Treatment decision-making for older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia: problems and approaches

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Background and Objectives. High-risk myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are mainly diseases of patients over the age of 60 years. In these patients, intensive chemotherapy and/or allogeneic blood stem cell transplantation are the only curative treatment approaches, while non-curative options include low-dose chemotherapy or best supportive care alone. The basis for treatment decision-making in this clinically and biologically heterogeneous group is not well defined.

Design and Methods. In order to investigate treatment stratification patterns and outcomes in this population, we performed a systematic literature search in MedLine for relevant clinical reports published between 1989 and 2006. Only large population-based investigations and publications of clinical trials with more than 40 patients were analyzed.

Results. In 36 AML studies involving a total of 12,370 patients (median age 70 years) median overall survival approached 30 weeks for intensively treated patients. In patients receiving best supportive care alone, or best supportive care plus non-intensive treatment, median overall survival was 7.5 and 12 weeks, respectively. The complete remission rate after induction was 44%, and in those patients who achieved complete remission age no longer influenced prognosis. In 18 large studies approximately 50% of AML patients received induction therapy, 30% non-intensive chemotherapy and 20% supportive care only.

Interpretation and Conclusions. Due to the scarcity of randomized AML/MDS trials in which older patients are assigned to either induction or less intense therapy, predictors to identify older patients most likely to benefit from intensive therapy and novel tools to optimize (or even standardize) recommendations are needed. We propose that in this patient population in the future, geriatric assessment instruments and comorbidity scoring are implemented in treatment decision-making.

Key words: geriatric assessment, comorbidity, induction chemotherapy, allogeneic transplantation.

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Advanced age is not only associated with a higher risk of developing malignant diseases, but also an increased vulnerability to other, less well quantifiable age-related health and social problems. Older patients with myelodysplastic syndrome (MDS) fare significantly worse than their younger counterparts. In the case of acute myeloid leukemia (AML) the difference in clinical outcome is so striking that it can even be hypothesized to be a distinct disease from AML in younger patients. MDS and AML appear to form a biological continuum in an aging population. While patients depend on expert recommendations from their physicians, uncertainty persists on how to identify patients who would benefit most from either intensive induction or low-intensive treatment or even best supportive care alone. Both patient- and disease-specific factors have been shown to be of prognostic relevance and to influence the decision-process. We searched the recent literature to find evidence supporting the use of either curative or non-curative treatment. To facilitate the decision-making process for both patients and physicians, we recommend further study and validation of geriatric assessment tools.

High-risk MDS and AML: a biological and clinical continuum

Epidemiology and key facts

MDS are hematologic disorders predominantly of older patients, with an incidence of about 3.5-4 per 100,000 population per year. In people over the age of 70 years, incidence rates rise to 15 to 50 per 100,000 individuals.[1] The primary goals for patients with MDS are to improve quality of life, control clinical symptoms due to cytopenias, improve overall survival and slow the evolution to AML.[2] Options range from high-intensity treatment requiring hospitalization (e.g. AML-type induction chemotherapy) to low-intensity treatment in an outpatient-setting (e.g. differentiation-inducing agents,[3] biological response modifiers and immunosuppressive agents)[4] and to supportive care only. For results on overall survival achieved by different therapeutic approaches see Table 1. AML, like MDS, is also primarily a disease of later adulthood: patients newly diagnosed with AML have a median age of 65 years.[5] From 2000 to 2003, the USA incidence rate in people under the age of 65 was only 1.8 per 100,000, while

Table 1. Survival of patients with MDS - large clinical trials with various treatments.*

