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Associations Between Coping and Survival Time of Adult Leukemia Patients Receiving Allogeneic Bone Marrow Transplantation

Results of a Prospective Study

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ABSTRACT

BACKGROUND: To investigate associations between coping strategies and length of survival in a sample of 52 adult leukemia patients receiving allogeneic Bone Marrow Transplantation (BMT).

METHODS. A total of 52 adult patients, diagnosed with acute and chronic myeloid leukemia admitted for allogeneic BMT to a University Hospital BMT unit, in preparation for a transplantion of genotypically matched HLA donor marrow were interviewed immediately after informed consent and prior to preparatory treatment for transplantation. Semi-structured interviews were conducted and recorded for analysis to assess coping styles and were evaluated by a new content analytic coping measure (Ulm Coping Manual). Patients were a random sample of all eligible patients on the BMT unit between May 1990 and May 1994.

RESULTS. Complete audiotaped interviews were rated by blind raters, employing a newly developed content analysis for the identification of patients' coping strategies. Multivariate analysis using a Cox model revealed three pretransplant variables that demonstrated a statistically significant influence on 5-years survival: Stage of Disease at transplant ($p < 0.012$), Distraction ($p < 0.007$) and Fighting Spirit as coping modalities ($p < 0.013$).

CONCLUSIONS. The results of this prospective study document the impact of certain psychological variables, notably coping style on survival with Bone Marrow Transplantation. This suggests the necessity of utilizing psychosocial interventions to address stress and anxiety in patients awaiting transplantation in order to reduce anxieties and to employ more effective coping techniques to deal more appropriately with their situation and to enhance Fighting Spirit. The effects on survival of such psychosocial interventions need to be tested in a randomized controlled study.

KEYWORDS: leukemia, Bone Marrow Transplantation, coping, fighting spirit, cancer survival, cancer progression

BONE MARROW TRANSPLANTATION (BMT) has become an important treatment for malignant diseases of the hematopoietic system[1-3]. Results have improved considerably during the last decade and the procedure has become a standard therapeutic modality. The contribution of psychosocial factors to treatment outcome is rarely studied[4-7], except in largely retrospective studies dealing with psychosocial adaptation to long-term survival[8-9]. The pre-BMT period is a very difficult time psychologically in relation to the conditioning regimen - high dose chemotherapy and total body irradiation - as well as anxiety provoking while awaiting treatment in a transplantation unit[9]. Research examining psychological aspects of the pre-BMT waiting period and its possible impact on the course of the disease and the success of rehabilitation is nevertheless nearly nonexistent[10], and these issues remain underexamined in the literature.

The few studies that addressed some of these issues more recently, found that depressed mood and lower levels of social support assessed pre-BMT, were predictive of shorter post-BMT survival[6]. As well, higher levels of anxious preoccupation predict shorter post-BMT survival time[5]. Studies from an American and a British investigation failed to find evidence for a Fighting Spirit factor predicting longer survival in BMT patients[5, 7], in contrast to other studies dealing with relationships between cancer progression and psychosocial factors that supports the relevance of coping to survival[11, 12].

Coping styles and personality variables have also drawn study in other than leukemia patients. Greer and coworkers found that patients' mental adjustment to their early breast cancer Stage of Disease was significantly related to recurrence-free survival at 15 years[13]. Patients who responded to the diagnosis with either a Fighting Spirit or Denial had longer survival, in contrast to those who adopted a hopeless attitude, or one of stoic acceptance. Similarly patients with malignant melanoma who minimized the importance and threat of their cancer to their well-being had significantly poorer survival rates compared to patients who utilized

active-behavioral coping[14]. Psychosocial intervention that aimed at improving coping predicted better survival[14].

Women with malignant melanoma who exhibited significantly more stoic acceptance, and male melanoma patients with more helplessness/hopelessness coping reactions were found to have significantly worse disease progression at follow-up 18 to 20 months later[15]. Other studies have emphasized the role of patients' inability to express negative emotions, particularly anger or aggressiveness as being significantly related with cancer progression[16-18]. A recent major effort to confirm the hypothesis of prognostic significance of a fighting spirit among a larger cohort of early stage breast cancer patients (stages I and II) failed to confirm any relationships between the amount or intensity of fighting spirit attitudes and improved survival[19].

