Bone Marrow Transplantation, (1997) 20, 307–315

Quality of life in patients with acute myelogenous leukemia in prolonged first complete remission after bone marrow transplantation (allogeneic or autologous) or chemotherapy: a cross-sectional study of the EORTC-GIMEMA AML 8A trial

R Zittoun[1], S Suciu[2], M Watson[3], G Solbu[2], P Muus[4], F Mandelli[5], P Stryckmans[6], M Peetermans[7], J Thaler[8], L Resegotti[9], M Dardenne[2] and R Willemze[10]

[1]*Department of Hematology, Hotel-Dieu, Paris, France;* [2]*EORTC Data Centre, Brussels, Belgium;* [3]*The Royal Marsden NHS Trust and Institute of Cancer Research, UK;* [4]*Department of Hematology, St Radboud University Hospital, Nijmegen, The Netherlands;* [5]*Universita La Sapienza, Rome, Italy;* [6]*Institut Jules Bordet, Brussels, Belgium;* [7]*Department of Hematology, University Ziekenhuis Antwepen, Edegem, Belgium;* [8]*Department of Internal Medicine, Innsbruck, Austria;* [9]*Ospedale Molinette, Torino, Italy; and* [10]*Department of Hematology, University Hospital, Leiden, The Netherlands*

Summary:

A cross-sectional study of quality of life (QOL) was performed in 98 patients in continued first complete remission (CR) for 1–7.4 years, after inclusion in the AML 8A trial which prospectively compared allogeneic bone marrow transplantation (AlloBMT), autologous BMT (ABMT) and intensive consolidation chemotherapy. Several significant differences between the three treatment groups were observed, on the basis of patient self-reports, with regard to somatic symptoms (mouth sores, cough, hair loss, headache), repeated acute medical problems, physical functioning, role functioning, leisure activities and, above all, sexual functioning. There were also significant differences for overall physical condition, and overall quality of life. For all these parameters, the ranking was uniformly AlloBMT lower than ABMT lower than chemotherapy. These differences remain significant after adjustment for time interval between CR and QOL evaluation, sex or age. These results, confirming a higher risk of permanent impairment of QOL after BMT, may have an impact on medical decisions and warrant further studies.

Keywords: quality of life; acute myeloid leukemia; bone marrow transplantation

Allogeneic bone marrow transplantation (AlloBMT), autologous bone marrow transplantation (ABMT), or intensive consolidation chemotherapy (ICC) are currently proposed for patients with acute myelogenous leukemia (AML) once they enter into complete remission (CR). The relative value of these three treatment options has been assessed by several multicenter trials, patients being assigned to AlloBMT when an HLA-matched sibling was available, while ABMT and ICC were randomized.[1–4] Although the results may vary from one study to another, they show generally a lower risk of relapse, and a longer disease-free survival (DFS) after AlloBMT and ABMT than after ICC.

From 1986 to 1992, the EORTC and GIMEMA Leukemia Cooperative Groups prospectively compared these three therapeutic options: patients with newly diagnosed AML were entered in the AML 8A trial, and, after the same induction and intensive consolidation course, were assigned, according to availability of a family HLA-matched donor or randomization, to AlloBMT, ABMT or a second ICC course. At a median follow-up time of 3.3 years, there was a significantly longer DFS in the AlloBMT (55%) and ABMT (48%) arms than in the ICC arm (30%).[5] However, the overall survival after CR was similar in the three arms, patients relapsing after ICC being more easily salvaged and frequently receiving an ABMT during second CR.

The conclusions of this study were based on analyses made according to the intention-to-treat principle. In addition, we have observed a significant difference with regard to the short-term toxicity of the treatment actually administered, the treatment-related mortality being 20, 10 and 6% after AlloBMT, ABMT and second ICC, respectively. Furthermore, the final results may also be hampered by long-term toxicity, especially due to the conditioning regimens, with or without total body irradiation (TBI), for both BMT procedures, and to chronic graft-versus-host disease (GVHD) after AlloBMT. Such long-term somatic toxicity is also likely to induce psychosocial sequelae. Indeed, some previous studies have shown that quality of life (QOL) might be more or less markedly impaired after AlloBMT,[6–8] especially in the case of severe chronic GVHD.[9] We considered, therefore, that the comparison between AlloBMT, ABMT and ICC options in the AML 8A trial should also be performed in terms of QOL for patients surviving in first CR.

Assessment of QOL is difficult in the setting of clinical trials. Since QOL is a multidimensional concept including at least physical, psychological and social domains, one has to select multi-item instruments that meet the requirements of validity, sensitivity and reliability for assessment of the

Correspondence: Dr R Zittoun, Department of Hematology, Hotel-Dieu, 1, place du Parvis Notre-Dame, 75181 Paris cedex 01, France
Received 5 December 1996; accepted 15 May 1997

various components of these domains.[10] It is generally assumed that self-report questionnaires are more reliable than proxy evaluations.[11] Specific instruments may allow better evaluation of the impact of treatments, and are usually preferred to generic questionnaires. In addition, transcultural problems must be adequately solved, in order to provide acceptable questionnaires to patients enrolled in international trials.[12] We decided, therefore, to perform a cross-sectional study using the EORTC Quality of Life Questionnaire (QLQ-C30) combined with specific modules designed to assess QOL after treatment of acute leukemia including BMT.