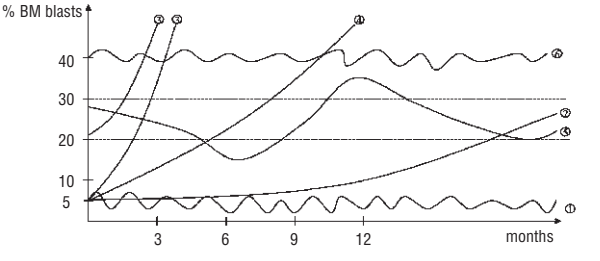
Study	*Number of patients*	*Median age (years)*	*Treatment (% overall responses)*	*Median Survival (months)*
Miller 1992[80]	141	70	Low-dose-ARA-C (32)	6.9
			Best supportive care (0)	5.1
Gerhartz 1994[81]	108	65	LD-ARA-C +GMCSF (39)	n.g.
			-GMCSF (39)	
Hornsten 1995[82]	113	73	various (n.g.)	13
Greenberg 1997[2]	816	69	Best supportive care, growth factors or low-dose chemotherapy[4] (n.g.)	IPSS low: 5.7 yrs IPSS intermediate 1: 3.5 yrs IPSS intermediate 2: 1.2 yrs IPSS high: 4.8 months
Hellström-Lindberg 1998[83]	71	69	G-CSF ± EPO (38)	26
Wijermans 2005[67]	177	68	Decitabine (49)	15
Beran 2001 *et al.* [84]	394	58	IA n=67 (n.g.)	22
		63	FA n=76 (n.g.)	8
		62	FAI n=118 (n.g.)	7.5
		64	TA n=74 (n.g.)	11
		63	CAT-G n=59[2] (n.g.)	n.g.
de Witte 2001[85]	184	47	Intensive chemotherapy and allogeneic or autologous stem cell transplantation[3] (n.g.)	13
Silverman 2002[86]	191	68	Low-dose azacitidine (60)	20
			Best supportive care (5)	14
Zwierzina 2005[87]	201	65	Low-dose ARA-C (44.1)	18.7
			Low-dose ARA-C + GM-CSF (33.9)	14.7
			Low-dose ARA-C + Il-3 (40.3)	20.2
Kantarjian 2006[78]	170	70	Decitabine (30)	12.1 (without AML)
			Best supportive care (0)	7.8 (without AML)

*Variations in treatment results should be considered in the context of MDS being a heterogeneous disease and the confounding effect of patient selection.*only studies with >40 patients included. IA: Idarubicin+high-dose ARA-C, FA: fludarabine+high-dose ARA-C, FAI: fludarabine; ARA-C: idarubicin; TA: topotecan; ARA-C; CAT-G: cyclophosphamide.*

the incidence rate in people aged 65 or over was 17 per 100,000.[6] Treatment options will be discussed below.

Similarities and differences between MDS and AML

MDS are classified into subgroups depending on the percentage of bone marrow blasts as set out by the French-American-British (FAB) consensus conference (1982).[7] However, subgroups are clearly not static over time and often the disease evolves into AML, rendering the separation between AML and MDS difficult (Figure 1). The blast threshold for the diagnosis of AML in the WHO classification has been lowered from 30% to 20%. What was established as refractory anemia with excess blasts in transformation (RAEB-t) has now been proposed to be excluded from the MDS category.[8-12] The new WHO classification of MDS has recently been proven to be of relevant prognostic value.[13] The International Prognostic Scoring System (IPSS)[2] was established to discriminate prognostic subgroups of MDS, taking into account variables such as age, clinical data, presence of cytopenias and cytogenetic abnormalities. This system defines four risk groups for both survival and AML evolution: low, intermediate-1, intermediate-2, and high risk.[14-18] That MDS and AML constitute a biological continuum is also reflected by the fact that in the majority of AML multicenter clinical trials the blast percentage threshold has been lowered to include also those patients who, according to the FAB classification, have MDS, as revealed by a systemat-



1 indolent *low risk* MDS
2 evolving *high risk* MDS
3 acute myeloid leukemia (with or withou multilineage dysplasia)
4 AML from MDS (>6 months duration)
5 RAEB-t (FAB classification) = AML (WHO classification)
6 smouldering AML (FAB and WHO classification)

Figure 1. MDS and AML - biological continuum.

Table 2. Cytogenetic similarities between MDS and AML in population-based studies.

	Age (years)	n.	Karyotype abnormalities (%)						
			no	single	double	complex	numerical	chromosome 5	chromosome 7
Rossi 2000[27]	n.g.	35	31	14	17	37	89	20	27
MDS/AML	>65	48	27	13	14	46	93	31	27
Mauritzson 1999[26]									
MDS	>65	281	48	28	7	16	49	22	12
AML	>65	161	51	24	6	20	49	16	8
Preiss 2003[88]									
AML	median 67	303	47	41	15	44	24	15	16
Sanderson[25]	median 62	1709	45	n.g.	n.g.	24	n.g.	17	n.g.
AML									

Table 3. Population-based studies in acute myeloid leukemia.

