Leukemia Research 53 (2017) 74–81

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Clinical outcome of myeloid sarcoma in adult patients and effect of allogeneic stem cell transplantation. Results from a multicenter survey

Davide Lazzarotto[a,*], Anna Candoni[a], Carla Filì[a], Fabio Forghieri[b], Livio Pagano[c], Alessandro Busca[d], Giuseppina Spinosa[e], Maria Elena Zannier[a], Erica Simeone[a], Miriam Isola[f], Erika Borlenghi[g], Lorella Melillo[h], Federico Mosna[i], Federica Lessi[j], Renato Fanin[a]

[a] Division of Hematology and Bone Marrow Transplantation, Azienda Sanitaria-Universitaria Integrata, University of Udine, Italy
[b] Section of Hematology, Department of Surgical and Medical Sciences, University of Modena and Reggio Emilia, Italy
[c] Department of Hematology, Università Cattolica Sacro Cuore, Rome, Italy
[d] Division of Hematology, Ospedale S. Giovanni Battista, Torino, Italy
[e] Division of Hematology, Azienda Ospedaliera Universitaria Ospedali Riuniti di Foggia, Italy
[f] Department of Medical and Biological Sciences, Section of Statistics, University of Udine, Italy
[g] Division of Hematology, Azienda Ospedaliera Spedali Civili di Brescia, Italy
[h] Division of Hematology, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy
[i] Division of Hematology, Department of Specialty Medicine, Ospedale Ca' Foncello, Treviso, Italy
[j] Padua University School of Medicine, Department of Medicine, Hematology and Clinical Immunology, Italy

ARTICLE INFO

Article history:
Received 8 September 2016
Received in revised form
14 December 2016
Accepted 19 December 2016
Available online 20 December 2016

Keywords:
Myeloid Sarcoma
Allogeneic SCT
Acute Myeloid Leukemia

ABSTRACT

Introduction: Myeloid Sarcoma (MS) is a rare hematologic myeloid neoplasm that can involve any site of the body. It can occur as an exclusively extramedullary form or it can be associated with an acute myeloid leukemia (AML), a chronic myeloproliferative neoplasm (MPN) or a myelodysplastic syndrome (MDS) at onset or at relapse. The rarity of MS does not enable prospective clinical trials and therefore a specific multicenter register can be useful for the clinical and biological studies of this rare disease.
Patients and results: we report the clinical characteristics and outcome of 48 histologically confirmed MS, diagnosed and treated in 9 Italian Hematological Centers in the last 10 years. The patient's median age was 46 years. There were 9/48 *de novo extramedullary* MS, 24/48 *de novo AML-related* MS and 15/48 were *secondary AML-related* MS. The most common extramedullary anatomic sites of disease were: skin, lymph nodes and soft tissues. Forty-three patients (90%) underwent a program of intensive chemotherapy including FLAI, HDAC-IDA, HyperCVAD and MEC schemes, with a DDI of 5% and a CR Rate of 45%. Twenty-two (46%) patients underwent Allogeneic SCT, 13 from a MUD, 8 from an HLA-identical sibling donor and 1 from an haploidentical donor. The median OS of the whole population (48 pts) was 16.7 months. The OS probability at 1, 2 and 5 years was 64%, 39% and 33%, respectively. The OS was better in patients that underwent an intensive therapeutic program (median OS: 18 months vs 5 months). Among the intensively treated patients, in univariate analysis, the OS was better in young patients (P = 0,008), in patients that underwent Allo-SCT (P = 0,009) and in patients that achieved a CR during treatment (P = 0,001), and was worse in pts with *secondary AML-related* MS (P = 0,007). Age, response to intensive chemotherapy and Allo-SCT were the only three variables that significantly influenced DFS (P = 0,02, P = 0,01 and P = 0,04, respectively). In multivariable analysis, Allo-SCT and response to intensive chemotherapy remained significant in predicting a better OS (P = 0,04 and P = 0,001, respectively), and response to intensive chemotherapy was the only significant variable in predicting DFS (P = 0,01). After Allo-SCT we observe a survival advantage

* Corresponding author at: Division of Hematology and Bone Marrow Transplantation, Azienda Sanitaria–Universitaria Integrata di Udine, Italy. Piazzale Santa Maria della Misericordia 15, Udine (UD), 33100, Italy.
E-mail address: davidelazzar8@gmail.com (D. Lazzarotto).

http://dx.doi.org/10.1016/j.leukres.2016.12.003

in patients who achieved a pre-transplant CR (P = 0,008) and in those who developed a chronic GvHD (P = 0,05).

Conclusions: Patients with MS, both with *de novo* and secondary forms, still have a very unfavorable outcome and require an intensive therapeutic program, that includes Allo-SCT whenever possible. The outcome after Allo-SCT is positively influenced by the development of chronic GvHD suggesting a Graft versus MS effect.

