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Adverse impact of bone marrow transplantation on quality of life in acute myeloid leukaemia patients: analysis of the UK Medical Research Council AML 10 Trial

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Abstract

The increasing success of intensive consolidation chemotherapy (CCT) as an alternative to bone marrow transplant (BMT) in acute myeloid leukaemia (AML) necessitates comparison of the impact on quality of life (QoL) of these two treatment modalities. Most QoL studies following BMT involve small patient numbers and provide ambivalent results. The present study examines QoL in a large number of patients 1 year from the end of treatment within the United Kingdom Medical Research Council (UK MRC) AML10 trial of BMT versus CCT. Allogeneic-BMT (Allo-BMT) was observed to have an adverse impact on most QoL dimensions compared with Autologous-BMT (A-BMT) and CCT. More patients receiving BMT had mouth dryness problems and worse sexual and social relationships, professional and leisure activities than CCT patients. QoL in A-BMT patients was less impacted than Allo-BMT. Intention-to-treat analysis showed similar results. These results indicate that a reconsideration of treatment strategies is warranted, and that further, good prospective studies are needed to evaluate more clearly the effects of these treatments in long-term survivors.
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Keywords: Quality of Life; Acute myeloid leukaemia; Bone marrow transplantation; MRC AML10 trial

1. Background

We have previously reported a severe adverse impact of bone marrow transplantation (BMT) on sexual health and fertility compared with intensive consolidation chemotherapy (CCT) in the treatment of acute myeloid leukaemia (AML) in the United Kingdom Medical Research Council (UK MRC) AML10 trial [1]. Data from the AML10 trial show an advantage for BMT (either allogeneic or autologous) on relapse-free survival, but no significant overall survival advantage autologous-BMT ((A-BMT) 57% versus CCT 45% at 7 years, $P = 0.2$) [2–5].

Issues surrounding the impact of BMT on patients' quality of life (QoL) remain unclear, primarily due to difficulties in obtaining data from large samples. Many existing studies are underpowered or have failed to assess the effects of specific disease on QoL [6,7]. The importance of assessing QoL using disease-specific methods alongside generic measures has been emphasised because this allows a more precise evaluation of co-morbidity and long-term effects, in addition to useful clinical data to guide specific treatment decisions [8,9]. QoL has been assessed using both methods in the context of the European Organisation for Research and

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Treatment of Cancer (EORTC) and Gruppo Italiano Malattie EMatogiche dell'Adulto (GIMEMA) AML 8A trial in a sample of 98 patients in first complete remission. Contrary to previous publications, which have found a normal or near-normal long-term QoL in most patients treated by BMT, this study confirmed a higher risk of QoL impairment after BMT [10]. Significant differences were found between patients treated by allogeneic-BMT (Allo-BMT) or A-BMT versus CCT on side-effects such as mouth sores, cough, headaches, hair loss and acute illness episodes. These results required further investigation given the modest sample size in the AML8A trial.

We report here, the assessment of QoL within the context of the larger MRC AML10 trial, thereby allowing a more robust analysis of the impact of BMT and CCT on long-term QoL.

2. Patients and methods

2.1. Patients

The UK MRC AML 10 trial was open from May 1988 to April 1995. Treatment consisted of a total of four courses of intensive chemotherapy (CCT) given to all patients, after which patients were scheduled to receive either Allo-BMT, if they had a human leucocyte antigen (HLA)-matched sibling, or, if no donor was available, they were eligible for randomisation to A-BMT versus no further therapy (i.e. the CCT only group). Patients receiving CCT only, Auto-BMT or Allo-BMT from a sibling donor were included and eligibility for the QoL study was restricted to literate patients $\geqslant$18 years 1 year from the end of treatment. Patients completed a self-report questionnaire issued via their treatment centre either when they returned for follow-up outpatient visits or by post.