Patients and methods

Patients

Patients were eligible for the QOL study if they had been enrolled in the EORTC-GIMEMA AML 8A trial and were in continued first CR 1 year or more after completion of the treatment protocol. The main inclusion criteria in the trial were: a diagnosis of AML in previously untreated patients, and absence of severe concomitant disease. Patients had to be more than 10 and less than 60 years old, but 25 patients (2.7%) were less than 15 and are not included in the present study. Of the 623 patients from 59 centers who achieved CR after the induction regimen, 576 received a first ICC. Of them 168 patients had an HLA-identical sibling and 144 underwent an AlloBMT. Two hundred and fifty-four patients were randomized to ABMT or second ICC, which were completed in 95 and 104 patients, respectively. Eighteen centers agreed to participate in the QOL study. Out of 155 patients from these centers who were alive and in first CR for 1 year or more at the time of study, 98 (63%) agreed to enter the QOL study: 35 had an AlloBMT, 29 an ABMT, while 34 received only chemotherapy.

Methods

Informed consent was required for the QOL study, according to local rules. The allocated anti-leukemic treatments received by these patients are shown in Table 1. The QOL evaluation was performed from January 1993 to March 1995. All eligible patients received a set of questionnaires from their local investigator with a covering letter guaranteeing strict confidentiality and suggesting they contact a locally appointed person in case of any problem. Medical information, especially that related to treatment side-effects, eg acute and chronic GVHD, was collected from the case report forms filled in by the responsible physicians.

The patient self-administered questionnaires included a demographic questionnaire, the EORT QLQ-C30 questionnaire, a Leukemia-BMT-specific module, a short questionnaire on sexual functioning and fertility, and a questionnaire on patient perception of changes in the various domains of QOL (ie disease-related modifications).

The demographic questionnaire was derived from Hollingshead.[13] Patients were also asked to indicate their marital and employment status both pre-diagnosis and at the present time.

The EORTC QLQ-C30 is a 30 item questionnaire which has been developed to cover a wide range of cancers, and is expected to be combined, for each study, with a disease- and/or treatment-specific module.[14] It includes five multi-item functional scales (Physical, Role, Cognitive, Emotional and Social functioning), several single item symptom measures and two items for global assessment of the overall physical condition and of QOL. Combination of the perceived Overall Physical Condition and Overall Quality of Life results in a Global Health Status score. This questionnaire meets acceptable standards for reliability, and its external validity has been checked in several hundreds of patients with lung cancer,[14] and various types of cancer.[15] Its psychometric properties have been also evaluated in 125 adults surviving several years after BMT,[16] with a high internal consistency, and good reliability of the Role, Emotional and Cognitive functioning scales, and of the Global Health Status.

The Leukemia-BMT module (QLQ-LEU-BMT) is a 32 item questionnaire which was designed on the basis of the known late side-effects of BMT in adult patients treated for leukemia. Most of the items explore somatic symptoms, especially those currently experienced by patients suffering from GVHD. The psychometric properties of this module were analyzed in 388 patients entered into the present

Table 1 Treatment received by the 98 patients whose quality of life was assessed

No. of patients	*Treatment*	*No. of patients and modality of treatment of allocation*	*Total body irradiation No. of patients (%)*
35	Allogeneic BMT	HLA-identical sibling	30 (86)
29	Autologous BMT		20 (69)
		28 randomization	
		1 individual choice	
34	Chemotherapy		0 (0)
		17 ICC_2[a] by randomization	
		10 ICC_2[a] by individual choice	
		6 ICC_1[a] only[b]	
		1 salvage induction only[+]	

[a]ICC_1 First intensive consolidation course, administered to all patients before assignment to AlloBMT or randomization to ABMT or ICC_2. ICC_2: second intensive consolidation course.
[b]These patients received chemotherapy but went off-study afterwards because of toxicity and/or refusal of further treatment.

EORTC-GIMEMA AML 8A trial and into the MRC AML 10 trial in the UK, and who were in CR for at least 1 year after completion of treatment.[17] All 32 variables had individual measures of sampling adequacy greater than 0.5. Item total correlations and Cronbach alpha coefficients indicate good internal consistency, many items being grouped into two subscales (alpha coefficients 0.79 and 0.71), which appear to correspond to GVHD and infection, respectively.

Most items of the EORTC QLQ-C30 and the QLQ-LEU-BMT use a 4-point Likert scale from 1 (not at all) to 4 (very much); overall physical condition and QOL were assessed by two 7-point Likert scales. In addition, the first seven items of the EORTC QLQ-C30 correspond to two Guttman scales with dichotomous response categories (yes or no).

