Impact of different post-remission strategies on quality of life in patients with acute myeloid leukemia

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ABSTRACT

Background

The impact on quality of life of allogeneic stem cell transplantation or conventional chemotherapy in patients with acute myeloid leukemia remains unclear, mainly because of a lack of studies with long-term follow-up. The German AML-Intergroup, therefore, initiated a survey on quality of life of patients with a relapse-free survival of at least 5 years after first-line treatment.

Design and Methods

The EORTC Quality of Life Core Questionnaire (QLQ-C30), supplemented by information on self-assessed concomitant diseases, late treatment effects, and demographics was used. The questionnaire was returned by 419 of 818 patients (51.2%) identified by six study groups. The patients' median age at diagnosis was 42 years, and the median follow-up period was 8 years. One hundred and seventy patients were treated with stem cell transplantation (121 allogenic, 49 autologous) in first complete remission; the other 249 patients were treated with conventional chemotherapy.

Results

The ECOG activity index revealed normal activity in 45% *vs.* 60% of the patients in the allogeneic stem cell transplantation *vs.* conventional chemotherapy groups, respectively and disabled person status in 60% *vs.* 35%. All QLQ-C30 functions, except physical functioning and pain, were poorer in allogeneic stem cell transplantation patients. Problems in leisure-time activities, social life, and financial management, sexual limitations and adverse effects were significantly more frequent in patients after allogeneic stem cell transplantation than after conventional chemotherapy. Multivariate logistic regression models on global health status revealed concomitant disease, age >45 years, and allogeneic stem cell transplantation as significant risk factors.

Conclusions

These results indicate that, compared to conventional chemotherapy, allogeneic stem cell transplantation has a significantly worse long-term impact on quality of life. This needs to be considered when treatment options are discussed.

Key words: long-term quality of life, allogeneic stem cell transplantation, acute myeloid leukemia.

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Introduction

Acute myeloid leukemia (AML) was a fatal disease 25 years ago, with a median survival time of a few months and a 2-year survival rate below 5%.[1] Today, the long-term survival is about 30-40% in adults (aged 18-60 years) and up to 60% in pediatric patients, due to intensification of chemotherapy and the introduction of stem cell transplantation (SCT) in first-line treatment.[2,3]

Assessment of quality of life (QOL) and late effects after completion of anti-leukemic treatment has increasingly become a focus of research.[4-17] Measurement of QOL shortly after diagnosis and during the course of conventional chemotherapy (CCT) showed that QOL improved steadily over time, paralleling the normalization of bone marrow function.[11] After completion of treatment, physical, psychological, and emotional well-being appeared to recover to almost normal levels.[15] However, the different post-remission strategies, CCT, autologous SCT and allogeneic SCT, seem to affect QOL differently.[9,17] Significantly higher rates of somatic symptoms, repeated acute medical problems, physical impairment, role impairment, leisure restriction, and sexual impairment have been reported to occur during the first years after allogeneic SCT.[9,16,17] The studies yielding this information were, however, limited by small sample size, heterogeneous cohorts, or an inadequately short time interval between completion of treatment and QOL assessment.

The German AML-Intergroup, therefore,[18] initiated a survey of QOL in patients who were relapse-free for over 5 years after first-line treatment. The main objectives of this cross-sectional study were to assess QOL in a large cohort of AML patients late after completion of treatment and to compare the influence of different post-remission strategies on QOL.

Design and Methods

Study population

Long-term survivors of AML were identified by all major German AML trial groups within their prospective multicenter treatment trials.[19-27] The inclusion criteria were a diagnosis of AML according to French-American-British criteria, age 15 to 60 years at diagnosis, post-remission therapy with SCT or CCT, and being relapse-free for at least 5 years after first-line treatment. As adolescent patients were sometimes treated in children's hospitals, the pediatric AML-BFM trial group was included. Eight hundred and eighteen patients were identified.

Procedure and measures

Each long-term survivor received a self-administered questionnaire from the central study offices. The patients were asked to return the questionnaires either personally to the clinic or by mail.