The aim of the present study was to examine prospectively the relationships between survival in adult leukemia patients undergoing allogeneic BMT and psychosocial variables prior to treatment. Specifically we assessed the effects of pre-transplant social and coping resources as well as basic demographic variables on mortality and long-term survival of 52 adult HLA-identical sibling donor patients admitted for allogeneic BMT. In this study we aimed to address major criticisms that have regularly be advanced against research findings pertaining to the relationships between psychosocial factors and cancer survival[5], therefore

- standardized, prospective measures for the assessments of coping and social support were utilized
- detailed objective expert ratings were used for assessments of coping and social support, to ensure validity
- the study addressed a homogeneous patient sample of acute or chronic myeloid adult leukemia patients undergoing allogeneic BMT
- all relevant biological disease and treatment factors, as well as pertinent sociodemographic variables were controlled for in the study.

PATIENTS AND METHODS

Patients

The study sample consisted of 52 adult leukemia patients with HLA-identical sibling donors admitted for allogeneic Bone Marrow Transplantation (BMT) to the BMT unit, Department of Internal Medicine of Ulm University Hospital between May 1990 and May 1994.

Patients with the following three diagnoses were included in the study (see also Table 1).

Acute Lymphoblastic Leukemia (ALL). - This form of leukemia is a hematological malignancy characterized by rapid proliferation and subsequent accumulation of immature lymphocytes and their progenitor cells. Patients receiving BMT after remission generally have a lower incidence of recurrent leukemia and demonstrate improved survival[20]. 7 ALL patients entered the study.

Acute Myeloid Leukemia (AML). - The majority of patients with AML in first remission will relapse if treated with conventional chemotherapy alone. Transplanted patients' disease-free survival chances range from 45 - 65%[21]. 26 AML patients were included in the study.

Chronic Myeloid Leukemia (CML). - Although CML may have a prolonged course, it is a universally fatal disease with conventional therapy. Allogeneic or syngeneic BMT is an effective treatment, capable of producing long-term disease-free survival with prospects of survival between 50 and 60% if transplanted in the chronic phase[22]. 19 CML patients were included in this study.

Since it was essential for the study that patients spoke and understood the German language properly, only German patients were included in the study. 52 of all 54 suitable patients with an appropriate German language standard (because of the content analytic rating procedure) assigned to the transplantation unit from May

1990 till May 1994 agreed to participate (i.e. 96%). Two patients refused to participate in the study.

Furthermore only patients with HLA-identical sibling donors were included in the study.

The study was approved by the local ethical committee following the principles of the Declaration of Helsinki. All patients were informed explicitly by their doctors and additionally by research interviewers that participation in the study was voluntary and non-participation would have no influence on the regular oncological treatment on the unit. Informed consent was obtained from all patients.

Coping Ratings

All participating patients had to be fluent in the German language as they were being interviewed by trained psychologists using a semi-structured interview technique to evaluate coping. The interviews were audiotaped and subjected to content analytic ratings using the *Ulm Coping Manual (UCM)*, a coping measure that assesses the subjective psycho-social situation and the coping resources of patients with life-threatening diseases objectively[23, 24]. Interviewers addressed coping very broadly, exploring coping as it relates to the diagnosis, the BMT decision making process, course of the donor search and the donor-patient relationship, experience with the disease and with prior treatments, the impact of the disease on patients' personal life and job situation, pre-admission waiting, personal fears and hopes regarding to high dose chemotherapy and total body irradiation (TBI), as well as other concerns. Interviews lasted mostly between 25 and 40 minutes.