Sexual disorders categorized according to the Diagnostic and Statistical Manual of Mental Disorder (DSM IV) were divided into problems of sexual drive (interest), sexual arousal, orgasm disorder and pain disorder (eg dyspareunia). Four study specific single-item questions asked about: (1) interest, (2) pleasure or satisfaction, (3) level of sexual activity and, (4) ability to engage in sexual intercourse since their leukemia treatment (ie increased, decreased or remained the same). Level of pain during sexual intercourse was also assessed by one item from the Leukemia-BMT module on a 4-point scale ranging from 'not at all' to 'very much', with a high score indicating more of a problem. Problems with fertility were assessed by study-specific items; patients were asked if their treatment had caused infertility and, in those indicating that it had, if they had been aware of the possibility of infertility at the time they were initially treated. The extent to which they were bothered by infertility was assessed by a 7-point rating scale ranging from 'not at all' to 'very much'. Those who reported that they considered themselves rendered infertile by the treatment were asked if they were seeking a resolution to their infertility (eg adoption, artificial insemination by donor) and whether this had been successful.

Finally the questionnaire included a Disease-Related Modifications module, where patients were asked to evaluate the changes induced by their disease and treatment on several domains, each covered by a single item (Energy, Mood, Intellectual Capacity, Family Life, Sexual Relationship, Professional Life, Social Relationships, Leisure Activities and Quality of Life) with a 5 point scale of changes, ranging from 'far worse' to 'far better'.

All these questionnaires, first developed in English, were translated into four European languages, French, Dutch, German, Italian, using a 'forward-backward' translation procedure. The reliability and validity of the EORTC QLQ-C30 is highly consistent across the three language–cultural groups studied: patients from English-speaking countries, Northern Europe and Southern Europe.[14]

Statistical methods

The usual χ^2 test[18] with the correction for continuity was used to test the balance of the initial characteristics among the treatment groups. The treatment differences regarding the QOL assessments (ie questions having as possible answers ordered categories) were tested using the Kruskal–Wallis test.[19] The treatment comparisons leading to significant differences were adjusted *a posteriori* by some variables having a possible impact on QOL. For this purpose, the following categorized variables were considered for the bi-variate analyses: sex (male *vs* female), age (<46 years *vs* ⩾46 years), time from CR to the evaluation of QOL (<3 years, 3–4 years, ⩾5 years). In case of ordered outcomes (overall physical condition, quality of life or global health status – see below), the stratified generalized Gehan–Wilcoxon test was used,[19] whereas for all other ordered outcomes ('not at all', 'a little', 'quite', 'much' or 'increased', 'same', 'decreased' or 'absent', 'present'), which were categorized as binary outcomes, the usual stratified χ^2 test[18] was used. The Global Health Status score (grading from 0 to 100) has been constructed from the Overall Physical Condition (1–7) and Overall Quality of Life (1–7) using the recommendations of the EORTC QOL Study Group.[20] The Goodman–Kruskal γ coefficient[18] was used to measure the association between these two last scales. The Kendall's τ test[18] was used to measure the relationship between patient characteristics and the QOL items.

The planned sample size for the QOL study was 135 (45 patients for each treatment group), as quite large differences between the treatment groups in terms of side-effects and QOL were expected. For instance, 30% difference (20 *vs* 50%) between two treatment groups regarding the occurrence of side-effects requires a total of 90 patients (alpha = 0.05, beta = 0.20). However, due to administrative difficulties, the QOL assessment was implemented in only 18 out of 59 centers which participated in the AML 8A study. Therefore, the reported P values should be considered cautiously: due to a relative low statistical power for detection of moderate treatment differences (range 20–30%), a result which yields a P value >0.05 does not necessarily mean that treatment impact on QOL is negligible. Conversely, due to the multiple comparisons, a P value which is significant according to the classical rule (⩽0.05), does not necessarily mean that one may reject with full confidence the null hypothesis (no treatment difference), as the risk of a false positive result is high in this instance.

Results

The QOL study was performed at a median time of 53 months after achievement of CR (range 12–89 months). The characteristics of the patients at the time of QOL evaluation are shown in Table 2. There are slight differences between the three treatment groups, but only the difference for age at time of QOL evaluation was significant (χ^2 test; $P = 0.05$). This is explained by the fact that in some participating centers the upper age limit for randomization between ABMT and ICC was 60, whereas for AlloBMT the age limit of 45 was kept more often. The time elapsed between achievement of CR and evaluation of QOL was similar in the three treatment groups.

Patients included in the QOL study differed significantly from those who were not included, despite a similar DFS, with regards to age (a higher proportion above 46 years),

Table 2 Patients' characteristics at time of quality of life evaluation

	Chemotherapy	*Autologous BMT*	*Allogeneic BMT*
No. of patients	34	29	35
Age			
median (range)	44 (19–65)	39 (22–65)	39 (20–51)
<46 years (%)	56	65	83
Sex M/F	19/15	22/7	20/15
College graduate level or above (%)	32	31	29
Children (% with)	67	62	66
Living in big city (%)	48	45	28
Time from CR (months)			
mean (s.e.)	50 (3.5)	56 (3.0)	48 (3.0)
median (range)	53 (12–81)	58 (28–89)	47 (19–79)

sex (more males), treatment completion (less premature stop for toxicity or refusal), and proportion of randomized patients (higher). However, they were not different with regards to response to the first induction course, to balance between the randomized arms, and to incidence and grade of acute or chronic GVHD.