Study (Country)	Publ. year	Median age (yrs) (range)	Total no. of pts	Induction: n. (%)	Other therapy: n. %)	Supp: n. (%)	Median survival (weeks)			
							all	IC	NIC	Supp.
Wahlin (Northern Sweden)[30]	1991	63 (17-91)	113	77(68)	n.g.	n.g.	7	n.g.	n.g.	n.g.
Taylor (Northern England)[89]	1995	71 (56-95)	200	84(42)	39 (20)	77 (38)	8	20	4	<4
Bauduer (France)[90]	1999	77 (65-91)	56	27(48)	27 (48)	2 (4)	12	n.g.	n.g.	n.g.
Menzin[91] (USA)	2002	>65 (n.g.)	2657	790 (30)	n.g.	n.g.	n.g.	28	4	n.g.
Pulsoni (Italy)[34]	2004	69 (n.g.)	1005	621(62)	280 (28)	104(10)	n.g.	28	20	n.g.

Supp.: supportive treatment only; n.g.: not given; IC: intensive chemotherapy; NIC: non-intensive chemotherapy.

ic evaluation of 24 AML trials active within the European-LeukemiaNet (ELN). (*Lübbert M, Deschler B, Haas PS, unpublished result, June, 2005*). Due to the frequent progression of high-risk MDS to AML, an increased incidence rate of MDS with age appears to partly explain both the high incidence and poor prognosis of AML in the elderly. It is characterized by common cytogenetic abnormalities shared with MDS and frequent multilineage dysplastic morphology in residual hematopoietic precursors.[19,20] Acquired clonal chromosomal abnormalities are found in at least 50% of AML,[21-24] with higher incidences in patients with secondary leukemia[25] or of older age.[26,27] Multiple studies including population-based investigations[25] (Table 2) have demonstrated the prognostic importance of cytogenetic abnormalities in AML, making this at present the most important predictor of short-[22,23,28-30] and long-term[31] outcome.

Treatment of older patients with high-risk MDS or AML

Induction chemotherapy versus non-curative approaches

The discussion of whether intensive chemotherapy - offering a limited but significant survival benefit - should be applied to patients with MDS or AML is still a topical and unresolved matter. In 1989, Löwenberg *et al.* compared survival in a prospective study of intensive induction therapy versus a *wait and see* strategy in patients >65 years with AML. Patients with good performance status and organ function given standard treatment lived longer (median survival: 21 weeks) than those given initial supportive care only (median survival: 11 weeks). Both groups spent an equal amount of time in hospital (55 vs 50%).[32] No comparable large randomized investigation has been performed in recent years, nor has a meta-analysis on the available data been published.

Table 3 summarizes our literature search results (Medline 1989-2006) of population-based studies including more than 40 patients. These results reveal that outside of clinical trials, a large number of older patients were never referred to a center where induction chemotherapy could be performed. Patient selection regarding referral for treatment appeared to be the first of several steps of withholding intensive treatment from elderly and adopting palliative measures. Yet, once remission had been achieved, age no longer appeared to have an impact on prognosis.[33] A recent retrospective study[34] by the GIMEMA focusing on survival of 1,004 consecutively documented patients >60 years with AML revealed that two-thirds of patients were referred for induction treatment, but patients in the low-dose or palliative group had a higher median age, a worse performance status and a