The six scales of the UCM are comprised of all 33 categories of the UCM. They are operationalized as follows: "Passive Reception/Resignation" (6 categories: active avoidance, hesitation, resignation/hopelessness, rumination, social withdrawal, stoicism/fatalism), "Distraction" (7 categories: activity, cognitive distraction,

compensation, positive fantasies, stimulus control, wishful thinking, wish fulfillment), "Cognitive Structuring" (7 categories: anticipation, attribution, humor, positive reframing, problem analysis, obtaining perspective, attribution of meaning), "Social Contacts" (4 categories: altruism, emotional support, model learning via contacts with other patients, social distraction), "Compliance" (4 categories: active compliance [explicit wish to collaborate], passive compliance, acceptance of disease/situation, information seeking [wish to learn about the disease]) and "Fighting Spirit" (5 categories: rebellion against fate [determination to beat the disease], seizing initiative, optimism/hope, self-valorization [encouraging oneself by recalling earlier life crises and mastery], taking control).

Coping scores are derived by adding up raw scores of scale related sub-categories across the whole interview and by dividing sum-scores by the total amount of time a particular patient had spent talking during the interview, since the amount of spoken time correlates positively with the probability that a specific coping content (category, scale event) appears. The interviewers' amount of speaking time was controlled for and did not differentiate statistically between subgroups. The resulting coping scores of patients could therefore be compared across the total sample and met the criteria of interval scales (see formula in the Appendix).

Raw scores were derived by summing up the total amount of categories belonging to a scale that were being rated across the whole interview. For example, fighting spirit raw scores were made up by two times „optimism/hope“ ratings, four times „rebellion against fate“, three times „self-valorization“ and five times „taking control“ over oneself, i.e. the total raw for scale „Fighting Spirit“ in this case would add up to 14. The Score results from the multiplication of 14 with 100, divided by 5 subcategories in this scale, multiplied with 37 minutes (given that this particular interview lasted 37 minutes in total) and would therefore be: 14 X 100/5 X 37 = 7,57. Consequently Scores can be compared across different interviews since length of interview is been taken into account. Interviewers‘ intervention times were also

controlled and showed to be roughly comparable across all interviews and could therefore be neglected.

This content analytic procedure follows the methodological principles of one of the well-established content analytic measures in the field of psychology, psychophysiology, psychopharmacology and psychosomatic medicine, as it is described by Gottschalk and Gleser[25].

Statistical Analysis

Univariate comparisons between the survivor and non-survivor groups were evaluated with Kruskal-Wallis or Chi[2]-tests and 95% confidence intervals. The effect of several independent variables (significantly or in tendency discriminating between both groups: Stage of Disease, Distraction, Resignation, and Fighting Spirit) were then studied in a multivariate analysis using the Cox proportional hazards regression model. Survival was analyzed using the product-limit method of Kaplan-Meier[26].

RESULTS

The study group consisted of 33 patients with acute leukemia (AL, either ALL or AML) and 19 patients with chronic myeloid leukemia (CML). 35 patients were in first remission or first chronic phase at the time of transplant, 17 were transplanted at a more advanced stage of their disease. The median age of patients at transplant was 38 years (range 17-55 years), the median interval from diagnosis to transplant was 303 days (range 118-1.427). 21 out of the 52 patients died (Table 1). The median survival time for the 31 survivors of the study is 3 years and 4 months and for the 21 non-survivors approx. 6 months after transplant (see Table 1).

	Survivors (n_1 = 31)	**Non-Survivors** (n_2= 21)	Difference ($p <$)
	(Percent in parenthesis)		KW = Kruskal-Wallis Test or chi^2-Test (likelihood ratio)
Age (years)	*Mean*		
	35.4	37.9	0.35 (KW)
	Range		
	17 - 55	18 - 55	
Sex	*Male*		
	21 (67.7)	15 (71.4)	0.78 (chi^2)
	Female		
	10 (32.3)	6 (28.6)	
Married	21 (67.7)	14 (66.7)	0.94 (chi^2)
*GSI * (SCL-90-R)*	n_1=24	n_2=10	
	Mean		
	0.61	0.56	0.79 (KW)
	Range		
	0 - 1.33	0.08 - 1.30	
Depression (SCL-90-R)	n_1=24	n_2=10	
	Mean		
	0.57	0.67	0.60 (KW)
	Range		
	0 - 1.50	0 - 1.73	
Anxiety (SCL-90-R)	n_1=24	n_2=10	
	Mean		
	0.71	0.65	0.27 (KW)
	Range		
	0 - 1.90	0 - 2.50	
*Education***			
	Level 1		
	14 (45.2)	9 (42.9)	0.93 (chi^2)
	Level 2		
	11 (35.5)	7 (33.3)	
	Level 3		
	6 (19.3)	5 (23.8)	
Type of Leukemia			
	AL		
	19 (61.3)	14 (66.7)	0.69 (chi^2)
	CML		
	12 (38.7)	7 (33.3)	
Stage of Disease (Status)			
	CR or CP = 1		
	25 (80.6)	10 (47.6)	0.01 (chi^2)
	CR or CP > 1		
	6 (19.4)	11 (52.4)	
GvHD Prophylaxis			
	*CsA/MTX****		
	19 (61.3)	15 (71.4)	0.45 (chi^2)
	*T-cell depletion*****		
	12 (38.7)	6 (28.6)	
Follow-up after transplant (in days)			
	Mean		