EORTC QLQ-C30 questionnaire

Significant differences were observed between the treatment groups for items evaluating physical functioning ('Do you have any trouble in taking a long walk?') and role functioning ('Are you limited in any way in doing either your work or doing household jobs?') (Table 3). Differences for the other items and scales assessing cognitive, emotional and social functioning were not significant. The overall physical condition and quality of life were significantly different between the three treatment groups with mean scores for AlloBMT < ABMT < chemotherapy. The resulting mean global health status on a 0–100 scale was therefore about 70 for AlloBMT, 75 for ABMT and 80 for chemotherapy. Of note, a high association was observed between overall physical condition and overall QOL (Goodman–Kruskal $\gamma = 0.70$, $P < 0.001$). More often (26 cases), patients rated their QOL as being higher than their physical condition, than the reverse (15 cases).

Leukemia-BMT module

Although the somatic items included in the EORTC QLQ-C30 were not significantly different between the treatment groups (especially those relating to pain, nausea/vomiting, lack of appetite, fatigue), several differences were observed with the QLQ-LEU-BMT. Table 4 shows those items for which differences were significant. For all those items except two ('taking pills/medicine or having seen a doctor during the last month') the same ranking was observed regarding the frequency/severity of problems, being higher in the AlloBMT group, compared with the ABMT group, both of which were higher than in the chemotherapy group. There was no significant difference between the treatment groups for the other items, although a trend with the same ranking was observed for chills, changes in appearance, eye dryness, and skin dryness (Table 5).

Some items of the QOL-LEU-BMT module correlated significantly with the use (50 cases) or not (14 cases) of TBI during the conditioning regimen for AlloBMT or ABMT (eye dryness: TBI (65%) *vs* no TBI (7%), $P = 0.011$, and headache: TBI (54%) *vs* no TBI (29%), $P = 0.05$). On the other hand mouth sores correlated with the occurrence and grade of chronic GVHD (no GVHD: 1/13 (8%); mild GVHD: 5/11 (45%), moderate/severe GVHD: 6/11 (55%) $P = 0.01$).

Sexuality-Fertility

The main results for sexual functioning are shown in Table 6. Sexual functioning was impaired in about one third of patients and was significantly more frequently impaired after AlloBMT (47–68% according to the items) than after ABMT (18–30%) or chemotherapy (15–22%). In addition, there was significantly more pain during sexual intercourse in patients treated by both BMT procedures (Table 4). Patients who received TBI had impaired sexuality more often than those not receiving TBI, but none of the comparisons reached statistical significance, probably due to an

Table 3 Results of the EORTC Core questionnaire QLQ-C30

	Chemotherapy	*Autologous BMT*	*Allogeneic BMT*	*P value*[b]
Trouble in taking a long walk (%)	23	28	49	0.05
Limited in doing work/household jobs (%)	18	34	49	0.026
Overall physical condition (1–7)[a]	5.68 (0.21)	5.55 (0.26)	5.09 (0.16)	0.05
Overall quality of life (1–7)[a]	6.0 (0.20)	5.41 (0.25)	5.29 (0.16)	0.017
Global health status (0–100)[a]	80.6 (3.14)	74.7 (3.82)	70.1 (2.39)	0.03

[a]Mean score (s.e.)
[b]Kruskal–Wallis test.

Table 4 Results (%) of Leukemia/BMT module

	Chemotherapy	*Autologous BMT*	*Allogeneic BMT*	*P value*[a]
Fever	9	7	31	0.012
Mouth sores	6	31	34	0.017
Dental problems	23	34	43	0.046
Cough	32	38	66	0.046
Hair loss	9	34	46	0.004
Headache	29	30	64	0.009
Pain during sexual intercourse	3	15	28	0.026
Any acute disease last month	15	30	45	0.024
See a doctor	41	33	64	0.048
Taking pills/medicine	50	33	76	0.004

[a]Kruskal–Wallis test.

Table 5 Results (%) of the Leukemia/BMT module: items with no significant differences between treatment groups

	Chemotherapy	*Autologous BMT*	*Allogeneic BMT*	*P value*[a]
Chills	**12**	**24**	**31**	**0.18**[b]
Infection	26	24	34	0.56
Weight loss	15	10	26	0.26
Weight gain	29	28	26	0.86
Changed sense of taste	6	14	20	0.27
Changed sense of smell	6	17	11	0.36
Changes in appearance	**9**	**14**	**31**	**0.05**
Pain in abdomen	23	17	34	0.35
Mouth dryness	23	38	37	0.36
Eye dryness	**15**	**21**	**35**	**0.10**
Difficulty swallowing	6	10	15	0.48
Skin itching	29	34	43	0.44
Skin dryness	**47**	**52**	**69**	**0.12**
Abnormal hair growth	3	7	9	0.61
Stiff joints	35	43	51	0.37
Difficulty combing	6	3	6	0.88
Difficulty shaving/making up	0	3	6	0.38
Dizziness	29	17	26	0.54
Feeling cold	24	34	43	0.25
Flushes	30	22	27	0.87
Blurred vision	26	33	51	0.17
Hearing loss	15	37	21	0.11
Anal pain	3	4	0	0.57
Painful urination	9	0	0	0.07
Blood in urine	0	0	0	–
Admitted hospital last month	9	4	0	0.21
Treated				
for cataract	0	7	3	0.31
for hormonal disorders	16	19	27	0.49
for joint problems	6	15	15	0.45

[a]Kruskal–Wallis test.
[b]Data with a trend, and a ranking consistent with the other results, are labelled in bold characters.