2.2. Measures

Patients completed the EORTC Quality of Life-Core 30 Questionnaire (QLQ-C30) (version 1.0) [11] and a leukaemia-specific measure [12]. The EORTC QLQ-C30 is a 30-item checklist with five functional scales (physical, role, cognitive, emotional and social) and three symptom scales (fatigue, pain and nausea and vomiting). Specific items assess dyspnoea, appetite loss, sleep disturbance, constipation and diarrhoea, as well as global health and QoL, and the financial impact of the disease and/or treatment. Patients made ratings using standard instructions. Most items of the EORTC QLQ-C30 use a four-point Likert scale from 1 (not at all) to 4 (very much); overall physical condition and global QoL were assessed by two seven-point scales. Reliability and validity have been reported elsewhere in Ref. [13]. The psychometric properties have been evaluated in adults surviving several years after BMT, with high internal consistency, and good reliability [14]. Scoring was according to EORTC guidelines [15] transforming all scores to a 0–100 scale using the recommended standardisation algorithm. Increased functional scores indicate a benefit to patients, whereas increased symptom scores indicate a poorer QoL.

The leukaemia module (QLQ-LEU) is a 32-item questionnaire designed to assess known late effects of BMT. Scale development and psychometrics indicate that the measure is useful in evaluating the long-term effects of treatment in relation to chronic graft-versus-host disease (GVHD including; itchy and dry skin, stiff joints, chills, feeling cold, flushes, headaches, hearing loss, pain during sexual intercourse) and susceptibility to infection (fever, infection, sores in mouth, weight loss, abdominal pain, painful urination, blood in urine). Other items assess sensory loss (changes in sense of taste/smell) and functional status (difficulties combing hair, shaving or making-up). Specific items assess weight gain, mouth and eye dryness, difficulty in swallowing, dental problems, cough, hair loss and abnormal growth, changes in appearance, dizziness, blurred vision and anal pain. All items of the QLQ-LEU use a four-point Likert scale, as described above, and assessment covers the preceding month.

A disease-related modification scale [1,12] evaluated changes induced by their disease and treatment on energy, mood, intellectual capacity, family life, sexual relationship, professional life, social relationships, leisure activities and QoL with a five-point scale, ranging from 'far worse' to 'far better' compared with before disease onset for each item. Patients also specify their current and pre-treatment marital and employment status.

2.3. Statistical methods

Pearson's Chi-square tested for differences in preparatory BMT regimen by type of transplant, and gender differences between treatment groups, whereas treatment group differences in patients' age and time of QoL assessment were analysed with the Wilcoxon two sample test. Gender differences were analysed with the Student's *t*-test, whilst generalised linear models were used to allow for relationships between age and treatment. Treatment interactions with age and gender were investigated and are quoted where $P<0.01$; patient numbers were too small to investigate three-way interactions between treatment, age and gender.

Age at entry into AML10 was analysed in four groups: 15–24, 25–34, 35–44, and $\geqslant$45 years (to simplify the tables, the age groups are presented as 15–34 years and $\geqslant$35 years, see Table 1 for example). To make the data more readable, Tables 2 and 3 show the percentage of patients with a less than optimal score (i.e. those with problems) and Table 4 the percent with worsening

Table 1
Demographic characteristics of the study sample

	Number (%) of patients			
	Total	Allo-BMT	A-BMT	CCT
Total	481	97	74	310
Gender				
Male	218 (45%)	46 (47%)	28 (38%)	144 (46%)
Female	263 (55%)	51 (53%)	46 (62%)	166 (54%)
Age at entry (in years)				
Median (range)	39 (15–58)	32 (16–49)	37 (15–52)	43 (15–58)
15–34	190 (40%)	58 (60%)	32 (43%)	100 (32%)
⩾35	291 (60%)	39 (40%)	42 (57%)	210 (68%)
Pretreatment employment status				
Full-time	322 (67%)	66 (68%)	49 (66%)	207 (67%)
Part-time	80 (17%)	16 (16%)	16 (22%)	48 (15%)
Sick leave/unemployed/ housewife/husband	52 (11%)	9 (9%)	3 (4%)	40 (13%)
Other	21 (4%)	3 (3%)	5 (7%)	13 (4%)
Unknown	6 (1%)	3 (3%)	1 (1%)	2 (1%)
Pretreatment marital status				
Single	97 (20%)	23 (24%)	14 (19%)	60 (19%)
Married	343 (71%)	71 (73%)	50 (68%)	222 (72%)
Widowed/divorced	31 (6%)	2 (2%)	7 (9%)	22 (7%)
Unknown	10 (2%)	1 (1%)	3 (4%)	6 (2%)

Allo-BMT, allogeneic-bone marrow transplantation; A-BMT, autologous-BMT; CCT, intensive consolidation chemotherapy.
Percentages may not add up to 100 due to rounding.