The questionnaire consisted of three parts. In the first section, patients were asked about any disease, their employment situation before having leukemia and at the time of filiing in the questionnaire, and their current ECOG performance status.[28] The questions about current symptoms were developed by the Munich Cancer Registry (MCR) of the Munich Comprehensive Cancer Center (MCCC) and had already been used in various surveys of breast cancer and rectal cancer patients.[29-31] The second part of the questionnaire was the EORTC QLQ-C30, a validated QOL evaluation tool.[32-34] This questionnaire contains 30 questions covering five functional scales (physical, emotional, cognitive, social, and role), a global QOL measure, and symptoms including pain, fatigue, diarrhea, and constipation. Patients' responses were combined and converted to a score on a 0 to 100 scale according to the guidelines.[35] On this scale, high functional scores indicate good function, and high symptom scores significant problems. However, the symptom scores were reversed, as recommended,[29] so that high scores represent positive outcomes for all variables.

In the third part of the survey, patients were asked to indicate leukemia-specific late effects and whether there had been any changes in their lives since the onset of leukemia. The study co-ordinating centers provided data from the time of diagnosis on age, sex, lactate dehydrogenase level, white blood cell count, karyotype, date of treatment onset, and major treatment strategy.

Statistical analysis

Pearson's χ^2 tests were used to analyze treatment and age differences. Stratified Mantel-Haenszel tests were used to examine a possible confounding effect of patients' age. The patients' gender was not correlated with either age or treatment, so tests were not stratified for this variable. Non-parametric tests were employed for QOL variables. The main functioning and global QOL scores from the EORTC QLQ-C30 were dichotomized according to the median for logistic regression analyses assessing clinical and demographic predictors of QOL. QOL scores below the median were coded "0", and all others "1". Each median-dichotomized QOL score was entered separately as a dependent variable in the logistic regression analysis. The independent variables used in the analyses were selected from the literature and our own univariate analyses. The following variables were entered simultaneously as independent variables: AML study group cohort, age (<45/≥45 years), sex, post-remission treatment (allogeneic SCT/CCT), and current concomitant disease (absent/present). An *a priori* error probability of 0.01 was assumed, therefore p values below 0.01 should be considered statistically significant.

Results

Study population

Questionnaires were returned by 419 patients (Table 1). The overall response rate was 51%, but ranged from 35% to 71% in the different trial groups. The trial-spe-

Table 1. Patients' characteristics according to post-remission treatment.

		All patients n=818 %	*Patients who returned the questionnaires n=419%*	*CCT n=221 %*	*Allo-SCT n=121 %*	*Auto-SCT n=49 %*	*p-value CCT vs. allo-SCT*
Sex	female	55	60	60	52	76	
Age at diagnosis (years)	15-29	18	13	13	20	18	
	30-39	28	20	20	39	35	
	40-49	27	28	28	32	27	<0.001
	50-59	27	39	39	8	20	
Median age		41	47	47	38	39	
Karyotype		*n %*	*n %*	*n %*	*n %*	*n %*	
Normal		261 47	152 48	83 55	57 58	12 30	–
CBF-AML		127 23	72 23	49 32	12 12	11 28	<0.001
other		114 21	67 21	20 13	30 30	17 43	–
t(15;17)		54 10	28 9				
WBC x 10^3 at diagnosis	median (range)	12.8 (0.3-34)	13.1 (0.3-153)	14.5 (0.3-153)	18.1 (0.5-290)	32 (0.70-175.1)	–
Follow-up (years)	median (range)			9.0 (5.0-22.0)	8.1 (5.0-21.8)	7.4 (5.0-18.6)	

AML: acute myeloid leukemia; CCT: conventional chemotherapy auto autologous allo allogeneic; SCT: stem cell transplantation; CBF-AML core-binding-factor AML WBC white blood cell count.

cific response-rate depended on the length of the follow-up period. The shorter the follow-up period, the more probable a high response rate was. There was no difference between participating and non-participating patients with respect to pretreatment variables (age and karyotype) or post-remission strategy

