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Change of prognosis of patients with myelodysplastic syndromes during the last 30 years☆

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ABSTRACT

During the last years, more and more treatment modalities are available for MDS patients. Therefore, we were interested if this is reflected in an improvement of the outcome of the patients. We analyzed the survival and rate of leukemic progression of 4147 patients from the Duesseldorf MDS registry diagnosed during the last 30 years and found an improvement of survival in those patients diagnosed after 2002 (30 vs. 23 months, $p < 0.0001$). In detail, the improvement of the prognosis was restricted to high-risk MDS patients diagnosed between 2002 and 2014 in comparison to the patient group diagnosed between 1982 and 2001 (19 vs. 13 months, $p < 0.001$), whereas the prognosis of low-risk MDS patients did not change significantly. The improvement of survival was still measurable after exclusion of RAEB-t patients and of those, that received an allogeneic stem cell transplantation. In line with this finding, we found a lower AML progression rate in the later diagnosed group. Unfortunately, we could not identify a clear reason for this finding but rather a multifactorial cause should be assumed. As death due to bleeding complications and infections was significantly lower, an improvement of BSC may be one of the underlying causes.

1. Introduction

Myelodysplastic syndromes (MDS) are clonal stem cell disorders and are characterized by a dysplastic hematopoiesis in the bone marrow and various degrees of cytopenia in the peripheral blood [1]. Accordingly, clinical symptoms vary from anemia with transfusion dependency, bleeding complications, fatigue and an increased risk of infections. Approximately 20% of the patients develop an acute myeloid leukemia (AML). The classification system of the World Health Organization (WHO) is based on cytomorphologic criteria, the bone marrow blast count, chromosomal findings and cell counts [2]. To assess the prognosis of MDS patients, the International Prognostic Scoring System (IPSS) has served as a gold standard since its publication and was revised by the International Working Group for Prognosis in MDS (IWG-PM) taking into account five rather than three cytogenetic risk groups including a number of less common cytogenetic alterations, new categories of marrow blast percentage values and a substitution of the number of cytopenias by the depth of cytopenias [3,4]. As MDS is more frequent in elderly patients, most of them are no suitable candidates for intensive treatment and allogeneic stem cell transplantation as the only curative therapy for MDS patients. Therefore, best supportive care (BSC) remains the most often-indicated treatment option. During the last decade, the amount of potential treatment options grew. Beside intensive chemotherapy and allogeneic transplantation, hypomethylating agents have shown to improve overall survival in high-risk MDS patients [5]. In addition to transfusion of red blood cells or platelets, growth factors as erythropoiesis stimulating agents alone or in combination with granulocyte growth factors and thrombopoietin analogs can improve the cytopenia in the peripheral blood [6–8]. Additionally, there is an increasing amount of clinical trials investigating new treatment options for MDS patients.

Despite the growing treatment modalities, an improvement of survival of MDS patients receiving best supportive care during the last decades has not been shown [9]. The aim of our study was to

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analyze if the survival and leukemic progression rates of treated as well as untreated MDS patients has changed over a period of 30 years.

2. Methods

In this retrospective analysis, 4147 patients from the Düsseldorf MDS registry were included. As all patients within the registry are followed on the basis of standardized procedures, an evaluation of prognosis can be performed. The 30-year period between 1982 and 2002 was divided into six quinquennial intervals (1982–1986, 1987–1991, 1992–1996, 1997–2001, 2002–2006, and 2007–2011). Patients were allocated depending on their dates of diagnosis. In a first step, we determined the survival times according to the various risk categories of WHO subtypes without taking into account the type of treatment that they received. Low-risk MDS was defined as WHO subtypes RCUD, RARS, RCMD or MDS with del(5q). High-risk MDS included the subtypes RAEB-I and RAEB-II as well as RAEB-t and CMML. We then looked at the different treatment modalities as cytotoxic chemotherapy, allogeneic blood stem cell transplantation, hypomethylating agents or best supportive care (BSC) which includes red blood cell and platelet transfusions, growth factors, and iron chelation. Besides survival, the progression date to acute myeloid leukemia and the causes of death were evaluated if the patient data were available.

2.1. Statistics

Descriptive statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 22 (SPSS, Chicago, IL, USA). Clinical and hematological data at the time of diagnosis were compared using the χ-square and Wilcoxon rank sum test. A two-sided p-value of less than 0.05 was considered as statistically significant. The probability of survival was estimated using the product limit method (Kaplan–Meier) [10].

Table 1
Baseline characteristics.

