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ORIGINAL ARTICLE

Long-term outcome of high risk patients with myelodysplastic syndromes or secondary acute myeloid leukemia receiving intensive chemotherapy

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Abstract

Intensive chemotherapy (IC) used to be a common treatment approach for patients with higher-risk myelodysplastic syndromes (MDS) or acute myeloid leukemia after MDS (sAML). We conducted a retrospective analysis of 299 patients, including a matched pair analysis comparing 96 patients receiving IC with 96 patients not undergoing IC, in order to evaluate the impact of IC on overall survival (OS) and to identify factors that influence remission rates and OS. Complete remission (CR) after first induction chemotherapy was reached in 50% of patients. Parameters influencing the probability of achieving CR were blast count in the bone marrow (< 30%), age < 65 years, presence of Auer rods, duration of antecedent MDS shorter than 6 months, and timing of IC in relation to first diagnosis. The difference in survival time was not significantly better for patients receiving IC (median OS 12.7 months vs. 7 months). Parameters favorably influencing survival were the presence of Auer rods, age below 60 years, blast count below 30%, IC given shortly after first diagnosis, and achievement of CR. On multivariate analysis, achieving CR, presence of Auer rods, and percentage of blasts below or above 30% significantly influenced median survival. Relapse occurred in 63% of patients after a median of 9.9 months with a median survival of 7.6 months. Considering the high relapse rate and short survival, we conclude that intensive chemotherapy is not promising for high-risk MDS or sAML.

Keywords MDS · Secondary AML · Intensive chemotherapy · Induction chemotherapy · Prognosis

Introduction

The appraisal of intensive chemotherapy (IC) in patients with high risk myelodysplastic syndromes (MDS) and patients with acute myeloid leukemia (AML) secondary to MDS (sAML) changed during the last decades. In the 1980s and 1990s, more than 10% of MDS patients were treated with IC. Since the turn of the millennium, this rate decreased to below 5% [1]. The development is at least partly due to the fact that parameters were identified that are associated with low complete remission (CR) rates and poor overall survival after IC [2]. Furthermore, hypomethylating agents became available [3, 4] and are widely used for this patient population. Finally, the use of allogeneic stem cell transplantation (alloSCT) has been fostered by increased availability of donors and decreased toxicity, mostly due to reduced intensity conditioning regimens [5].

In this retrospective study, we analyzed predictive parameters for treatment outcome, and evaluated if intensive chemotherapy is still a useful treatment option with acceptable long-term results.

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Methods

We retrospectively identified and analyzed 299 patients with high-risk MDS or sAML from the Duesseldorf MDS registry, diagnosed between 1981 and 2014, who received intensive chemotherapy at first diagnosis or at disease progression. The potential benefit of IC was analyzed by means of a matched pair analysis including 96 patients for whom a matching partner was found in the MDS registry. Best supportive care as well as all types of treatment except IC were permissible in the matching partner. The matching criteria were gender, age (± 5 years), WHO classification at first diagnosis, timing of IC, AML evolution at the time of IC, and karyotype-risk group according to the revised international prognostic scoring system (IPSS-R). For the other 203 patients, no adequate matching partner was found or the karyotype was missing. Patients receiving allogeneic stem cell transplantation were excluded from the matched pair analysis.

Diagnoses were adopted according to the proposals of the WHO 2016 classification [6]. Clinical data were gathered from the original patients' charts. Follow-up data were obtained from our outpatient clinic or by contacting the primary care physician. Patients were censored at the date of last follow-up. Overall survival was calculated using the Kaplan-Meier method, for comparison of parameter *t* test or χ^2 test was used. For multivariate analyses, Cox regression analysis was used. The study was approved by the ethics committee of the Medical Faculty of Heinrich Heine University Düsseldorf.