Table 2
Percent of patients reporting problems in the EORTC QLQ-C30 functional and symptom scales and additional items

EORTC QLQ-C30	Total	Gender		Age (years)		Treatment			*P* values	
		Male	Female	15–34	⩾35	Allo-BMT	A-BMT	CCT	Allo-BMT versus CCT	Allo-BMT versus A-BMT
Functioning										
Physical functioning	41	37	44	31	47***	55	35	38	***	***
Role functioning	35	36	34	24	42***	52	31	31	***	***
Cognitive functioning	53	50	55	46	57**	59	54	50		
Emotional functioning	75	73	76	73	76	78	76	73		
Social functioning	56	57	56	51	60*	72	69	48	***	***
Symptoms										
Fatigue	79	76	81	77	80	87	81	76	**	*
Pain	34	34	34	29	37	43	28	33	**	**
Nausea and vomiting	20	19	20	21	19	32	16	16	**	**
Additional items										
Dyspnoea	40	39	40	35	42	51	34	37	*	**
Sleep disturbance	45	43	46	35	51***	49	46	43		
Appetite loss	17	15	18	20	15	33	16	12	**	**
Constipation	13	9	17***	12	14	18	8	13		
Diarrhoea	14	14	14	13	15	16	7	15		
Financial difficulties	46	50	42	44	47	64	45	40	**	*
Global health/QoL	80	79	80	77	81**	88	86	75	***	***

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire; QoL, quality of life.
Percent of patients with no problems = 100−percent of patients with problems.
P values are for Student's *t*-test (gender) and generalised linear models (age-adjusted for treatment and pairwise treatments adjusted for age group), $P > 0.05$ in each case except: *$P \leqslant 0.05$, **$P \leqslant 0.01$, ***$P \leqslant 0.001$.
No significant differences (at $P \leqslant 0.05$) for A-BMT versus CCT.

Table 3
Percent of patients reporting problems in the QLQ-LEU subscales and additional items

QLQ-LEU	Total	Gender		Age (years)		Treatment			*P* values		
		Male	Female	15–34	⩾35	Allo-BMT	A-BMT	CCT	Allo-BMT versus CCT	A-BMT versus CCT	Allo-BMT versus A-BMT
Subscale											
GVHD	86	82	89***	82	89	98	85	82	***		***
Infection susceptibility	51	52	50	55	48	64	49	47	**		**
Sensory loss	18	16	19	19	17	33	15	14	**		**
Functional status	6	7	5	5	7	7	4	6			
Additional items											
Weight gain	41	40	42	34	45	27	37	46	**		
Mouth dryness	31	30	32	28	33	54	39	22	***	**	**
Eye dryness	21	19	22	19	22	38	24	15	***		*
Difficulty swallowing	10	8	12*	9	10	19	8	8	*		*
Dental problems	25	24	25	28	22**	31	22	23			
Cough	43	45	41	50	39**	55	32	42	*		**
Hair loss	7	11	5	9	6	10	7	6			
Abnormal hair growth	7	7	6	8	6	9	4	6			
Change in appearance	10	9	11	11	10	14	8	9			
Dizziness	26	24	28	27	26	31	23	26			
Blurred vision	22	25	19	17	25	26	21	21			
Anal pain	9	11	7	8	9	14	4	8			*

GVHD, graft-versus-host disease; QLQ-LEU, leukaemia module questionnaire.
Percent of patients with no problems = 100−percent of patients with problems.
P values are for Student's *t*-test (gender) and generalised linear models (age-adjusted for treatment and pairwise treatments adjusted for age group), $P > 0.05$ in each case except: *$P \leqslant 0.05$, **$P \leqslant 0.01$, ***$P \leqslant 0.001$.