Table 6 Results for sexual functioning (%)

	Overall results (%)			*Decreased by treatment arm (%)*			
	Increased	*Unchanged*	*Decreased*	*Chemotherapy*	*ABMT*	*AlloBMT*	*P value*[a]
Interest in sex	5	62	33	15	21	60	<0.001
Sexual activity	5	54	41	22	30	68	<0.001
Pleasure from sex	7	63	30	22	18	47	0.006
Ability to engage a sexual activity	3	62	35	21	29	53	0.014

[a]Kruskal–Wallis test.

insufficient number of patients. Moreover, in the 35 patients who underwent AlloBMT, while the grade of acute GVHD seems to be associated with impaired sexuality, the grade of chronic GVHD did not correlate with the results of the Sexuality module.

Treatment-related infertility was reported by 63, 48 and 3% of patients who underwent AlloBMT, ABMT and chemotherapy, respectively, while 3, 14 and 32% of them in each treatment group declared themselves not to be infertile, and the remaining patients did not know their status in this regard (overall χ^2; $P < 0.001$). Most of the BMT patients said they had been informed about the risk of infertility at time of allocation of treatment (20, 62 and 83% in the three treatment groups, respectively). Only three patients looked for a resolution to their infertility, with only one male patient treated by ABMT being successful through the use of cryopreserved sperm. There was no significant difference between the three treatment groups when patients were asked whether they were bothered by infertility.

Treatment adjustment and prognostic factors

After adjustment for sex as well as age at time of evaluation, the evaluation of differences between the treatment groups led to similar results to those presented in Table 3. In addition, the treatment comparisons yielded similar results after adjustment for time interval between achieving CR and evaluation of QOL. For most items, there was no trend towards improvement as this time interval increased, except for mouth sores which tended to be more frequently observed in patients studied within the first 3 years after achieving CR. Furthermore, sexual problems were more frequently reported by females, who more often indicated a decrease of interest in sex (46 *vs* 25%, $P = 0.021$), and in older patients (ie 46 years and above) who reported less sexual pleasure than younger patients (70 *vs* 25%, $P = 0.016$).

Perceived changes by the patients

Table 7 shows the changes perceived by patients when asked to compare, for the main domains of QOL, and the overall QOL, their present status with their pre-disease status. It can be seen that a wide range of perceived changes was reported by patients, from 'far worse' to 'far better'. However, there was a trend in reporting the present status as being worse rather than better. When the three treatment groups were compared, a worsening was significantly more frequently reported for leisure activities after AlloBMT or ABMT than after chemotherapy. There was also a trend towards a worsening in AlloBMT and ABMT groups with regards to sexual relationship and mood. A worsening of the overall QOL was reported by 51% of patients who underwent AlloBMT, *vs* 38% of ABMT patients and 30% of the ICC patients, but the difference was not statistically significant.

Discussion

Our study shows some significant differences between AlloBMT, ABMT and chemotherapy, when assessing the long-term side-effects and multiple dimensions of QOL. These relate to somatic side-effects such as mouth sores, cough, headache, hair loss, and frequent acute episodes leading to referral to physicians. The most important long-term side-effects reported by patients were, however, infertility, decrease of sexual activity and loss of libido. These consequences of treatment consolidation of AML were more frequently observed after AlloBMT, and, to a lesser degree, after ABMT, than after chemotherapy. The same ranking was observed, using the EORTC QOL core questionnaire, for physical and role functionings, with more limitations in physical and work performances in patients who had received AlloBMT. This ranking was consistent for most comparisons, giving more strength to the statistical comparisons, despite the caveat emphasized in the Methods section. Although our study was based on an empirical analysis through the main domains of QOL, most results correspond to what was expected from the known toxicity of the compared treatment modalities.

