Efficacy and toxicity of low-dose melphalan in myelodysplastic syndromes and acute myeloid leukemia with multilineage dysplasia

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Effective therapy of myelodysplatic syndromes and acute myeloid leukemia originating from myelodysplastic syndrome has remained an unresolved problem. Advanced age of the patients and persistent pancytopenia make the treatment difficult. Despite large number of therapeutic options none of them is satisfactory. Recently palliative treatment with low-dose melphalan has been reported to have certain activity.

The aim of the study was to evaluate the efficacy of low-dose melphalan in high-risk myelodysplastic syndromes (MDS) and acute myeloid leukemia with multilineage dysplasia (AML). Twenty three patients were eligible for the study: 8 with MDS and 15 with AML with multilineage dysplasia. All of them received oral melphalan in a daily dose of 2 mg. Median total dose of the drug was 120 mg (40–840 mg). Ten patients responded to the therapy. We observed complete remission (CR) in 4, partial remission (PR) in 3 and stabilization of the disease in 3 patients. Thirteen patients did not respond to the therapy. The survival time of the patients from the day of diagnosis and from the beginning of the treatment with melphalan was longer in patients responding to the therapy (median 15 and 10 months, respectively) than in non-responders (4.5 and 4 months, p=0.003 and p=0.008, respectively).

Low-dose melphalan shows significant activity in high-risk MDS and AML with mulitlineage dysplasia with acceptable toxicity.

Key words: Myelodysplastic syndromes, myeloid leukemia with multilineage dysplasia, treatment, melphalan.

Myelodysplastic syndromes (MDS) form a heterogenous group of hematologic malignancies, characterized mainly by ineffective erythropoiesis, trilineage dysplasia and increased blast percentage in bone marrow [7, 11, 12]. The prognosis is poor, because of longlasting pancytopenia and progression to acute myelogenous leukemia (AML). Although many therapeutic strategies have been employed, the disease remains incurable [10, 13, 14, 16, 17]. Younger patients with high-risk MDS may be given aggressive chemotherapy, however the longlasting remissions are infrequent and relapse inevitable [3, 6]. Most patients with MDS are aged 60 or more and this makes the therapeutic decisions even more difficult. Supportive care is still the treatment of choice for those, who are not eligible to receive standard chemotherapy. Low-dose cytosine arabinoside and mercaptopurine are applied most often as palliative treatment resulting in 20–40% of responses [6, 14]. Recently low-dose melphalan has been evaluated in MDS and AML with some activity and acceptable toxicity [5, 9, 15]. Here we report our exprience with low-dose melphalan in high-risk MDS and AML evolving from MDS.

Patients. Twenty three patients with MDS or AML with multilineage dysplasia, diagnosed according to WHO criteria (2,19), were enrolled to the study. MDS (refractory anemia with excess of blasts, RAEB) was diagnosed in 8 patients and AML after MDS in the rest of them. Bone marrow biopsy was normocellular or hypercellular in twenty and hypocellular in three cases. The patients were eligible for the study if they had performance status according to WHO 3 or less and life expectancy of 6 weeks or more. Abnormal hepatic or renal function excluded patients from the study. Clinical characteristics of the treated group is

Table 1. Clinical data of the MDS and AML patients treated with melphalan

		Number of patients
Age (years) – median (range)	75.5 (48.0–82.0)	
Sex	Male	14
	Female	9
Disease	MDS (RAEB)	8
	sAML	15
Prior therapy	Mercaptopurine	4
	Danazol	2
	None	17

Table 2. Peripheral blood parameters at the beginning of treatment with Melphalan

Peripheral blood parameters	Median (range)	SD
Leukocytes x 10^9/L	2.8 (1.0–22.6)	5.7
Neutrophils (%)	28.0 (4.0–74.0)	16.4
Blasts (%)	0.5 (0–48)	11.2
Erythrocytes x 10^{12}/L	2.0 (0.9–4.8)	0.8
Hb g/L	68 (41–129)	21
PLT x 10^9/L	80.0 (17.0–764)	159.7

given in Table 1. Mercaptopurine was used prior to chemotherapy with melphalan in 4 cases and danazol in 2 cases. Seventeen patients were previously untreated. The patients were given orally 2 mg of melphalan daily untill maximal response or progression. The dose was reduced twice in case of worsening of pancytopenia. Peripheral blood counts were assessed routinely.