Patients' characteristics

The median age was 42, and the median follow-up period was 8 years. Post-remission treatment was CCT in 249 (59.4%) patients, allogeneic SCT in 121 (28.9%) and autologous SCT in 49 (11.7%). The median ages of the allogeneic SCT (38 years) and autologous SCT (39 years) groups were significantly lower than that of the CCT group (47 years). In addition, there were imbalances with respect to cytogenetics: patients with CBF-AML were underrepresented in the allogeneic SCT group (p=0.007). There was no difference in white blood cell count between the three groups. Patients in the autologous SCT group were excluded from further analyses because this group was numerically small. As none of the patients with acute promyelocytic leukemia underwent allogeneic SCT in first complete remission, this special subgroup might bias the results, and the 28 patients with this type of leukemia were, therefore, also excluded from comparative analyses of the two treatment groups.

Concomitant disease/symptoms

Of all responding patients, 88% indicated that they suffered from at least one concomitant disease/symptom. The most frequent disease/symptom was lower back pain (41%), followed by impaired vision (29%) and hypertension (27%). Table 2 gives the incidences and relative frequencies of concomitant problems according to the different post-remission therapies. Impaired vision, cataract surgery, and treatment of hormonal disorders were significantly more frequent in the allogeneic SCT group than in the CCT group. There was also a slightly high rate of chronic skin disorders in the allogeneic SCT group. The ECOG activity index revealed normal activity in 60% and 45% of the CCT group and allogeneic SCT group, respectively (Table 3). Higher age was significantly associated with a lower rate of employment, mainly due to retirement. There was no significant difference in employment when comparing patients under 50 years who had been treated with CCT (77%) or allogeneic SCT (68%). Disabled person cards were held by 60% of the patients in the allogeneic SCT group and by 35% of those treated with CCT.

Reproduction

Nine male and nine female patients became parents after CCT (n=12) or allogeneic SCT (n=6). Considering female patients under the age of 40 and male patients under 45 years old at treatment onset (n=200), there was a reproduction rate of 9%.

Personal outcome

Long-term-survivors complained about leukemia-related problems (5-31% after CCT and 12-48% after allogeneic SCT) in various areas, with an emphasis on physical problems. Problems related to adverse effects, leisure activities, sexual limitations, and daily habits were significantly more frequent in patients after allogeneic SCT than in patients after CCT (Table 4). The general feeling/perception of a positive attitude in life was not different between the two groups: 64% for CCT patients *vs.* 63% for allogeneic SCT patients.

QLQ-C30

Emotional functioning ("*Do you feel tense, irritable, depressed, are you worried?*"), fatigue, financial difficulties, insomnia, social functioning, and global health status were rated below 70 in the EORTC QLQ-C30 questionnaire by all long-term survivors (Table 5); however, the scores for almost all variables were significantly higher in the CCT group than in the group of patients treated with allogeneic SCT.

Multivariate analyses on global health status

A logistic regression model was used to identify factors related to global health status, with their odds ratio (OR) and 95% confidence intervals (CI). Concomitant disease (OR: 6.62; CI: 3.79-11.59), being over the median age of 45 at diagnosis (OR: 2.53; CI: 1.38-4.53), and allogeneic SCT (OR: 2.10; CI: 1.18-3.71) were found to be independent adverse factors for global health status.

Discussion

In this study of the QOL status of AML patients who were relapse-free for at least 5 years after initial, first-line treatment, almost all measures of QOL were superior for

patients treated with CCT than for those treated with allogeneic SCT, even though this latter group of patients had a 9-year lower median age and higher age was an independent variable for adverse effects. Now that a considerable proportion of patients with AML can be definitively cured from their disease, the long-term consequences of their antileukemic therapy have become increasingly relevant. In order to study these consequences, we investigated a total of 419 patients who had survived disease-free for at least 5 years. The results were compared especially between patients who had undergone allogeneic transplantation and those who had received chemotherapy with no allogeneic transplantation. As the individual disease characteristics and treatment modalities dated at least 5 years back, two largely representative populations of patients could be analyzed and enabled an estimate of the price, in terms of quality of life, of their curative treatment.