Several studies have been published recently on various aspects of QOL in adults surviving after BMT.[6–9,16,21–28] Except for one prospective study,[9] they were cross-sectional analyses from 6–12 months and up to 18 years,[16]

Table 7 Patients perceived changes (%)

	Overall changes (%)					*(% worsened)*			
	Far better	*A bit better*	*No change*	*A bit worse*	*Far worse*	*Chemotherapy*	*ABMT*	*AlloBMT*	*P*[a]
Energy	5	5	31	30	28	44	69	63	0.22
Mood	5	15	43	25	11	**24**	**48**	**40**	**0.18**[b]
Intellectual capacity	3	3	65	18	9	28	28	24	0.88
Family life	8	7	68	10	8	12	17	21	0.99
Sexual relationship	3	4	61	17	14	**13**	**29**	**50**	**0.07**
Professional life	8	10	31	30	21	39	55	59	0.45
Social relationship	5	13	54	18	9	18	28	34	0.83
Leisure activities	9	11	49	24	8	**15**	**31**	**49**	**0.02**
Overall quality of life	12	16	32	33	8	30	38	51	0.68

[a]Kruskal–Wallis test
[b]Data with a marked trend, although not necessarily statistically significant, are labelled in bold characters.

after completion of BMT. Transplantation procedures performed included AlloBMT only, or combined AlloBMT, syngeneic BMT, and ABMT groups, while two studies focused on ABMT, in patients mainly treated for lymphoid malignancies.[29,30] Usually these publications included a variety of diseases. Few studies were intended to compare BMT and chemotherapy.[22,23,29] Only one was specific for AML, and compared AlloBMT and intensive consolidation chemotherapy, for patients included in two consecutive prospective trials.[25] Our study is, therefore, the first which evaluates specifically the long-term QOL of AML patients included in a multicenter international prospective trial comparing AlloBMT, ABMT and intensive chemotherapy. Although not all participating centers and eligible patients of the AML 8A trial collaborated in the QOL study, the number of patients, centers and countries represented makes a selection bias unlikely.

Most of the previous publications have emphasized a normal or near normal QOL in the vast majority of patients treated by AlloBMT, after some emotional and social adjustment.[7,31] A high prevalence of depression was observed by Jenkins *et al*,[8] especially in patients with antecedent psychiatric disorders, with no difference between AlloBMT and ABMT. However, several studies have pointed out the possibility of long-term physical, psychological or social problems after BMT. Permanent fatigue and lack of energy/stamina are frequently reported.[6,7,16] Cognitive dysfunction has been also observed,[16] which might be related to the dose of TBI.[32] Although most of these young adult patients return to work, have good social support, and keep or restore satisfying family/partner relationships, unemployment, financial and marital problems have been reported in a substantial proportion.[7,9,24,26,28] The risk of job discrimination and problems in obtaining insurance have also been emphasized.[26]

Comparison of AlloBMT with alternative treatments yielded controversial results: Lesko *et al*,[22] Litwins *et al*,[23] and Wellisch *et al*[25] failed to observe differences between BMT and CT with regard to various domains of QOL, whereas Altmaier *et al*[28] found more physical symptoms, unemployment, financial and marital problems in BMT than in matched CT patients.[28] However these comparisons were based on small patient numbers, and, except for one,[25] were performed outside prospective trials.

Despite the limited number of patients in each treatment group, our results indicate differences which consistently confirm the same ranking: AlloBMT < ABMT < CT, most CT patients being treated with high-dose Ara-C consolidation courses. These differences were found for physical symptoms, role functioning, leisure activities, and, especially, for sexual functioning. Probably as a consequence, using the EORTC-QLQ C30 questionnaire, significant differences with the same ranking were observed between the three treatment modalities for overall physical condition, overall QOL, and the resulting global health status. These differences must be viewed, however, in terms of relative weighting of the average scores: the differences between the less severe (ICC) and the more severe (AlloBMT) might appear small (10% for the global health status), not important enough to indicate that CT prevails. Therefore some caution is necessary when helping individual patients to make a decision, after taking into consideration the relative risks of relapse and treatment-related mortality. In addition, patient rating of their own QOL was more frequently better than their rating of overall physical condition and there was no significant change in the perceived global post-treatment QOL. These results might indicate that the majority of patients adapt their perception of QOL, despite post-treatment somatic sequelae, but could also be related to a lack of sensitivity of global QOL scale in picking up specific problems.

The most important difference between the treatment groups was related to sexual functioning and psychosexual sequelae. Although our Sexuality-Fertility module was quite simple and brief, and deserves further validation, the data indicate a significantly greater impairment after AlloBMT and, to a lesser degree, after ABMT than after CT. These differences correlated with infertility which resulted from BMT. Sexual dysfunction has been highlighted by two important studies dealing with problems in long-term survivors after AlloBMT.[16,24] Surprisingly, other authors have not found differences with regards to psychosexual functioning in patients treated by AlloBMT or CT.[25,33] However, as shown by several other analyses focused on both psychosexual, hormonal and fertility aspects[34–38] sexual dysfunction is likely to occur in patients with sexual organ failure due to conditioning with intensive chemotherapy or radio-chemotherapy.[39]

One can hypothesize several factors to explain the higher frequency of sexual dysfunction after BMT – especially AlloBMT – such as the use of TBI during conditioning, or the occurrence of acute GVHD. We did not observe significant correlations with these factors, perhaps due to the relatively limited number of patients in each group. Further studies are required, to identify the etiological factors (eg impact of dosage in TBI on gonadal function). Of note, some predictive variables have already been reported to influence sexual satisfaction of long-term survivors such as a younger age at time of transplant, overall life satisfaction and satisfying relationship with spouse or partner.[39] However, hormonal failure is likely to be the most important etiological factor, and along with infertility, represents an important part of an eventual permanent impairment of QOL after BMT. Several measures are available to treat these long-term side-effects such as cryopreservation of sperm or ova, and hormonal replacement. For other patients, who, for individual preference, would not accept the risk of these permanent side-effects, another possible solution is to give preference to ICC consolidation during first CR, and to choose BMT only as a salvage treatment in case of relapse.