Table 4
Percent of patients reporting worsening functioning for disease-related modifications

Score	Total	Gender		Age (years)		Treatment			*P* values		
		Male	Female	13–34	⩾35	Allo-BMT	A-BMT	CCT	Allo-BMT versus CCT	A-BMT versus CCT	Allo-BMT versus A-BMT
Energy	58	64	54**	54	61	77	63	51	**		
Mood	38	39	37	42	35	52	38	34	**		*
Intellectual capacity	22	22	21	21	23*	33	19	19	**		*
Family life	17	21	14*	14	19***	28	11	15	*		*
Sexual relationships	37	35	39	34	39***	56	44	29	***	*	
Professional life	45	47	42	38	49***	59	54	38	***	**	
Social relationships	23	26	20	19	25**	36	22	18	**	*	
Leisure activities	42	45	39	39	43	63	47	34	***	*	
Quality of life	35	38	33*	29	39***	49	36	30	***		

Percent of patients with better or unchanged functioning = 100−percent of patients with worse functioning.
P values are for Student's *t*-test (gender) and generalised linear models (age-adjusted for treatment and pairwise treatments adjusted for age group), $P > 0.05$ in each case except: *$P \leqslant 0.05$, **$P \leqslant 0.01$, ***$P \leqslant 0.001$.

symptoms. However, the analysis used the full range of values.

Due to the large number of comparisons, the risk of a false-positive result ($P < 0.05$) due to chance is increased, so caution must be exercised in interpreting marginally significant results. All *P* values are two-tailed, those relating to treatment are age-adjusted and those relating to age are treatment-adjusted.

To use as much data as possible, analysis was by treatment received. To overcome any potential bias, the analysis was repeated on an intention-to-treat basis. Patients randomised to A-BMT were compared with those allocated no further therapy and patients with an HLA-matched sibling donor (all of whom should have had Allo-BMT) were compared with those who were tissue-typed, but no donor was found.

3. Results

1276 (81%) of 1579 eligible patients aged 15 years or over entered into AML10 achieved complete remission (CR). 3 patients had a transplant before achieving CR and 3 had other types of transplant in first CR (mismatched-related, syngeneic and matched unrelated donor transplants) and were therefore excluded. 605 eligible patients were alive in first CR 1 year after finishing treatment. Their doctors considered 23 patients unsuitable for QoL assessment and did not reply to the request for participation in 48 cases. 481 of the remaining 534 patients returned competed questionnaires, yielding a patient compliance rate of 90%. Of these, 97 (20%) received an Allo-BMT (including 2 who received allogeneic peripheral blood stem cell transplantation (PBSCT)), 74 (15%) received an A-BMT (including one autologous PBSCT), and 310 (64%) received CCT only. In total, 124 eligible patients did not participate in the study.

As a preparatory regimen, cyclophosphamide was given to 147 of 168 BMT patients (3 unknown) (80 of 95, 84% Allo-BMT; 67 of 73, 92% A-BMT patients; $P = 0.1$) and 69 patients received other drugs (busulphan ($n = 26$), mesna ($n = 27$), and melphalan ($n = 18$)). 135 of 167 BMT patients (4 unknown) received total body irradiation (TBI), (85 of 94 (90%) Allo-BMT patients and 50 of 73 (68%) A-BMT patients, $P < 0.001$). All Allo-BMT patients had GVHD prevention therapy: 85 received cyclosporin, 66 received methotrexate, 13 received T-cell depletion, and 6 received other forms.

There were no major differences in either patient's gender or type of treatment between the 481 participating and 124 non-participating eligible patients ($P > 0.1$ in each case), but participating patients tended to be older (median age 39 years versus 34 years, $P = 0.02$).