The assessment of QOL and late effects after completion of anti-leukemic treatment have increasingly become a focus of research. Unfortunately, most previous studies had limitations. The study by Zittoun *et al*. was based on only 98 patients, of whom 35 had undergone allogeneic SCT, and the time of assessment was heterogeneous, ranging from 19 to 79 months.[9] The study by Watson *et al*.[16,17] was adequately powered being based on 481 patients of whom 98 had received an allogeneic transplant, but QOL assessment was performed only 1 year after completion of treatment. Taking into account that less than half of the patients had a recovery of peripheral lymphocyte counts during the first year,[36] and that consequently the incidence of infectious complications was highest during the first years after allogeneic SCT, a QOL assessment 1 year after completion of consolidation therapy seems to be inappropriate for determining the impact of different treatment strategies on the long-term outcome.

The overall response rate to the questionnaires of 51% in our survey is moderate and we, therefore, examined the selection of patients. There was no identifiable selection bias, based on known prognostic factors in AML such as cytogenetics and white cell count. The karyotype risk profile of our long-term survivors (Table 1) is comparable to that published for younger AML patients at diagnosis.[26] Seriously ill patients may prefer not to answer questionnaires, or long-term survivors in excellent shape might no longer want to be confronted with their disease again.

In our study the response rate to the questionnaires correlated with the duration of follow-up since diagnosis. The response rate in the QOL study of patients in the MRC AML 10 trial was 78%, but the study was performed only 1 year after completion of consolidation treatment[16,17] and, therefore, cannot be compared to our cross-sectional study with a median follow-up period of 8 years. Other cross-sectional studies addressing the

Table 2. Concomitant disease/symptoms.*

	Total n=342			*CCT n=221*		*Allo-SCT n=121*		*p value*
	n	*%*		*n*	*%*	*n*	*%*	
Age at response (years)								
16-29	16	5		10	5	6	5	
30-39	55	16		29	13	26	21	
40-49	84	25		39	18	45	37	<0.001
50-59	87	25		50	23	37	31	
60-69	91	27		84	38	7	6	
≥70	9	3		9	4	–	–	
median age	*51 years*		*Missing*	*55 years*		*47 years*		
Hypertension	90	27	5	61	28	29	24	–
Coronary heart disease	20	6	8	13	6	7	6	–
Congestive heart failure	50	15	7	36	17	14	12	–
Diabetes	30	9	3	23	11	7	6	–
Allergies	63	19	9	43	20	20	17	–
Rheumatism, arthrosis, osteoarthritis	69	21	8	50	23	19	16	–
Lower back pain	143	43	7	97	45	46	38	–
Impaired vision	96	29	6	42	20	54	45	<0.001
Cataract surgery	35	10	7	15	7	20	17	0.004
Thyroid disorders	48	14	7	29	14	19	16	–
Chronic lung diseases	50	15	3	26	12	24	20	0.049
Chronic skin disorders	34	10	8	16	8	18	15	0.032
Impaired hearing	48	14	8	33	15	15	12	–
Impaired extremities	52	15	6	31	14	21	18	–
Stomach/gut diseases	34	10	7	17	8	17	14	–
Hepatic disorders	32	10	10	20	9	12	10	–
Chronic genito-urinary diseases	21	6	5	13	6	8	7	–
Hormonal disorders	65	19	7	24	11	41	35	<0.001

**The patients were asked: "Has your physician ever said that you suffer from one of these diseases?".*

Table 3. ECOG performance, employment and disability.

ECOG performance status	*Total n=342*		*CCT n=221*		*Allo-SCT n=121*		*p value*
	n	*%*	*n*	*%*	*n*	*%*	
Fully active, able to carry out all pre-disease activities without restriction	182	54	128	60	54	45	
Restricted in physically strenuous activity	117	35	70	33	47	39	
Ambulatory and capable of all self-care but unable to carry out any work activities.	26	8	14	7	12	10	0.017
Capable of only limited self-care	10	3	3	1	7	6	
Completely disabled	–	–	–	–	–	–	