	1.365	306	0.0001 (KW)
	Median		
	1.222	179	
	Range		
	528 - 2.247	26 - 1.343	
Interval between diagnosis and BMT (in days)			
	Mean		
	414.6	455	0.88 (KW)
	Median		
	323	254	
	Range		
	118 - 1.368	128 - 1.427	

Table 1: **Patients with an HLA identical sibling donor (n = 52)**
Patient characteristics - Survivors (n_1 = 31) vs. Non-Survivors (n_2 = 21) - Basic sociodemographic and haematological variables prior to transplant
* Global Severity Index [22]
** Level 1: Elementary School or less, no job training;
Level 2: Graduate School and completed job training;
Level 3: High School Degree, University studies and/or academic position
*** Cyclosporin A/Methotrexat according to [52]
****In vivo/ex vivo T-cell depletion with Campath [53]

In terms of disease related factors both patient groups differed significantly in Stage of Disease at BMT with the survivors group containing significantly more patients in an early Stage of Disease (either 1^{st} complete remission in acute leukemia patients or 1^{st} chronical phase in chronic myeloid leukemia patients) compared to the non-survivors group ($p < 0.01$). There were no statistical differences with regards to the distribution of diagnosis (type of leukemia), GvHD prophylaxis, or time span between diagnosis and BMT. Survival time for AL and CML patients across the whole sample did not differ (AL: 942 days vs. CML: 935 days post-BMT; Kruskal-Wallis $chi^2 = 0.009$, $p < 0.92$).

Acute and chronic leukemia patients did not differ with regards to relevant coping styles per se (Kruskal-Wallis $Chi^2 = 1.17$, $p < 0.28$ for Distraction and $Chi^2 = 2.46$, $p < 0.12$ for Fighting Spirit).

Interviews were rated by intensively trained raters (psychologists) who were different from the interviewers. Interrater reliability (Kappa) varied across sub-categories from +0.68 to +0.97 with an average of +0.86. Raters were blind towards disease, rehabilitation progress and towards possible complications or death of patients, since ratings occured prior to the death of patients.

All patients received identical supportive care on the transplantation unit. No additional psycho-social support was provided either before or after admission to the unit beyond the initial interview immediately after informed consent and prior to TBI and high dose chemotherapy.

Multivariate Analysis

The importance of basic hematological and coping variables was tested by multivariate analysis using a Cox regression model: Stage of Disease at transplant, Type of leukemia, Distraction, Compliance, and Fighting Spirit as coping variables, as well as Age and Sex as sociodemographic variables. Distraction was the most

potent factor (Wald = 7.29, p = 0.0069) followed by Stage of Disease (Wald = 6.31, p < 0.0120), then by the intensity of a Fighting Spirit coping response (Wald = 6.18, p = 0.0129) (Table 2). No other variable discriminated significantly between long-term survivors and non-survivors.

	Survivors ($n_1 = 31$)	*Non-Survivors* ($n_2 = 21$)	*p*
Stage of Disease			
CR or CP = 1	25	10	
CR or CP > 1	6	11	0.0120
Distraction coping	1.34 (0.90)	1.88 (1.46)	0.0069
Fighting Spirit coping	6.08 (3.65)	4.35 (2.38)	0.0129
Resignation coping	2.35 (1.73)	3.27 (2.31)	n.s.