Table 4. Intensive versus non-intensive chemotherapy in AML patients ≥55 years.*

Study	Year	Median Age (years; Range)	Pts: n	IC: n (%)	NIC: n (%)	Supp. : n (%)	IC: CR-Rate (%)	Median overall survival (weeks) IC	Median overall survival (weeks) NIC	Median overall survival (weeks) Supp.
Sebban[92]	1988	70 (n.g.)	69	35(50)	22 (32)	12(18).	48	30	34	4
Löwenberg[32]	1989	>65 (65-85)	71	31(51)	n.a.	29(49)	58	21	n.a.	11
Orlandi[93]	1990	67(60-85)	103	52(50)	28(27)	23(22)	34	14	n.g.	n.g.
Bassan[94]	1992	n.g.(60-82)	118	78(66)	40(34)	0	29	n.g.	13	n.g.
Baudard[95]	1994	72 (60-94)	235	108(46)	127(54)	n.g.	33	~ 35	3	n.g.
Ferrara[96]	1998	79 (76-86)	70	22(31)	7 (10)	41 (58)	32	16	16	20
Baudard[97]	1999	71 (60-99)	372	207 (56)	92 (25)	72 (19)	29	22	n.g.	n.g.
Spataro[98]	2000	74 (65-88)	74	51(69)	23(31)	0	57	36	6	n.a.
Lopez[99]	2001	70(60-98)	265	176(67)	89(33)	n.g.	36	n.g.	n.g.	n.g.
Yoshiba[100]	2001	72(60-92)	112	29(26)	58(56)	19(17)	69	n.g.	n.g.	n.g.
Wahlin[30]	2001	73 (60-90)	211	27(48)	27(48)	2(4)	43	n.g.	n.g.	n.g.
Behringer[101]	2003	67 (56-89)	138	73(53)	65(47)	n.g.	47	34	11	n.g.
Vey[102]	2004	72 (65-91) 69 (65-74) 78 (75-91)	310 200 110	 156(78) 62(56)	 34(17) 40(36)	 10(5) 8(7)	 49 45	 40 16	 n.g. n.g.	 n.g. n.g.

*IC: intensive chemotherapy; NIC: non-intensive chemotherapy; Supp.: supportive care only; CR: complete remission; n.g.: not given; *only studies involving more than 40 patients are listed.*

higher rate of antecedent hematologic disease. Contrary to several other reports, the intensive treatment group had - despite the selection of *lower-risk patients* - a survival advantage of only 2 months (median survival 7 versus 5 months) while spending twice the time in the hospital (41 versus 22 days). Table 4 summarizes the results of large, mainly retrospective studies investigating the outcomes of older patients treated with curative intent (intensive chemotherapy) or non-curative approaches (non-intensive therapy). The study outcomes - obtained during a broad span of time - must be considered in the light of possible differences in patient management over time. However, consistently throughout these trials, about 50% of patients were treated intensively, 30% with non-intensive modalities, and 20% received supportive care only. Table 5 lists results of studies involving a total of 4,798 patients receiving various remission-induction treatments. Varying dose intensities of ARA-C and anthracyclines to optimize the risk/benefit ratio have decreased both early mortality and efficacy, resulting in no improvement in survival.[35-41] These data, without resembling a Cochrane analysis, provide relevant information. Averaging all the results of the 36 mentioned larger AML trials and retrospective evaluations (Tables 2-5), the intensive approach resulted in a median survival of 30 weeks (~7 months) as compared to 12 weeks (<3 months) for non-intensively treated patients and 7.5 weeks for patients receiving supportive treatment only.

To further delineate prognostic factors influencing treatment outcome of intensively treated older high-risk MDS and AML patients, 998 patients (age >65 years) treated intensively were retrospectively analyzed for independent poor prognostic risk factors for complete remission, 8-week mortality, and survival. These factors were: age >75 years, unfavorable karyotype (often complex), poor performance status (ECOG 3-4), antecedent hematologic disorder lasting >12 months, treatment outside the laminar airflow room, and abnormal organ function. It was possible to divide the patients into three risk groups with complete remission rates ranging from <24% to >72% and treatment-related mortality rates from <10% to >50%.[42] Wheatley *et al*. identified cytogenetics, secondary AML and high white cell count as factors related to poor overall survival in older patients treated with intensive chemotherapy within the UK AML11and AML14 trials. (*Wheatley K, Brookes C, Hills R et al. Blood 2005;106: Abstract 674*). Gupta *et al*. also identified disease biology (specifically cytogenetics, previous history of MDS/AHD, leukocyte count) and performance status rather than age as the most important determinants of survival in older patients (≥60 years) treated with intensive chemotherapy.

Allografting

Allogeneic hematopoietic stem-cell transplantation has a high potential to cure patients with myeloid neoplasias.