Results

Two hundred ninety-nine MDS and sAML patients were diagnosed between 1981 and 2014 and received IC during that period. Median age at the time of IC was 59.1 years (range 18.3–79.3), and 44% of patients were female. The majority of patients (69%) received IC not at first diagnosis but after progression to higher risk MDS or AML. Median time from diagnosis to IC was 4 months (0.1–69.6). Most patients (76.6%) had a very low, low, or intermediate-risk karyotype according to the IPSS-R. More than half of the patients (60%) had a low-risk MDS-specific comorbidity index (MDS-CI). The most frequently used chemotherapy schedule was idarubicine, cytarabine, and etoposide (ICE), or an ICE-like protocol (e.g., anthracycline plus cytarabine, 3 + 7) (59.5%). All patients received cytarabine in combination with an anthracycline. Complete remission (CR) after first induction was reached by 62% of patients. Among patients not achieving CR, 70% were not given another cycle of IC. Altogether, only 40% of the patients received more than 1 cycle of IC, as a continued induction and/or consolidation therapy: 32% received 2 cycles, 7% received 3 cycles, and 1% received 4 cycles of chemotherapy. Early death rate was low (6%). Median survival after IC was 13.8 months (range 0.1–303.0). Patients receiving alloSCT ($n = 68$) were censored at the time of aSCT). Karyotypes were available in 265 patients, with 203 patients belonging to the very good, good, or intermediate karyotype risk groups according to IPSS-R, and 62 belonging to the high or very high risk groups. Complete remission was achieved by 67% of patients with lower risks karyotypes and 51% of patients with higher risk karyotypes ($p = 0.03$). Survival times were 18.9 versus 7.7 months, respectively ($p < 0.001$).

Matched pair analysis

Since MDS patients selected for IC are younger and fitter than the general MDS patient population, we conducted a matched pair analysis to permit evaluation of a possible survival benefit of induction chemotherapy. To avoid potential bias, we did not include patients undergoing allogeneic transplantation at any point in patient history into the matched pair analysis. An adequate matching partner was identified for 96 patients with MDS or sAML. Hematologic parameters, gender, distribution of karyotype risk groups, and blast count below or above 30% were not different from the entire population of 299 patients. Diagnosis was made between 1988 and 2013, and IC was administered between 1989 and 2013. Patients were 63 years old at diagnosis and 39% were female. Seventy-four percent of patients had progressed to higher risk MDS or AML at time of IC. Like in the entire study population, the majority of patients (77%) had a very low, low, or intermediate risk karyotype according to IPSS-R, and a low-risk MDS-CI (67%). Again, the most common chemotherapy regimen was ICE or an ICE-like protocol (68%). Patients included in the matched pair analysis were significantly older (*t* test; mean 54 vs. 62 years; $p = 0.?0.001$) than the entire study population, probably due to the fact that most of the younger patients were treated with alloSCT and thus excluded from the matched pair analysis.

Among patients included in the matched pair analysis, 32% received more than 1 cycle of IC, as induction and/or consolidation therapy: 28% received 2 cycles, and 4% received 3 cycles. Again, early death rate was low (5%). Median survival from the time of IC was 12.6 months (range 0.16–279.1 months). Median survival from first diagnosis was 23.3 months. Patients' characteristics are summarized in Table 1.

Remission

Complete remission after first induction therapy was reached in 50% of patients with known remission status ($n = 44$); another 19 patients (22%) reached partial remission (PR). Parameters influencing the probability to achieve CR were blast count in the bone marrow (< 30%), age < 65, presence

Table 1 Characteristics of patients included in the matched pair analysis

	IC group	Control group	
n	96	96	
Year of dx	1998 (1988–2013)	2003 (1984–2013)	$p = 0.03$
Year of ic	1999 (1989–2013)		
Age at dx	63.3 (25.9–78.1)	64.3 (37–78)	n.s.
Age at ic	64.5 (31.9–79.3)		
Female (%)	39	39	n.s.
Male (%)	61	61	
Time to IC (months)	4.1 (0.03–69.6)	n.a.	
Timing of IC		n.a.	
At first dx (%)	25		
At progression to higher-risk MDS including RAEB-T (%)	5		
AML progression (%)	70		
Blast count in BM (%)	30 (5–93)		
< 30 (%)	41		
> 30 (%)	59		
Auer rods in BM at IC (n)	7		
WHO/FAB at IC (%)			
MDS-EB I	5		
MDS-EB II	23		
CMML I	0		
CMML II	1		
RAEB-T	12		
AML (> 30% BM blasts)	59		
Karyotype risk group at IC			
Low risk	76		
High risk	24		
IPSS-R at IC in %			
Very low risk	0		
Low risk	0		
Intermediate risk	4		
High risk	9		
Very high risk	49		
Missing	38		
Hematologic parameter			
Hb (g/dl)	9.3 (3.9–12.8)	9.9 (5.8–14–5)	n.s.
WBC ×1000/μl	3.0 (0.4–184)	1.1 (0.1–14)	$p < 0.001$
NC ×1000/μl	0.67 (0–29.1)	0.3 (0.07.2.8)	$p = 0.001$
PLT ×1000/μl	54 (7–1295)	55 (2–356)	n.s.
LDH in U/l	239 (97–2817)	163 (24–378)	$p = 0.001$
MDS-CI risk group	$n = 90$	$n = 47$	
Low risk (%)	67	55	$p =$ n.s.
Intermediate risk (%)	31	35	
High risk (%)	2	10	
Type of IC (%)		n.a	
ICE/ICE-like	68		
HAM	5		
TAD	27		
Treatment with HMA (n)	4	16	
Outcome		n.a	