Table 2 **Variables included in multivariate analysis (Cox Regression Analysis)**
Absolute numbers (Stage of Disease) or score means (Distraction, Fighting Spirit, Resignation)
(SD = Standard Deviation in Parenthesis)

Univariate Analyses

On univariate analysis Stage of Disease was the major significant hematological and transplant-related variable impacting survival (p < 0.01). Type of leukemia (AL or CML), the interval between diagnosis and BMT, type of Graft-versus-Host-Disease prophylaxis, sociodemographic variables (Sex, Age, Education, Marriage) did not discriminate between survivors and nonsurvivors (Table 1). All patients received HLA-identical donor marrow. One coping factor, Fighting Spirit, was a significant predictor of survival rate (p < 0.05). Resignation (p < 0.13), Distraction (p < 0.14), and Compliance (p < 0.19) were non significant but showed some tendency to discriminate between both groups.

Follow-up data show that the difference in survival between the two groups is not due to the differences in transplant-related mortality (infections, acute or chronic

GvHD). Relapse rates of the primary disease, however, were in tendency a predictor (Table 3).

	Survivors (n_1 = 31)	**Percent**	**Non-Survivors (n_2 = 21)**	**Percent**	**p***
Relapse	7	22.6	10	47.6	0.06
Pneumonia	5	16.1	6	28.6	0.28
Other infections	22	71.0	12	57.1	0.53
Total infections	27	87.1	18	85.7	0.89
acute GvHD	14	45.2	9	42.9	0.87
chronic GvHD	12	38.7	5	23.8	0.24
Total GvHD	18	58.1	11	52.4	0.69

Table 3: Post transplant course - survivors versus nonsurvivors
* Chi^2-Test (Likelihood Ratio Chi^2-Test)

A comparison of Kaplan-Meier survival curves for 26 patients with a high score for Distraction versus 26 patients with a low score in Distraction coping (split by the median) revealed that the level of Distraction coping prior to transplant significantly predicts survival (Figure 1). Both groups were statistically indistinguishable in regards to the following variables: Stage of Disease, Type of Leukemia, GvHD-Prophylaxis, Age, Gender, Education, Marriage Status, Social Support.

Patients in the lower Distraction group had a significantly higher rate of survival (approx. 72%) compared to patients in the high Distraction coping group (approx. 44%).

Figure 1

Figure 1: Kaplan-Meier survival plot - Distraction coping

Solid line patients with low Distraction coping ($n_1 = 26$)
Broken line patients with high Distraction coping ($n_2 = 26$)
Log-Rank Test, $p = 0.045$

A similar comparison of the 26 patients with higher Fighting Spirit coping versus those 26 patients with a low score in Fighting Spirit (split by the median) revealed that the intensity of Fighting Spirit was an independent predictor of survival at five years (Figure 2). Again both subgroups were statistically not different in regards to the following variables: Stage of Disease, Type of Leukemia, GvHD-Prophylaxis, Age, Gender, Education, Marriage Status, Social Support.

Figure 2

Figure 2: Kaplan-Meier survival plot
Solid line patients with high Fighting Spirit coping ($n_1 = 26$)
Broken line patients with low Fighting Spirit coping ($n_2 = 26$)
Log-Rank Test, $p = 0.031$

Patients in the higher Fighting Spirit group had a significantly higher rate of survival (approx. 68%) than did patients in the low Fighting Spirit group (approx. 46%) ($p = 0.031$, Log-Rank Test) (Figure 2).