3.1. Demographic details

There were no significant gender differences in treatment ($P > 0.1$) (Table 1). Median age at entry was 39 years (range 15–58 years), with Allo-BMT patients being significantly younger (median 32 years, range 16–49 years) than patients treated with CCT (median 43 years, range 15–58 years, $P < 0.001$) and A-BMT (median 37 years, range 15–52 years, $P = 0.02$). Patients who received A-BMT were also younger than those who received CCT ($P = 0.003$). 71% of participants were married and 67% had been in full-time employment before treatment, with more males being employed full-time than females (88% versus 51%, $P < 0.001$), but there were no significant differences by treatment group. The median time from the end of treatment to completion of the questionnaire was 14 months (interquartile range 12–22 months), with no significant differences between the three treatment arms (median: 14 months in each arm).

3.2. EORTC QLQ-C30 questionnaire

Table 2 shows the percent of patients reporting problems in the EORTC QLQ30 functional and symptoms scales plus additional items and global health/QoL by gender, age and treatment.

3.2.1. Functional scales

Most patients reported some degree of problem with emotional (75%), social (56%) and cognitive functioning (53%), and some with physical (41%) and role functioning (35%). Older patients had significantly worse functioning than younger patients in each case except for emotional functioning. Allo-BMT patients had more problems in physical, role and social functioning than both CCT and A-BMT patients ($P < 0.001$ in each case). Treatment differences in cognitive and emotional functioning were in the same direction, but were not statistically significant ($P > 0.1$ in each case). A-BMT and CCT patients had similar functioning for each scale ($P > 0.1$ in each case).

3.2.2. Symptom scales

79% of patients reported problems with fatigue, 34% reported some degree of pain and 20% suffered nausea and/or vomiting. Allo-BMT patients had worse scores than both CCT and A-BMT patients for each symptom scale. Again there was no significant difference between A-BMT and CCT patients ($P > 0.1$).

3.2.3. Additional items in QLQ-C30

Some patients had financial difficulties (46%), sleep disturbance (45%) and dyspnoea (40%). A smaller proportion had problems with appetite loss (17%), diarrhoea (14%) and constipation (13%). Constipation was more common in females than males (17% versus 9% had problems, $P < 0.001$) and older patients had more sleep disturbance than younger (51% versus 35%, $P < 0.001$). Allo-BMT patients again scored worse than both CCT and A-BMT patients; this reached significance for dyspnoea ($P = 0.02$ and $P = 0.01$, respectively), appetite loss ($P = 0.002$ and $P = 0.01$) and financial difficulties ($P = 0.002$ and $P = 0.02$). There were no significant differences between A-BMT and CCT patients ($P > 0.05$ in each case).

3.2.4. Global health/QoL

80% of all patients had a less-than-perfect global health/QoL rating (88% Allo-BMT versus 86% A-BMT and 75% CCT (Table 2)), but global health/QoL was significantly poorer in Allo-BMT patients (median score = 67) than either A-BMT or CCT patients (median score = 83 $P < 0.001$, in both cases), with no significant difference between CCT and A-BMT ($P > 0.1$).

Younger patients had a better global health/QoL than older patients ($P=0.002$), but there was no significant gender differences ($P>0.1$).

3.3. Leukaemia-specific questionnaire (QLQ-LEU)

Table 3 gives the percent of patients reporting problems in the QLQ-LEU subscales and additional items by gender, age and treatment.

3.3.1. Subscales

Overall, 86% of patients had symptoms consistent with GVHD (e.g. itchy and dry skin, stiff joints and chills). However, most had a score relating to mild (score 1–24) or moderate (score 25–49) symptoms and only 2% were rated as severe (score $\geqslant 50$) (see Discussion). 51% had susceptibility to infection, most scored as mild, and a few had sensory loss (18%) and problems with functional status (6%). There were no significant age differences in the subscales ($P>0.1$), except for the GVHD subscale, where older patients had slightly worse problems than younger, ($P=0.07$). Females had worse GVHD-like symptoms than males ($P<0.001$). CCT and A-BMT patients, unsurprisingly, had fewer GVHD-like symptoms than Allo-BMT (both $P<0.001$). Similar treatment effects with regard to the susceptibility to infection and sensory loss were noted, with Allo-BMT patients doing less well than both A-BMT ($P=0.006$ and $P=0.008$) and CCT patients ($P=0.01$ and $P=0.006$). There were no significant treatment differences in functional status, but only 29 patients had problems, 22 of which were mild.