Table 5. Intensive chemotherapy: treatment results in older patients with AML.

Study	Year	Median age (yrs), (range)	Pts. No.	IC: n(%)	IC: CR(%)		Median overall survival (weeks)
Kahn[103]	1984	>70 (n.g.)	40	DAT 100%: 20(50) DAT reduced: 20(50)	28 28	23	4
Yin[104]	1991	68 (60-81)	104	104(100)	58		36
Wiernik[105]	1992	>60 (n.g.)	80	ARA-C+Ida: 39 (49) ARA-C+DNR: 41 (51)	46		14 13
Ruutu[106]	1994	74 (67-87) 72 (65-85)	51	27(51)[4] 25(49)[5]	23 60		14.8 39.6
Mayer[107]	1994	>60 (n.g.)	346	346(100)	47		n.g.
Reiffers[108]	1996	n.g. (55-75)	220	IDA: 112(51) DNR:[6] 108(49)	59 54	39	47
Archimbaud[109]	1999	69 (60-83)	160	160(100)	59		28
Löwenberg[110] EORTC-HOVON AML-9	1998	68 (n.g.)	489	DNR: 242(49) MTZ: 247(51)[7]	38 47		36 39
Bouabdallah[111]	1999	76 (61-89)	51	51(100%)[8]	n.g.		16
Goldstone[112] (MRC-AML-11)	2001	66 (n.g.)	1314	DAT[9] ADE MAC	62 50 55		n.g. n.g. n.g.
Baer[113]	2002	70 (60-84)	120	ADE: 61(51) ADEP:[10] 59(49)	46 39	32	28
Dalley[114]	2002	67 (60-83)	75	75(100)	45		52
Anderson[115]	2002	>55 (n.g.)	328	AD: 161(49) ME:[11] 167(51)	43 34	24	36
Öberg[116]	2002	70 (60-89)	90	TAD: 43(47) TAA : 47(53)	51 47	11	49
Haferlach[117]	2003	> 60 (n.g.)	204	TAD	56		38
Rowe[118]	2004	68 (56-86)	348	DA 116 (33) IA 118 (34) MA 114 (33)	40 46 30		31 30 29
Schlenk[119]	2004	66.6 (61-84)	242	ICE 120 (49.4) ATRA-ICE 122(50.4)	39 52	45,2	28
Büchner[120]	2006	> 60 (60-85)	930	TAD-HAM 473(50.9) HAM-HAM 457(49.1)	53 53	19% at 3 yrs	18% at 3 yrs.

IC: intensive chemotherapy; CR: complete remission; [4]TAD:ARA-C+daunorubicin+thioguanine; [5]ETI oral; [6]IDA: ARA-C+idarubicin; DNR: ARA-C+daunorubicin; [7]DNR: ARA-C+daunorubicin; MTZ: ARA-C+Mitoxantrone; [8]Idarubicin orally: 20 mg/m²/week for 4 weeks; [9]DAT 3+10: daunorubicin, ARA-C, thioguanine; ADE 10+3+5: ARA-C, daunorubicin, Etoposide; MAC 3+5: mitoxantrone, ARA-C; [10]ADE: ARA-C, daunorubicin, etoposide, ADEP: ARA-C, daunorubicin, etoposide, PSC-833; [11]AD: ARA-C+daunorubicin; ME: mitoxantrone+etoposide; [12]TAA: thioguanine, aclarubicin, ARA-C.

The use of high-dose myeloablative conditioning regimen has been limited usually to younger patients (< 55 years old) in good clinical condition. A decision analysis of allogeneic bone marrow transplantation, based on IPSS risk scores, has been proposed for patients <60 years old.[44] Until recently, advanced age and comorbidities predisposing patients to an increased risk of treatment-related morbidity and mortality were the rationale for withholding myeloablative therapy from older patients.[45] However, sibling donor transplantation for older patients with AML or MDS has now been shown to produce sustained remissions after reduced–intensity conditioning regimens. Because of the frequent lack of a healthy HLA-identical relative, studies evaluating the role of matched unrelated donor transplantation for patients in this age group have been conducted. Overall, the results are overall promising for selected patients, even when used as front-line therapy with 1-year survival data ranging from 44 to 60% for patients with AML/MDS with a median age in the sixth or seventh decade of life.[46-55]