Table 1 (continued)

	IC group	Control group
CR n (%)	44 (50%)	
PR n (%)	19 (22%)	
Missing n (%)	14 (16%)	
Surviving patients		
1 yr. (%)	52	36
2 yr. (%)	27	25
5 yr. (%)	7	11
10 yr. (%)	2	1

dx diagnosis, *IC* intensive chemotherapy, *BM* bone marrow, *karyotype low risk* IPSS-R very low, low, and *intermediate risk groups and high risk* IPSS-R high and very high risk groups; *ICE* idarubicine, cytarabine, etopsoside; *HAM* high dose cytarabine, mitoxantrone; *TAD* thioguanine, cytarabine, daunorubicine; *CR* complete remission, *PR* partial remission, *ms* months, *yr.* years, *wbc* white blood cell count, *plt* platelet, *hb* hemoglobin, nc neutrophile count

of Auer rods, time of antecedent MDS shorter than 6 months, and timing of IC in relation to first diagnosis (summarized in Table 2.) Gender, type of induction therapy, hemoglobin below or above 10 g/dl or 8 g/dl, LDH below or above 250 U/l, WBC below or above 13×10^3/μl, or karyotype risk group were not correlated with CR rates.

We did not find any parameters being relevant in the multivariate analyses.

Overall survival

We did not find a survival benefit for patients receiving IC (12.7 months vs. 7 months, log rank $p = 0.381$) (Fig. 1). Parameters favorably influencing survival are summarized in Table 3. In the matched pair analysis, the presence of Auer rods, age below 60 years, blast count below 30%, IC at first diagnosis, and achievement of CR had a favorable impact on survival. Gender, type of induction therapy, hemoglobin below or above 10 g/dl or 8 g/dl, LDH below or above 250 U/l, and WBC below or above 13×10^3/μl were not correlated with overall survival. Patients with very low, low, or intermediate risk karyotype ($n = 74$) had a median survival of 14.7 months, and patients with high- or very high-risk karyotypes ($n = 22$) survived for a median of 7.5 months (p = n.s.). A history of antecedent MDS shorter than 6 months had no significant influence on survival (14.3 vs. 8.9 months). In a multivariate forward stepwise Cox regression analysis, complete response, presence of Auer rods, and percentage of bone

Table 2 Parameters influencing the probability of achieving CR in univariate analysis

	CR	χ^2	p value
Blast count		5.73	0.03
< 30%	71%		
≥ 30%	42%		
Age		5.64	0.005
< 65 years	68%		
≥ 65 years	31%		
Auer rods		5.66	0.027
Yes	100%		
No	49%		
Timing of IC			
At first diagnosis	57%	6.06	0.025
Progression	42%		
AHD			
< 6 months	75%	10.29	0.002
> 6 months	25%		