Response to the treatment was assessed according to the criteria by Cheson et al [4]. A complete remission (CR) was diagnosed when normalisation of peripheral blood parameters was achieved (hemoglobin greater than 110 g/L, neutrophiles more than $1.5x10^9/mm^3$, platelets more than $100x10^9$/L) and less than 5% of blasts in bone marrow with no signs of dysplasia. Partial remission (PR) was stated when all peripheral blood parameters were normal and blast percentage decreased by 50% in bone marrow. Stabilization of the disease was defined as failure to achieve PR, with no signs of progression for at least two months.

Statistics. Statistical analysis was performed using log-rank test. Differences were significant when $p<0.05$.

Results

Response. The median total dose of melphalan given to the patients was 120 mg (range 40–840 mg). The median time of treatment was 2 months (range 0.75–14 months). Median survival time of patients treated with melphalan from the time of diagnosis was 7 months (range 1–22 months), and from the beginning of the therapy with melphalan – 6 months (range 1–19 months).

Ten (41%) of our patients responded to the therapy. Complete remission (CR) was observed in 4 (16%) of them, PR in 3 (12%) and a stabilization of the disease in 3 (12%) patients. Their survival time from the diagnosis and from the beginning of the treatment was longer (median 15, range 4–22 months and 10, range 3.5–19 months, respectively) than that of non-responding patients (median 4.5, range 1–18 months, $p=0.006$ and median 4.0, range 1–18 months, $p=0.038$). Survival time of the patients responding and non-responding to chemotherapy with melphalan are shown in Figures 1 and 2. Responses were achieved after median time of 2 months (range 1–4 months) and lasted for median 4 months (range 2–12).

Two of the patients achieving CR were diagnosed with MDS and two with AML. All of the patients with CR eventually relapsed. Two of them (both with MDS) received melphalan as first treatment of relapse and neither of them responded. Two of the patients achieving PR were treated because of AML and others because of MDS. One of the patients, aged 82, diagnosed with AML-M4 died because of cerebral stroke while in CR. In three cases stabilization of disease was observed. MDS was diagnosed in two of those patients and sAML in one. Melphalan therapy reduced hyperleukocytosis and blast percentage in peripheral blood in sAML patient as well as in both patients with MDS at the time of disease progression to AML. In one patient we observed two times lower transfusion requirement after treatment.

Toxicity. The toxicity related to the treatment was mild. We observed transient worsening of neutropenia in most patients. Three patients had grade III neutropenia with nadir of neutrophil count in the 6th week of treatment (range 5–8 weeks). In all those cases peripheral blood neutrophils increased 3 weeks after cessation of the therapy. There were no infectious complications related to the treatment. One of the patients received G-CSF because of severe neutropenia with related infections, however, in this case neutropenia resulted from the progression of the disease refractory to the treatment.

Discussion

Therapeutic strategies in MDS vary from supportive care in older patients through low-dose chemotherapy to intensive chemotherapy with autologous stem-cell transplantation. The only way to cure the disease is allogeneic stem cell transplantation, although this procedure is available in extremely rare cases, including only patients of age 50–55 years with HLA-matched donor. Differentiating agents

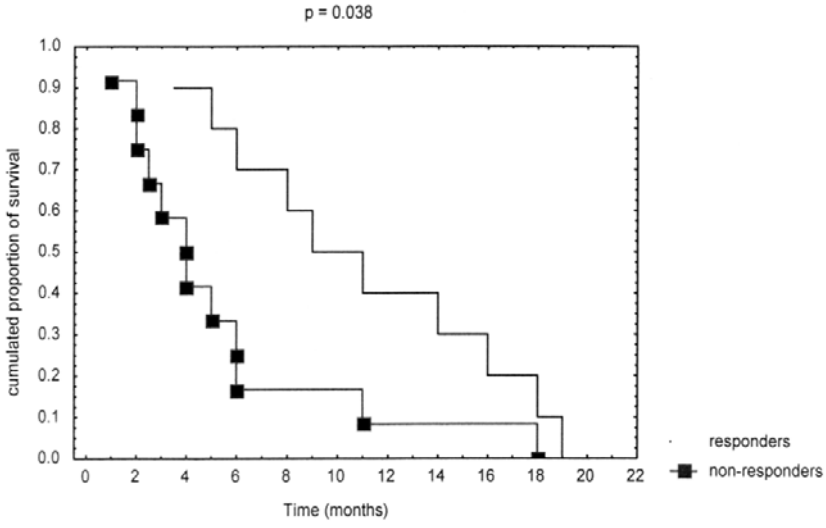

Figure 1. Survival time from the beginning of treatment of patients responding and non-responding to melphalan chemotherapy. Patients diagnosed with MDS and sAML were given 2 mg melphalan daily. Statistics was evaluated using log-rank test.