3.3.2. Additional items

Some patients had problems with weight gain (41%), mouth dryness (31%), eye dryness (21%), difficulty swallowing (10%), dental problems (25%), coughing (43%), hair loss (7%), abnormal hair growth (7%), changes in appearance (10%), dizziness (26%), blurred vision (22%) and anal pain (9%). The only significant associations with age were that younger patients had more dental problems ($P=0.007$) and coughing ($P=0.008$). Allo-BMT patients experienced worse leukaemia-specific problems than either A-BMT or CCT patients. Eye dryness, difficulty swallowing and coughing were more common in Allo-BMT than either CCT patients ($P<0.001$, $P=0.02$ and $P=0.04$. respectively) or A-BMT patients ($P=0.03$, $P=0.03$, $P=0.003$, respectively). Mouth dryness was most common in Allo-BMT patients and least common in CCT with A-BMT patients falling in between the two (Allo-BMT versus CCT $P<0.001$, Allo-BMT versus A-BMT $P=0.01$, A-BMT versus CCT $P=0.008$). Anal pain was more of a problem for Allo-BMT than A-BMT patients ($P=0.02$), but only 42 patients recorded any anal pain, and only 11 recorded major problems. Problems with weight gain were less common in Allo-BMT patients than CCT patients ($P=0.002$).

3.4. Disease-related modification scale

When asked to compare present with pre-disease status for the main domains of QoL and overall QoL, patients reported a wide range of perceived changes. Present status tended to be rated as worse than before diagnosis (Table 4). Compared with pre-treatment, males had worse energy ($P=0.003$), family life ($P=0.04$) and overall QoL ($P=0.03$) posttreatment than females. Older patients were more likely to have worse intellectual capacity ($P=0.02$), family life ($P<0.001$), professional life ($P<0.001$), sexual relationships ($P<0.001$), social relationships ($P=0.002$) and overall QoL ($P<0.001$) posttreatment than younger patients. When the three treatment groups were compared for each dimension, more Allo-BMT patients reported a change for the worse than CCT patients. More A-BMT patients reported a change for the worse than CCT patients, but not as many as in the other transplant group (although the differences were mainly of marginal significance).

Of the 322 study participants in full-time employment pretreatment, 163 (51%) were still in full-time employment, 42 (13%) were employed part-time, 51 (16%) were on medical leave, 33 (10%) unemployed and 20 (6%) retired. Of the 343 patients who were married pretreatment, 9 had divorced, 1 was widowed and 3 were single posttreatment. Older patients were more likely to remain married than younger patients (97% versus 93%, $P=0.05$) and were less likely to have remained in full-time employment (43% versus 62%, $P=0.002$), but there were no significant differences by gender or treatment.

3.5. Results by randomised treatment

Of the 481 patients with QoL data available, 120 (25%) were randomised to A-BMT (61) or no further treatment (59). In this small subset of patients, the only significant result was that those allocated to receive an A-BMT had more problems with mouth dryness than those allocated CCT ($P=0.04$). However, the results for the disease-related modification section were in the same direction as for treatment received (A-BMT slightly worse than CCT) and the lack of statistical significance may be due to the small sample size.

328 (68%) patients with an available QoL assessment were tissue-typed, of whom 141 patients had an HLA-identical sibling donor. 139 were not tissue-typed (62 no siblings, 57 too old, 20 other reasons) and it is unknown if tissue typing was performed in 14 cases. The results by the unbiased comparison of donor versus non-donor patients (either including or excluding those with no

siblings) are similar to those by treatment actually received (Allo BMT versus A-BMT/CCT).

4. Discussion

Previous data have shown a normal or near-normal QoL in the vast majority of patients treated by Allo-BMT [16]. However, later studies have shown a higher risk of impaired QoL which may be permanent after BMT and may have an impact on medical decisions [10].