Some studies have identified, through multivariate analyses, variables which might represent risk factors for impairment of QOL after BMT, especially TBI, GVHD, age, education level, role retention, and social support.[40] If confirmed, these factors would indicate which appropriate medical and psychosocial measures are needed to preserve or restore the QOL during and after such intensive treatments. For example, avoiding TBI during conditioning regimen for AlloBMT and ABMT might be recommended, since in AML a pure chemotherapy regimen seems to yield equivalent DFS as a radio-chemotherapy regimen.[41]

A final problem, essential when considering the long-term adverse effects on QOL of these treatments, is the chance of a progressive improvement over time. The lack of prospective, longitudinal analyses precludes any firm conclusion in this respect. Most previous studies have tried to approach this question through multivariate analyses, using the time from CR or completion of treatment as a covariate. This has resulted in controversial results, some studies showing no change over time[6,23] with others indicating a progressive late improvement.[16,21,25] In the present series, only the mouth sores which correlated with chronic GVHD, improved significantly after the first 3 years. Further longitudinal studies should be proposed, in order to evaluate these changes over time, and to adapt treatment and support according to needs.

Acknowledgements

The authors acknowledge and thank the following persons for their contribution to this study: S Achard, N Alby, N Delvaux, H Funaki, H De Haes, D Razavi, M Ruszniewski, psychologists and members of the EORTC Quality of Life Study Group; A Bacigalupo, J Burghouts, R De Bock, A Efira, W Feremans, B Labar, P Leoni, A Louwagie, MC Petti, A Thyss, G Torlontano, ML Vegna, G Visani, E Volpe; members of the EORTC and GIMEMA Leukemia Cooperative Groups; C Vey for her technical assistance; and the patients who gave their time to complete the questionnaire. This publication was supported by grant Nos 5U10CA11488-23 to 5U10CA11488-26 from the National Cancer Institute (Bethesda, Maryland, USA). Its content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute.

References

1 Appelbaum FR, Fisher LD, Thomas ED. Chemotherapy v marrow transplantation for adults with acute nonlymphocytic leukemia: a five-year follow-up. *Blood* 1988; **72**: 179–184.
2 Reiffers J, Gaspard MH, Maraninchi D *et al*. Comparison of allogeneic or autologous bone marrow transplantation and chemotherapy in patients with acute myeloid leukaemia in first remission: a prospective controlled trial. *Br J Haematol* 1989; **72**: 57–63.
3 Löwenberg B, Verdonck LJ, Dekker AW *et al*. Autologous bone marrow transplantation in acute myeloid leukemia in first remission: results of a Dutch prospective study. *J Clin Oncol* 1990; **8**: 287–294.
4 Cassileth PA, Lynch E, Hines JD *et al*. Varying intensity of postremission therapy in acute myeloid leukemia. *Blood* 1992; **79**: 1924–1930.
5 Zittoun R, Mandelli F, Willemze R *et al*. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. *New Engl J Med* 1995; **332**: 217–223.
6 Andrykowski MA, Henslee PJ, Farral MG. Physical and psychosocial functioning of adult survivors of allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1989; **4**: 75–81.
7 Belec RH. Quality of Life: perceptions of long-term survivors of bone marrow transplantation. *Oncol Nurs Forum* 1992; **19**: 31–37.
8 Jenkins PL, Linington A, Whittaker JA. A retrospective study of psychosocial morbidity in bone marrow transplantation recipients. *Psychosomatics* 1991; **32**: 65–71.
9 Syrjala KL, Chapko MK, Vitaliano PP *et al*. Recovery after allogeneic marrow transplantation: prospective study of predictors of long-term physical and psychosocial functioning. *Bone Marrow Transplant* 1993; **11**: 319–327.
10 Testa MA, Simonson DC. Assessment of quality-of-life outcomes. *New Engl J Med* 1996; **334**: 835–840.
11 Slevin ML, Plant H, Lynch D *et al*. Who should measure quality of life, the doctor or the patient? *Br J Cancer* 1988; **57**: 109–112.
12 Aaronson NK. Methodologic issues in assessing the quality of life of cancer patients. *Cancer* 1991; **67**: 844–850.
13 Hollingshead AB. *Four-factor Index of Social Status*. Yale University Press: New Haven, CT, 1995.
14 Aaronson NK, Ahmedzai S, Bergman B *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a Quality-of-Life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365–376.
15 Ringdal GI, Ringdal K. Testing the EORTC Quality of Life Questionnaire on cancer patients with heterogenous diagnoses. *Qual Life Res* 1993; **2**: 129–140.
16 Busch NE, Haberman M, Donaldson G, Sullivan KM. Quality of life of 125 adults surviving 6–18 years after bone marrow transplantation. *Soc Sci Med* 1995; **40**: 479–490.
17 Watson M, Zittoun R, Hall E *et al*. A modular questionnaire for the assessment of longterm quality of life in leukaemia patients: the MRC/EORTC QLQ-LEU. *Qual Life Res* 1996; **5**: 15–19.
18 Everitt BS. *The Analysis of Contingency Tables*. Monographs on applied probabilities and statistics. Chapman and Hall: London, 1977.
19 Kalbfleisch JD, Prentice RL. *Statistical Analysis of Failure Time Date*. John Wiley: New York, 1980.
20 EORTC QLQ-C30 Scoring Manual, prepared by Fayers P, Aaronson N, Bjordal K, Sullivan M, on behalf of EORTC Study Group on Quality of Life, Brussels, 1995.
21 Grant M, Ferrell B, Schmidt GM *et al*. Measurement of quality of life in bone marrow transplantation survivors. *Qual Life Res* 1992; **1**: 375–384.
22 Lesko LM, Ostroff J, Mumma GH *et al*. Long-term psychological adjustment of acute leukemia survivors: impact of bone marrow transplantation versus conventional chemotherapy. *Psychosom Med* 1992; **54**: 30–47.
23 Litwins NM, Rodrigue JR, Weiner RS. Quality of life in adult recipients of bone marrow transplantation. *Psychological Reports* 1994; **75**: 323–328.
24 Schmidt GM, Niland JC, Forman SJ *et al*. Extended follow-up in 212 long-term allogeneic bone marrow transplant survivors: issues of quality of life. *Transplantation* 1993; **55**: 551–557.
25 Wellisch DK, Centeno J, Guzman J *et al*. Bone marrow transplantation vs high-dose cytarabine-based consolidation chemotherapy for acute myelogenous leukemia: a long-term follow-up study of quality-of-life measures of survivors. *Psychosomatics* 1996; **37**: 144–154.
26 Wingard JR, Curbow B, Baker F, Piantadosi S. Health, functional status, and employment of adult survivors of bone marrow transplantation. *Ann Intern Med* 1991; **114**: 113–118.
27 Wolcott DL, Wellisch DK, Fawzy FI, Landsverk J. Adapation of adult bone marrow transplant recipient long-term survivors. *Transplantation* 1986; **41**: 478–484.
28 Altmaier EM, Gingrich RD, Fyfe MA. Two-year adjustment of bone marrow transplant survivors. *Bone Marrow Transplant* 1991; **7**: 311–316.
29 Vose JM, Kennedy BC, Bierman PJ *et al*. Long-term sequelae