IC intensive chemotherapy, *AHD* antecedent hematologic disease

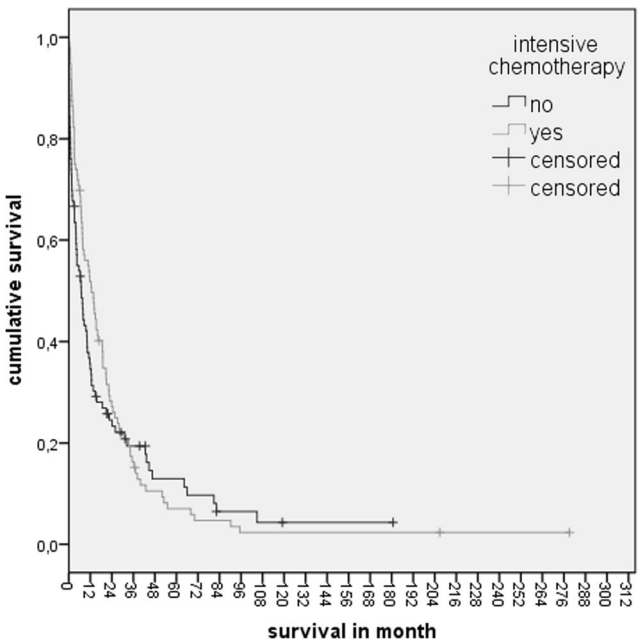

Fig. 1 Survival times in matched pair analysis

Table 3 Univariate analysis of parameters influencing survival

	Median survival in month	*p* value
Blast count at IC		0.001
< 30%	21	
≥ 30%	8.4	
Age		0.012
< 60 years	22.4	
> 60 years	11.7	
Auer rods		0.001
Yes	40	
No	7.8	
CR		< 0.001
Yes	6	
No	19	
Timing of IC		0.002
At first diagnosis	22.4	
At progression	10.7	

IC intensive chemotherapy, *CR* complete remission

marrow blasts below or above 30% significantly influenced median survival. Parameters not entered into the equation were age of the patient and timing of IC (Table 4).

Relapse

Relapse status was evaluable in 76 patients, of whom 48 (63%) relapsed after a median time of 9.9 months (1–51). Survival after relapse was 7.6 months (range 0.4–201.6). Relapse therapy was known for 31 patients: 8 patients received best supportive care, 1 patient received alloSCT, 10 patients IC, 10 patients low-dose chemotherapy or hypomethylating agents, and 2 patients immunosuppressive therapy.

Discussion

Our analysis shows that intensive chemotherapy for patients with high-risk MDS or secondary AML does not lead to substantial improvement of overall survival. We did not find a survival benefit of IC in comparison with any other, less intensive treatment. After intensive chemotherapy, the relapse rate was high (63%) and the time in remission was short (9.9 months). The comparatively small number of patients that could be included into the matched pair analysis is restricting the statistical power of our analyses.

Table 4 Multivariate analysis of parameters influencing survival

Variable	Wald	*p* value
CR after IC	7.564	0.006
Blast count < 30%	16.525	< 0.0005
Auer rods	8.757	0.003

IC intensive chemotherapy, *CR* complete remission

Our group has previously shown that intensive chemotherapy should not be recommended to older patients (> 60 years) with aberrant karyotypes [2]. This position was corroborated by other investigators [7]. We also reported that intensive chemotherapy is not significantly better than best supportive care (BSC) in such patients (21 vs. 14 months; $p = 0.36$) [8]. Accordingly, the use of intensive chemotherapy for patients with MDS decreased substantially at our institution, from 11.6 to 4.7%, comparing the period between 1982 and 2001 with the period between 2002 and 2011 [1].

Studies looking at the treatment of higher-risk MDS or sAML usually compare different chemotherapy regimens. The few studies that compare IC with an alternative treatment option, are in agreement with our results. Morita and colleagues did not find a survival benefit for patients with high risk MDS and secondary AML who received IC in comparison to patients treated with low-dose cytarabine (2-year survival rate; 28.1 vs. 32.1%) [9]. In 2009, Fenaux et al. published the results of a randomized clinical trial in patients with high-risk MDS or AML with low blast count (refractory anemia with excess of blast in transformation, RAEB-T), which compared azacitidine with conventional care regimens (BSC or low-dose cytarabine or IC). Overall survival was significantly better (24.5 vs. 15 months) with azacitidine treatment. However, the difference between azacitidine and IC (25.1 vs. 15.7 months) did not reach statistical significance ($p = 0.51$), due to a relatively small number of patients receiving IC [3]. A subgroup analysis in elderly patients (median age 70 years) also showed longer overall survival (24.5 vs. 16 months) with azacitidine, (azacitidine vs. IC, median not reached vs. 14.2 months). Patients receiving azacitidine spent significantly fewer days in hospital [10]. In our experience, patients treated with azacitidine received a median of six treatment cycles and spent an average of 12 days in hospital [11]. Induction chemotherapy can be associated with a mortality rate as high as 29% [12]. This problem can be avoided with hypomethylating agents (HMA). Accordingly, Kantarjian et al. showed that the results of treatment with another HMA, i.e., decitabine, were also superior to intensive chemotherapy for patients with high-risk MDS [13]. Taken together, treatment with HMAs is characterized by fewer side effects, better quality of life, and longer overall survival, compared with intensive chemotherapy in patients with higher-risk MDS or sAML.