The present study replicates and confirms these later findings in a much larger sample, broadening the picture previously described when the severe adverse impact of Allo-BMT on sexual functioning and fertility in the same cohort was reported [1]. For each functional scale, the ranking was consistent with the Zittoun study [10] (Allo-BMT was worse than A-BMT which was worse than CCT). This effect was highly significant for the physical, role and social functioning scales. This pattern recurred on the symptom, global health and additional item scales, reaching significance for global health, fatigue, pain, nausea and vomiting, dyspnoea, appetite loss, financial difficulties, and mouth and eye dryness, and marginal significance for cough and swallowing difficulties. Similarly, the subscales GVHD-like symptoms, susceptibility to infection and sensory loss showed the same ranking and significance. The same trend was noted in a wide range of symptoms posttreatment compared with predisease. The only exception was weight gain, where the ranking was reversed (Allo-BMT significantly less gain than A-BMT, who had less gain than CCT). This appears to be the only positive QoL benefit of Allo-BMT. However, Allo-BMT patients had more problems with weight loss (included in the infection susceptibility scale: 28% Allo-BMT, 12% A-BMT, 10% CCT had problems), which clinically is probably more worrying than weight gain. Placing these results in perspective, for most individual items of QoL, most patients reported no or only minor problems, although these appear to have a cumulative effect such that majors factors, including global health/QoL, professional life and emotional and social functioning, are quite seriously adversely affected. Fatigue also seems to affect most patients (79% reporting problems) and is worse in both BMT groups (Allo-BMT worse than A-BMT). More females than males reported fatigue problems (non-significant), which parallels the gender differences in QoL after Allo-BMT found by Heinonen and colleagues [17]. This is worthy of further investigation.

While randomised comparisons are the 'gold standard', we chose to compare primarily the treatment actually received because of the much larger number of patients available for this comparison. Analysis by randomised allocation gave results that were similar, suggesting that substantial bias was not introduced by the use of non-randomised comparisons in this study.

These findings show that treating leukaemia with Allo-BMT causes long-term QoL problems, probably related to the impact of chronic GVHD and to conditioning with TBI. (However, the fact that symptoms consistent with GVHD occurred in most patients suggests that this subscale overestimates the true incidence of chronic GVHD, since these symptoms also occurred in most patients in the A-BMT and CCT groups).

Whether these adverse effects resolve or improve over time is still unclear as the literature shows conflicting results. Early studies suggest that there is no change over time [18,19] and later studies indicate some late improvement [6,14]. In the Zittoun [10] study, only the mouth sores correlating with GVHD showed any significant improvement after 3 years. A Chinese study of patients receiving an unrelated donor BMT showed similar impairment; passage of time was unrelated to psychosocial improvement and fatigue was a major symptom interfering with daily life. Although long-term survivors appeared to have an acceptable QoL, rehabilitative services were still required for those exhibiting difficulties in daily life [20]. In a Dutch study, patients were doing well 3 years after their BMT, but an identifiable group needed help with ongoing psychological problems [21]. A Canadian study over three decades showed that QoL in patients surviving 10 years or more improves with time after the transplant, but may not return to normal. A small Swedish study found that 80% of patients described their general health as 'quite good' or 'excellent', 2–4 years after transplantation, despite impaired functioning and a high incidence of other symptoms [7]. There is considerable conflicting evidence regarding the long-term effects of BMT in survivors. Therefore, consideration of the effects reported here in the allo-BMT group, together with the previously reported serious adverse effect of BMT on sexual functioning relative to CCT [1], and the evidence from the main trial data that there is no clear survival benefit of BMT over CCT (A-BMT 57% versus CCT 45% at 7 years, $P = 0.2$; unbiased analysis of Allo-BMT versus not 56% versus 50% at 7 years $P = 0.1$) [22,23] warrants a reconsideration of treatment strategies. The uncertainty in the literature indicates that further prospective studies to help evaluate more clearly the effects of these treatments in long-term survivors are needed.

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