Established and novel non-intensive treatment options for older patients with AML/MDS

In the search for strategies to reduce toxicity and improve efficacy of anti-leukemic treatments in older adults with AML/MDS, promising therapeutic targets have been and are being discovered. There is rapid progress in this field, raising hope for novel therapeutic options: humanized anti-CD33 antibody (gemtuzumab ozogamicin),[56] tyrosine kinase inhibitors,[57] 5-azacytidine

(vidaza)[86] and 5-aza-2'deoxycytidine (decitabine™; dacogen),[58,59] multidrug resistance inhibitors,[60] farnesyl transferase inhibitors,[61] histone deacetylase[62] and proteosome inhibitors,[63] antiangiogenesis agents,[64] FLT3[65] and anti-apoptosis inhibitors,[66] are all options under investigation. As an example of a treatment option with a good side effect profile and largely suitable for outpatient management, demethylating agents have been shown to produce a benefit in at least 50% of MDS patients, including those with stable disease during therapy.[67,68] Since Decitabine treatment alone is probably not curative, we could show good feasibility of some of these patients aged >60 years, to proceed to reduced-intensity conditioning followed by allografting by a sibling or HLA-matched unrelated donor thereafter. (*Lübbert et al. Haematologica 2006;91(1), Abstract 829*). Tallman *et al.* have reviewed novel therapies based on targeting genetic and epigenetic patho-mechanisms of the disease.[69] The use of these substances will require extensive clinical trials in the future.

Curative or non-curative treatment for AML/MDS: how to reach a shared decision?

It will be of paramount importance to further distinguish and define subgroups of older patients who are likely to benefit from intensive chemotherapy. Some of the sparse published data are contradictory. The relationship between several categorical variables and the probability of adopting palliative therapy was examined by Neuss *et al.*[70] for AML patients who received palliative care either initially or after intensive treatment. They demonstrated that initial treatment outside a study protocol and older age, secondary leukemia, female gender, and not having dependent children were factors significantly associated with receiving palliative care. The physicians' identity was a major measurable factor which influenced whether or not a patient received less intensive treatment. This variability according to treating physicians, independent of patient factors, led the authors to suspect that, despite the goals of informed consent, the doctor and not the patient made major therapeutic decisions. A prospective, longitudinal study examined decision-making considerations and quality of life of older adults with AML and advanced MDS choosing between intensive and non-intensive chemotherapy/best supportive care.[5] In the group of 43 patients studied, the choice of administering intensive treatment was associated with younger age but not with performance status, comorbidities or quality of life. Interestingly, 63% of all patients reported not being offered other treatment options despite the physicians' documentation of alternatives. Patient and physician estimates of cure differed significantly. In the intensively treated group, quality of life decreased during hospitalization but rebounded after discharge, suggesting that time spent outside the hospital could be a powerful marker of quality of life. In a longitudinal study of the preferences of 77 cancer patients regarding physician consultations it became clear that patients desire information on treatment options and physicians' recommendations. Trial participants were less interested in prognostic information and generally more optimistic than their physicians about prognosis. (*Lee et al. Blood 2004;104:Abstract*). On the contrary, we could show in a retrospective analysis of 68 patients >60 years with AML that patients were able to state their own wishes and expectations regarding therapeutic approaches. (*Deschler et al. Blood 2003; 102, Abstract 4755*). To improve communication between physicians and cancer patients and to facilitate the evaluation of therapeutic interventions, attempts have been made to create standardized assessments. A comprehensive geriatric assessment (including performance status, evaluation of comorbidities and abilities to perform activities of daily living, geriatric depression scale) has been proven to be useful in detecting treatment-related changes in older cancer patients and has been recommended to be incorporated into clinical outcome analysis.[71-74] An index developed specifically for patients with hematologic malignancies has been developed: *the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI).* This index captures comorbidities that predict non-relapse mortality in patients considered for allogeneic transplant[75] and also proved to be a helpful tool for defining comorbid conditions in elderly untreated AML patients. (*Giles, F, Rizzieri D, Karp J, et al., Blood 2005, 106, Abstract 2787*). Further prospective investigations of treatment of older patients with AML after comprehensive geriatric assessments including a disease-specific comorbidity index are clearly warranted since none of these indices has been prospectively evaluated as a tool for assigning regimen intensity or for patient selection in clinical trials.