of autologous bone marrow or peripheral stem cell transplantation for lymphoid malignancies. *Cancer* 1992; **69**: 784–789.
30 Chao NJ, Tierney DK, Bloom JR *et al*. Dynamic assessment of quality of life after autologous bone marrow transplantation. *Blood* 1992; **3**: 825–830.
31 Hengeveld MW, Houtman RB, Zwaan FE. Psychological aspects of bone marrow transplantation: a retrospective study of 17 long-term survivors. *Bone Marrow Transplant* 1988; **3**: 69–75.
32 Andrykowski MA, Altmaier EM, Barnett RL *et al*. Cognitive dysfunction in adult survivors of allogeneic marrow transplantation: relationship to dose of total body irradiation. *Bone Marrow Transplant* 1990; **6**: 269–276.
33 Mumma GH, Mashberg D, Lesko LM. Long-term psychosexual adjustment of acute leukemia survivors: impact of marrow transplantation versus conventional chemotherapy. *Gen Hosp Psychiatry* 1992; **14**: 43–55.
34 Deeg HJ. Delayed complications and long-term effects after bone marrow transplantation. *Hematol/Oncol Clin N Am* 1990; **4**: 641–657.
35 Baruch J, Benjamin S, Treleaven J *et al*. Male sexual function following bone marrow transplantation. *Bone Marrow Transplant* 1991; **7**: 52.
36 Hinterberger-Fischer M, Kier P, Kalhs P *et al*. Fertility, pregnancies and offspring complications after bone marrow transplantation. *Bone Marrow Transplant* 1991; **7**: 5–9.
37 Sanders JE, Buckner CD, Amos D *et al*. Ovarian function following marrow transplantation for aplastic anemia or leukemia. *J Clin Oncol* 1988; **6**: 813–818.
38 Schubert MA, Sullivan KM, Schubert MM *et al*. Gynecological abnormalities following allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1990; **5**: 425–430.
39 Wingard JR, Curbow B, Baker F *et al*. Sexual satisfaction in survivors of bone marrow transplantation. *Bone Marrow Transplant* 1992; **9**: 185–190.
40 Baker F, Wingard JR, Curbow B *et al*. Quality of life of bone marrow transplant long-term survivors. *Bone Marrow Transplant* 1994; **13**: 589–596.
41 Ringden O, Labopin M, Tura S *et al*. A comparison of busulphan versus total body irradiation combined with cyclophosphamide as conditioning for autograft or allograft bone marrow transplantation in patients with acute leukaemia. *Br J Haematol* 1996; **93**: 637–645.