive value for survival) to 1.0 (if all patient pair scores agree with their survival times). The relationship between two categorical predictors (e.g. the presence of secondary MDS and a prognostic index) was analyzed using contingency tables and a test of independence. The analyses were mostly performed with the Statistica software package; the Cox regression model was implemented in the R software. Effects with p-values below 0.05 were considered statistically significant.

3. Results and discussion

3.1. Sample characteristics

Of the 73 patients, 50 cases (68.5%) had low-risk MDS, comprising refractory anemia (RA), refractory cytopenia with unilineage dysplasia (RCUD), refractory anemia with ring sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), unidentified MDS (MDS-U), and MDS with isolated deletion 5q. Another 17 patients (23.3%) were in the high-risk MDS group, that is, subtypes of refractory anemia with excess blasts I and II (RAEB I

Please cite this article in press as: Kadlčková E, et al., Verification of Survival Predictors in Elderly Patients with Myelodysplastic Syndrome from Outpatient Clinical Practice, International Journal of Gerontology (2017), http://dx.doi.org/10.1016/j.ijge.2017.06.001