Quality of life and duration of hospitalization: merely "soft" parameters of successful treatment of older patients?

Our awareness of quality of life, defined as an individual's estimation of personal wellbeing including physical, mental, social and spiritual aspects, has increased in the recent past. Even though several research projects on the definition, measurement and evaluation of quality of life are being conducted, little has been published on this matter. Results of a prospective evaluation indicated that negative effects of treatment on a patient's quality of life were limited to the time in the hospital. Intensively treated patients spent 79% of their remaining lifetime in hospitals, whereas non-intensively treated patients spent 14%. The quality of life of these patients and their ability to function improved once they left the hospital and scores after discharge were similar to pretreatment scores.[5] In this context, Pitako *et al.*[76] evaluated the percentage of remaining lifetime of high-risk MDS patients spent at home or in hospitals. A matched-pair analysis showed that patients treated with decitabine, with an aim of providing outpatient management, spent 16% of their remaining lifetime

in hospital (comparable to the time spent by patients treated with supportive approaches), yet achieved a median survival approximating that of intensively treated patients (16 months). In a comparable group of patients, Kornblith *et al.* found positive effects upon quality of life in patients treated with subcutaneous 5-azacytidine.[77] They noted a significant improvement in clinical parameters as well as physical functioning and psychological state. Although only limited data are available regarding quality of life instruments for assessing treatment outcomes in AML and MDS, decitabine treatment was shown to be valuable for patients in this study - yet, it is unclear how any intervention could have positively influenced the psychological parameters. Recent evidence of improved quality of life in patients receiving decitabine treatment compared with patients receiving supportive care only was provided by a phase III randomized study.[78] Another study showed that intensive and prolonged therapy for AML does not necessarily result in a decrease of patients' quality of life. Furthermore, outpatient treatment produced no significant changes in quality of life domains. It has been speculated that a subjective benefit of treatment may outweigh the adverse effects of anti-leukemic therapy on an individual's perception of quality of life.[79] Further studies investigating quality-of-life issues in defined treatment settings are needed.

Intensive therapy in older patients: yes, but for whom?

AML in the elderly is a disease for which there is no satisfactory treatment. Many questions regarding quality of life and age-specific domains are still unresolved. Thus, taking current evidence (*Knipp S et al. Blood 2004;104. Abstract n. 43*) into account, we suggest that the following factors should be considered when providing individual treatment for AML/MDS patients over 60 years old: evaluation of disease-specific factors such as cytogenetics, initial white blood cell count and lactate dehydrogenase concentration as well as patient-specific factors such as the wishes of the patient, performance status, comorbidities, current status of daily life activities and social support. For patients with poor disease-specific factors and reduced patient-specific factors, entry into clinical trials including novel, non-intensive therapy or best supportive care may be a very adequate option.

However, at present, the lack of an established and validated score implies that weighing and applying these factors for allocation to standard treatment (most of which are, of course, used to exclude patients from clinical trials) remains the task of physicians relying on their own clinical judgment.

Summary and conclusions

Since both AML and MDS are diseases occurring most frequently in people over 60 years old, decisions on which management, ranging from curative approaches to palliative care, is most appropriate depends on many factors. Parameters such as age and performance status, and more complex (and as yet insufficiently defined) factors such as comorbidity, socio-economic status and the patient's wishes strongly influence these decisions. Lowering the blast threshold from 30% to 20% in the WHO classification renders the MDS subtype of RAEB-t part of AML, prompting intensive treatment in this disease subgroup, at least for younger patients. In contrast, non-intensive treatment choices even in patients with AML on RAEB-t but of older age may be oriented more towards MDS-type treatment, emphasizing the biological continuum between both disease entities. Treatment decision-making for the individual patient relies on the physician's recommendations. We propose that in the future these issues can be properly addressed using criteria including the above-mentioned parameters and geriatric assessments, which ought to be validated within clinical trials.

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