	1982–2001 $n = 2161$	2002–2011 $n = 1996$
Median age (range)	71 (18–96)	70 (16–104)
Male	53.0%	58.8%
Female	47.0%	41.2%
IPSS	$n = 823$	$n = 902$
Low	20.7%	22.4%
Intermediate-1	30.3%	40.0%
Intermediate-2	18.7%	22.9%
High	30.4%	14.6%
IPSS-R	1982–2001 $n = 576$	2002–2011 $n = 738$
Very low	8.9%	10.7%
Low	24.3%	26.3%
Intermediate	26.2%	25.2%
High	20.8%	21.8%
Very high	19.8%	16.0%
WHO	1982–2001 $n = 2161$	2002–2011 $n = 1996$
RCUD	6.6%	8.1%
RCMD	31.9%	38.8%
RARS	7.0%	4.7%
5q-	2.8%	5.4%
RAEB-I	11.0%	15.1%
RAEB-II	14.3%	14.6%
CMML-I	10.9%	6.9%
CMML-II	2.7%	2.1%
RAEB-T	12.7%	4.2%

3. Results

In a first step, we determined the survival times of the patients diagnosed within the six quinquennials and found that those patients diagnosed between 1982 and 2001 had a similar survival within the four five-year time intervals covering this period. In contrast, since 2002 the survival time was significantly longer. Therefore, we merged the patients diagnosed within the respective quinquennials and continued our evaluation with these two patient groups, named in the following as the early and late patient group. As far as the time period from 1982 to 2001 is concerned, we are looking at 2145 MDS patients with a median age of 71 years (range 18–96 years) while the time period from 2002 to 2011 includes 1983 patients with a similar median age of 70 years (range 20–105 years).

The median time of follow up of the entire group of patients was 33 months (range 1–415 months). The median time of follow up in the early group diagnosed between 1982 and 2001 was 40 months and in the late group diagnosed after 2002, it was with 23 months shorter ($p < 0.0005$). The baseline characteristics of the patients are shown in Table 1. The median survival of the entire patient group was 26 months. In those patients diagnosed between 1982 and 2001, the median survival was 23 months. In the cohort diagnosed between 2002 and 2011, the median survival was with 30 months significant longer ($p < 0.0001$).

Asking if the improvement of survival concerns all MDS patients or particular subgroups, we divided the two time groups into low-risk and high-risk MDS patients according to the bone marrow blast count with a cut off of 5% and analyzed the survival for each of the four subgroups. The prognosis of low-risk MDS patients did not change significantly. In patients diagnosed between 1982 and 2001, the overall survival was 44 months and in those, diagnosed later, it was 42 months ($p = 0.916$). But we could find an improvement of survival in those high-risk MDS patients diagnosed between 2002 and 2011 of 19 months vs. 13 months in those patients diagnosed between 1982 and 2001 ($p = 0.001$, Fig. 1a). Until the introduction of the WHO classification in 2008, the FAB classification was used for MDS patients. This classification contains the group of RAEB-t patients with a medullary blast count up to 30%. According to the WHO classification, all patients with bone marrow blasts of more than 20% are now considered as AML patients. As in the early-diagnosed patient group the amount of RAEB-t patients was higher due to the application of the FAB classification, we performed the same analysis excluding the RAEB-t patients. Of interest, the improvement of survival of the high-risk MDS patients diagnosed since 2002 remained (21 vs. 16 months, $p = 0.007$). Therefore, the further analyses were performed including the RAEB-t group. We then looked at age as a potential discriminator for survival and found that the improvement of survival in patients with more than 5% medullary blasts was not restricted to younger patients, but was also true for patients with an age over 80 years (12 vs. 7 months; $p = 0.026$, Fig. 1b).

We asked for the reason for the observed survival improvement and looked at the different treatments. Most of the MDS patients received best supportive care including transfusions, growth factors and iron chelation, especially in the group of patients aged above 80 years. Comparing the two different time periods, the amount of patients, that received induction chemotherapy, decreased in the group diagnosed since 2002 and the amount of patients who underwent allogeneic stem cell transplantation increased in this cohort. Between both time periods, we also found an increase of patients that were treated with epigenetic compounds (Table 2). We then excluded those patients that were treated with cytotoxic chemotherapy as AML-like induction protocols or cytarabine (not summarized under cytotoxic chemotherapy were allogeneic stem cell transplantation and epigenetic treatment) but yielded the same result: the later diagnosed patient group had with 18 months in comparison to 14 months of the earlier diagnosed patients an improved survival ($p = 0.004$). After exclusion of those patients who received allogeneic blood stem cell transplantation, the survival advantage was still detectable (18 vs. 13 months; $p = 0.001$, Fig. 1c). In summary, we could not demonstrate an influence of the different treatment strategies on the improved survival in those MDS patients diagnosed since 2002. When only looking at the survival of patients that received best supportive care, the improvement of survival between both patient cohorts was still measurable (17 vs. 12 months, $p = 0.001$, Fig. 1d).