Regarding different chemotherapy regimens, we did not find an advantage for any of the protocols applied. Many attempts at improving CR rates and outcomes by changing the classical "3 + 7" anthracycline plus cytarabine protocol

have failed, like, for instance the combination of mitoxantrone and etoposide [14]. Beran et al. showed, by covariate adjusted analysis, that treatment with fludarabine and cytarabine with or without idarubicine is not superior to idarubicine and cytarabine [15]. The use of topotecan in combination with cytarabine produces similar CR and survival rates and may be an alternative for patients with cardiac contraindications for the use of anthracyclines [16].

The factors that influenced survival on multivariate analysis in our matched pair patients were achievement of complete response, presence of Auer rods, and percentage of medullary blasts below or above 30%.

Of interest, six out of seven patients with Auer rods, indicating a certain trend to differentiation, achieved CR, which is reminiscent of patients suffering from core-binding factor AML [17–19].

In the entire cohort, good-risk karyotypes were associated with a better outcome as well. Buckley and colleagues identified grade 4 neutropenia at the start of treatment to increase the risk of death during IC [20]. Oosterveld et al. developed a score to predict the outcome of IC on the basis of the CRIANT and AML-10 clinical trial data. The score includes cytogenetics, WBC, age, performance status, AHD, and number of cytopenias [21]. However, a major shortcoming of their analysis is the restriction to patients younger than 65 years; the results are thus not representative of the majority of patients with MDS. In our study, a shorter than 6-month duration of antecedent MDS was significant for reaching CR, potentially because less clonal evolution could happen, similar to the study of Bello et al. [7].

Gemtuzumab-Ozogamicin (GO) at a dosage of 5 mg/m^2 has also been tried in combination with IC in patients with AML, sAML, and high-risk MDS and has not improved survival [22, 23]. Nevertheless, on the basis of a meta-analysis showing a small survival benefit (5-year overall survival 35.5% vs. 32.2%) [24], a dosage of 3 mg/m^2 was further evaluated and yielded better results [25], especially in patients with good-risk cytogenetics. GO plus decitabine, in comparison to historic controls, also improved CR rates but did not increase overall survival in relapsed MDS or sAML [26]. While the role of GO is not conclusively defined, it is unlikely that the addition of GO will establish a new era of IC for patients with high-risk MDS or sAML.

Allogeneic stem cell transplantation is superior to IC alone in patients with MDS and CMML [5]. In 2010, a large multicentre study showed better survival with intensive chemotherapy followed by alloSCT, compared with IC plus autologous stem cell transplantation or IC alone, in a donor/no-donor design [27]. The question whether cytoreductive therapy is required prior to alloSCT is still a matter of debate [28–30] and an area of continued investigation [31]. We and others demonstrated encouraging results for upfront alloSCT [32, 33] in cases where a suitable donor is available without much delay. This approach is endorsed by the European Leukemia Net Guidelines, which recommend IC only for "fit patients without a suitable donor who are younger than age 65 to 70 years and have 10% or more bone marrow blasts without adverse cytogenetic characteristics" [34]. However, even those patients have a poor outcome with intensive chemotherapy.

In summary, considering that a matched related, unrelated, or haploidentical donor can be identified for the majority of patients, the results of our analysis allow the conclusion that induction chemotherapy is not recommendable for patients with high-risk MDS or sAML, unless such therapy is needed as a "bridge," leading to alloSCT later on.

Author contributions Esther Schuler performed the research, analyzed the data, and wrote the paper; Natalie Zadrozny performed the research, Sabine Blum contributed essential data, designed the research study, and approved the manuscript, Thomas Schroeder, Corinna Strupp, Barbara Hildebrandt, Andrea Kündgen, Norbert Gattermann, Carlo Aul, Mustafa Kondakci, Guido Kobbe, and Rainer Haas contributed essential data and approved the manuscript; Ulrich Germing designed the research study, analyzed the data, and wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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