Employment	*Before leukemia Total n=340*		*CCT Age* <50 n=78*		*CCT Age ≥50 n=141*		*Allo-SCT Age* <50 n=77*		*Allo-SCT Age ≥50 n=43*		*p-value*
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	
Training or part-time or full-time job	280	82	60	77	35	25	52	68	15	35	
Incapable of working	7	2	11	14	26	18	18	23	12	28	
Homemaker, retirement	53	16	7	9	80	57	7	9	16	37	

Severely handicapped pass (% of disability)	*Total n=342*		*CCT n=121*		*Allo-SCT n=221*		
	n	%	n	%	n	%	
None	192	56	144	65	48	40	
≥70%	108	31	55	25	53	43	< 0.001
80-100%	42	12	22	10	20	17	

**Age at survey.*

issue of QOL in AML-patients did not explicitly state potential selection biases.[4-10]

There might be a selection bias towards allogeneic SCT in younger patients with unfavorable cytogenetics or residual disease. However, these differences between the two treatment groups were taken into account as far as concerns patients' characteristics available for analysis. It is difficult to compare our results with those of previous studies because the external validity of these studies is rarely equivalent. In addition, there was considerable patient heterogeneity concerning diagnosis (chronic myeloid leukemia at least 10 years after SCT)[37], age (mainly children),[38] time of evaluation (at least 1 year after treatment)[39,40] and sample size.[4-12] Furthermore, a variety of different scales and self-made questionnaires were used.[4,6,7,10] The cross-sectional QOL study of the MRC AML 10 trial[16,17] used the EORTC QLQ-C30 score and further questions concerning sexual health and infertility in 479 patients, comparing the effects of allogeneic SCT, autologous SCT, and CCT, at least 1 year after consolidation treatment. The median age of the patients was lower than in our study (allogeneic SCT group 33 *vs.* 38 years; CCT 43 group *vs.* 47 years). That study found that significantly higher proportions of post-SCT patients than CCT patients suffered from mouth dryness and from worse sexual relationships, social relationships, professional activities, and leisure time activities. Hormonal disorders and infertility were also more common among the allogeneic SCT patients than among the CCT patients. Similar results were found in our study, except for mouth dryness which was not investigated.

Watson *et al.* did not publish scores but percentages of patients with problems in the EORTC QLQ-C30 functional and symptom scales and items, so the results of this study need to be converted for comparison to our results. The overall rates of our patients with problems were higher than in the MRC study: physical function 54% *vs.* 41%, role function 53% *vs.* 35%, cognitive function 59% *vs.* 53%, emotional function 84% *vs.* 76%, social function 61% *vs.* 56%, pain 49% *vs.* 34%, sleep disturbance 55% *vs.* 45%, and financial difficulties 53% *vs.* 46%. The results were nearly identical for global

Table 4. Negative and positive personal outcome.

Problems because of leukemia *"What has affected you because of leukemia very much or moderately?"*	*Total n=342*		*CCT n=221*		*Allo-SCT n=121*		*p value*
	n	*%*	*n*	*%*	*n*	*%*	
Physical problems	119	36	65	30	54	46	0.007
The leukemia is a problem for me psychologically	109	32	69	31	40	33	–
Relationships with my friends and family	28	9	12	5	16	14	–
Restrictions in my work and leisure pursuits	92	28	46	22	46	39	0.002
Side effects	105	33	49	24	56	48	< 0.001
Sexual limitations	78	23	37	17	41	36	< 0.001
Social restrictions (eg, financial disadvantages)	93	28	48	23	45	38	0.019
Lack of information	47	15	32	15	15	12	–
Daily habits	86	26	41	19	45	38	< 0.001
Changes in life *"Have there been any positive changes in your life since leukemia?"* The following feature has improved very much							
My attitude toward life	213	64	138	64	75	63	–
My lifestyle (work, hobbies)	163	49	104	48	59	50	–
My relationships with my friends, family, and colleagues	169	51	111	51	58	48	–
My attitude toward my health	166	49	101	46	65	54	–

health, being 81% *vs.* 80%, and fatigue, 75% *vs.* 79%, in our study and in the MRC study, respectively. The adverse impact of allogeneic SCT on role, social function, fatigue, nausea/vomiting, and financial difficulties was evident in both study cohorts. A different effect on cognitive or emotional function was seen only in our analysis. The main difference between the two studies was the time of assessment, which was 1 year compared to a median of 8 years in the MRC-QOL study and our study, respectively. However, the results of both studies suggest that problems in allogeneic SCT patients occur early after transplant and seem to persist.