1. Introduction

Myeloid Sarcoma (MS), as known as Granulocytic Sarcoma or Chloroma, is a very rare hematologic neoplasm characterized by extramedullary proliferation of myeloid blast cells, with or without maturation, that form one or more tumor masses [1,2]. It can be found in any site of the body, most commonly it involves skin, gastrointestinal tract, lymph nodes and bone [1–3]. The incidence of this disease is extremely low [3]. MS can develop *de novo* without bone marrow involvement (*de novo extramedullary* MS) or simultaneously to an Acute Myeloid Leukemia (AML) (*de novo AML-related* MS) or, rarely, to a Myelodysplastic Syndrome (MDS) or to a Chronic Myeloproliferative Neoplasm (MPN). Sometimes MS can be an expression of relapse of a previous hematologic myeloid neoplasm (*secondary* MS) [1,4,5]. In literature it has been reported that more than 70% of *de novo extramedullary* MS patients will develop a subsequent AML [6].

Due to the rarity of MS, there are several case reports in literature, but the published surveys are limited, retrospective and heterogeneous. Consequently there are no defined guidelines on MS treatment [5,7,8].

Here we report the results of a multicenter observational survey that analyzed the characteristics and the outcome of MS (mostly AML-related) diagnosed and treated in 9 Hematology Institutions in the last 10 years (2005–2015).

2. Materials and methods

This is a multicenter, retrospective survey that includes 48 MS patients with a diagnosis confirmed by histology and immunohistochemistry or immunophenotype. Patients' data were collected in 9 Italian Hematology Institutions and all cases were diagnosed between 2005 and 2015. Patients' clinical, immunohistochemical, cytogenetic and molecular data were collected in a proper Case Report Form (CRF) and inserted in a specific database/registry.

De novo extramedullary MS was defined as a "de novo" occurring sarcoma without cytological bone marrow involvement. *De novo AML-related* MS was defined as a "de novo" occurring sarcoma associated, at onset, to an AML. *Secondary AML-related* MS was defined as a sarcoma (with or without bone marrow involvement) expression of relapse of a previous AML [1].

Response to therapy was classified according to ELN recommendation [9] as far as medullary disease was concerned (CR, PR, SD, Relapse). Extramedullary involved sites were assessed and subsequently reevaluated with physical examination and radiological investigations as Computer Tomography (CT), Magnetic Resonance (MRI) or Positron Emission Tomography (PET) imaging. According to symptoms, physical examination, and radiological imaging, Complete Remission (CR) was defined as the complete disappearance of symptoms, physical and radiological signs of the disease; Partial Response (PR) was defined as any dimensional reduction of disease localizations; Stable Disease (SD) was defined as the unchanged persistence of symptoms and physical and radiological signs of the disease without dimensional changes; Progressive Disease was defined as the occurrence of new disease localizations or the dimensional increase of the present ones.

Table 1
Patients' Characteristics at MS Diagnosis.

Patients' Characteristics (48 pts)		
Sex M/F	26/22	
Mean Age ± SD.	46,6	± 18,5
Median Age (range)	46	(15–82)
MS SUBTYPE	**N°**	**%**
de novo extramedullary MS	9	19%
de novo AML-related MS	24	50%
secondary AML-related MS	15	31%
KARYOTYPE (available in 32/48)	**N°**	**%**
normal	14	44%
complex	7	22%
t(8;21), inv(16) or t(16;16)	5	15%
trisomy 8, other	6	19%
MOLECULAR BIOLOGY (available in 32/48)[a]	**N°**	**%**
no alterations	13	41%
NPM1	8	25%
FLT3-ITD or D835	10	31%
AML1-ETO or CBFbeta-MYH11	7	22%
CEBPA, ETV6-MLL or JAK2	1	3%

[a] Some patients had more than one molecular alteration.

The follow-up of the entire population was updated on the 31st May 2016.

The Overall Survival (OS) of the population was calculated from the date of diagnosis to the date of the last follow-up for alive patients or to the date of death for any cause. OS following Allogeneic Stem Cell Transplantation (Allo-SCT) was calculated from the date of reinfusion of hematopoietic stem cells. Disease Free Survival (DFS) of the population was calculated from the date of first remission to the date of the last follow-up or relapse for alive patients or to the date of death from any cause. DFS following Allo-SCT was calculated from the date of reinfusion of hematopoietic stem cells (patients in CR) or from the date of a subsequent remission. The Odds Ratio test was used to investigate the difference between frequencies.

OS was estimated with Kaplan-Meier method and the differences between groups were compared with the Log-rank test. Univariate and multivariable analysis were carried out with Cox regression. Statistical significance level in all cases was considered for a P value less than 0,05. Data were analyzed by MedCalc software, version 12.5.0.0 (MedCalc Software bvba, Belgium).

3. Results

3.1. Patients' characteristics

Clinical and biological characteristics of the 48 patients included in the study are summarized in Table 1.