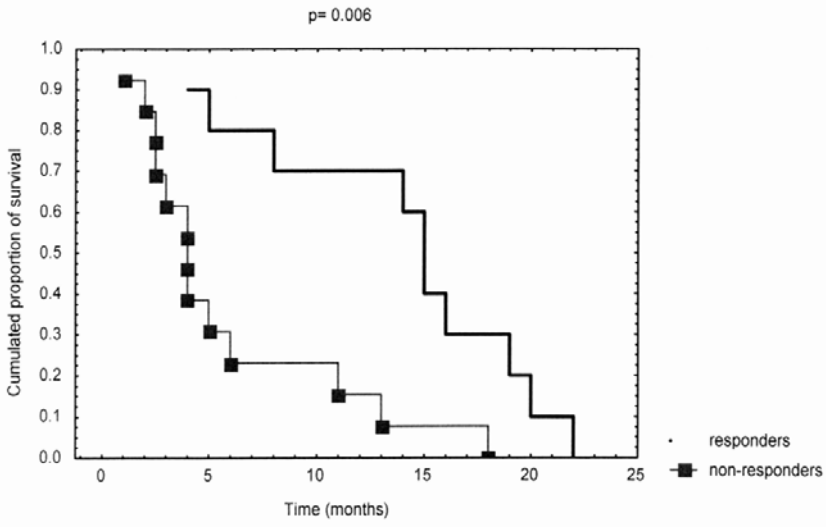

Figure 2. Cumulated proportion of survival from diagnosis of patients responding and non-responding to the treatment with melphalan. Patients diagnosed with MDS and sAML were given 2 mg melphalan daily. Statistics was evaluated using log-rank test.

such as cis-retinoic acid or amiphostine have limited activity and no influence on survival time of patients [10, 13]. Prolonged use of growth factors (granulocyte-macrophage colony stimulating factor, GM-CSF or granulocyte colony stimulating factor, G-CSF) instead of treating MDS may contribute to the shortening of survival time of the patients [8, 17]. Intensive chemotherapy is possible only in the minority of cases because of advanced age of most patients and comorbidities resulting in high mortality of chemotherapy. The option most often used is palliative treatment with cytostatics in low-doses.

Silverman et al [18] have recently presented results from the first randomized trial comparing supportive care and palliative chemotherapy with azacytidine in MDS patients. The authors observed higher response rate (both CR and PR), better quality of life, prolonged time to leukemic transformation, but no increase in survival time in the group receiving chemotherapy. The results of this trial indicate that efficacy of palliative chemotherapy should not be estimated only by CR or PR rates. Response criteria in MDS should include also improvement of quality of life, reduction in transfusion requirement or prolongation of time to leukemic transformation.

We observed the response to low-dose melphalan treatment in 41% of our patients. Our results are in agreement with previous reports [5, 15]. Lower CR rates in our study than those achieved by Denzlinger et al [5] or Omoto et al [15] may be due to different response criteria and classifications of the disease used in the trials. The clinical characteristics of the patients differed in all cases: all patients described by Omoto et al [15] were diagnosed with MDS, the majority of the patients in Denzlinger's [5] study were also diagnosed with MDS (14 of 21) and only 7 of 21 with AML according to FAB classification [1], while in our study 8 patients were diagnosed with MDS and 15 with AML according to WHO classification [2, 19]. The therapy was well-tolerated, as it had been described previously [5, 9, 15].

Omoto et al [15] and Denzlinger et al [5] observed that low bone marrow cellularity correlates with higher response rates, including CR, after melphalan administration. It is hard to evaluate the activity of melphalan in MDS with hypocellular bone marrow in our trial, because only three of our patients belong to this group. Two of them responded to the treatment, one achieving PR, the other a stabilization of disease and decrease in transfusion requirement. Third patient did not respond to the treatment.

It is not clear which of the cytostatics should be used as palliative treatment in MDS. Randomized trials comparing activity of different chemotherapeutics are necessary to answer this question. Best cytostatics used in palliative treatment should combine some features enabling an out-patient treatment: high oral bioavailability, high activity and low

toxicity. Taking this into account, melphalan seems to be a good choice.

In conclusion, low-dose melphalan is effective agent with acceptable toxicity in palliative treatment of MDS and AML with multilineage dysplasia and seems to be a good therapeutic option especially in older patients, even those with poor performance status. Further clinical trials are warranted to determine melphalan role in the treatment of these diseases.

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