Fatigue, feeling tired, and lacking energy are the most common symptoms reported by cancer patients,[41] but the exact causes are not known. There is a correlation between fatigue and depression, and even after adjusting for multiple factors, major depression was associated with mortality among cancer patients after SCT.[42] The symptom of fatigue was rather severe in our study, especially in the allogeneic SCT group. The challenge of future trials will be to evaluate prophylactic interventions in patients at high risk.

Fifty percent of the long-term survivors lead an as active a life as they did before the onset of leukemia; 72% of the respondents under the age of 50 years are employed, and more than 60% consider that their attitude in life has become more positive since the diagnosis and treatment of their leukemia. Significant effects of study group or duration of follow-up since diagnosis on QOL could not be shown.

Table 5. EORTC QLQ-C30 subscales.

	Total n=342 Mean (SD)	*CCT n=221 Mean (SD)*	*Allo-SCT n=121 Mean (SD)*	*p value*
Functioning				
physical	86.7* (17.8)	88.0 (16.0)	84.4 (20.6)	–
role	72.5 (31.5)	75.7 (30.6)	66.8 (32.4)	0.008
emotional	64.1 (28.4)	67.9 (27.2)	57.1 (29.2)	<0.001
cognitive	75.9 (27.2)	79.5 (24.5)	69.4 (30.6)	0.004
social	68.8 (33.0)	73.0 (31.3)	61.0 (34.8)	0.001
Global health status	69.8 (24.9)	71.6 (24.7)	66.4 (25.1)	0.041
Symptom scales				
fatigue	65.1 (30.5)	68.0 (30.3)	59.7 (30.3)	0.008
nausea/vomiting	93.7 (16.6)	95.1 (15.2)	91.0 (18.6)	<0.001
pain	73.8 (32.1)	75.0 (32.3)	71.8 (31.8)	–
Single Items				
dyspnea	71.7 (34.3)	74.6 (33.4)	66.4 (35.5)	0.023
insomnia	67.8 (34.2)	70.0 (33.2)	63.9 (35.8)	–
appetite loss	90.9 (20.1)	92.7 (18.6)	87.8 (22.4)	0.016
constipation	90.6 (22.4)	91.1 (22.3)	89.7 (22.8)	–
diarrhea	91.1 (20.7)	89.6 (23.3)	93.6 (14.5)	–
financial difficulties	67.4 (36.5)	72.6 (33.0)	57.8 (40.5)	0.002

**An average physical functioning of 86.7 means that the AML patients rated their physical ability as being, on average, 86.7% of that prior to leukemia at a median time of 8 years after initial AML treatment onset. There was no difference between the two post-remission treatment strategies with regards to physical functioning.*

Karyotype and response to induction therapy are among the most important prognostic factors in adult AML.[2] Initial results from studies with risk-adapted treatment strategies suggest that high-risk patients, in particular, benefit from allogeneic SCT; other risk groups show equivalent results.[43-46] The main result of our cross-sectional study – the negative impact of allogeneic SCT on QOL in long-term survivors – must, therefore, be taken into account in those risk groups without a clear survival benefit from either post-remission strategy.

In conclusion, these results indicate that a considerable number of long-term survivors live without major, restricting problems. However, QOL was significantly reduced in patients after allogeneic SCT, and this must be taken into account when choosing the treatment for AML patients in whom the benefit from such an intensive strategy is not obvious.

Authorship and Disclosures

DM: initiative and main author of the paper; JE: scientific co-worker in the same area; JH: methodological consultant; MS, GE, CS, TB, RK, JK, AG, UC, HD: contributor of data; AS: scientific consultant on score methodogy; DN: co-writer and contributor of data; RFS: main author of the paper. The authors reported no potential conflicts of interest.

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