Across the whole sample there is a low positive correlation between Distraction and Fighting Spirit ($r = .26$, $p < 0.06$, $df = 50$). However, taken extreme opposite subgroups of all 52 patients only - 12 patients with high Distraction and low Fighting Spirit versus those 12 patients who display low Distraction and high Fighting Spirit at the same time, Distraction and Fighting Spirit is strongly negative correlated ($r = -.53$, $p < 0.001$, $df = 22$). Both subgroups of 12 patients each are comparable regarding Stage of Disease (both have only 3 patients with an advanced disease at transplant = CR or CP > 1), and comparable regarding Sex, Age,

Marriage, Education. Both groups are not comparable regarding Form of Leukemia (8 out of the 12 patients in the low Distraction/high Fighting Spirit subgroup are diagnosed with CML versus 4 patients with an AL, while 9 out of the 12 high Distraction/low Fighting Spirit subgroup are diagnosed as AL and 3 are diagnosed as CML patients). However, Form of Leukemia does not discriminate between both subgroups regarding intensitiy in Distraction or Fighting Spirit coping per se.

Furthermore both subgroups of 12 patients each (12 low Distraction/high Fighting Spirit coping patients versus 12 high Distraction/low Fighting Spirit patients) differ significantly regarding survival rate. Only 1 patient out of the 12 low Distraction/high Fighting Spirit subgroup dies whereas 8 out of the 12 high Distraction/low Fighting Spirit patient group die (Likelihood Ratio $Chi^2 = 9.59$, $p < 0.002$).

DISCUSSION

The most striking finding of our study is the strong influence of the psychological coping variables - Distraction and Fighting Spirit - on the survival of a cohort of patients receiving an HLA-identical allogeneic bone marrow transplant. In fact the degree of Distraction, Fighting Spirit and the Stage of Disease prior to transplant were the only variables with a statistically significant effect on survival.

These results contrast with those of other studies which were unable to identify specific psychosocial variables such as Fighting Spirit coping that influenced survival in cancer patients[5, 19, 28, 29]. These discrepancies may in major part be due to methodological features of this study. Andrykowski and colleagues assessed comparable leukemia patients assigned to BMT prospectively with different questionnaires[5]. The authors were not able to find significant relationships between coping styles such as Fighting Spirit or Denial and Length of Survival for adult leukemia patients undergoing BMT compared to other

psychooncological studies that used extensive interview techniques[13, 15, 30]. As Andrykowski et al. themselves discuss, there might be a pre-selection among BMT patients in as much those low in Fighting Spirit or high in Hopelessness might deselect themselves out of consideration for BMT[5]. Our results challenge this hypothesis. Although our sample displayed a relatively low level of psychopathology and distress compared to psychiatric patients (see also Table 1) and the average coping level of 30 study patients was significantly higher in all scales but Resignation, in comparison to matched 30 persons (Age, Gender, Education) seeking for psychotherapeutic help (Resignation higher for psychotherapy patients compared to leukemia patients undergoing BMT)[31], coping strategies in this study did distinguish between BMT survivors and non-survivors. Even within this selected sample of well adjusted individuals, higher Fighting Spirit and lower Distraction coping add profoundly to length of survival in adult leukemia patients undergoing allogeneic BMT.

The results from the breast cancer study carried out by Watson and colleagues[19] are also based on questionnaires regarding coping strategies rather than on interviews as in this study. As some prior studies have shown[19], particularly an interview approach with more opportunities to reveal more subtle informations – e.g. by offering the patients more degrees of freedom to use the offered space to develop their own perspectives with accompanying emotions and thus approaching real behavior more appropriately rather than relying on restricted questionnaires with the possible danger of socially desirable answers and other restrictions that correlate with a lower validity of questionnaires and the well known fact that expressed believes (in this case regarding own coping behaviour) do not highly correlate with real behaviour – increase the probability to end up with significant relationships between coping behaviour strategies such as Fighting Spirit and survival of cancer.

Since the findings of our study have considerable implications for patient care it is essential to exclude confounding variables. One such variable is Social Support which has been demonstrated to influence mortality in previous studies[32]. We were able to exclude a significant role for Social Support as an explanation of our findings since both, survivors and non-survivors, experienced a comparable degree of support from relatives, friends, colleagues and hospital staff. The audiotaped interviews were investigated by applying a newly developed system for measuring subjectively experienced Social Support on a scale ranging from 1 (very low support) to 4 (very high support)[33]. No differences were detected between both survival subgroups regarding experienced social support.

The second potentially confounding variable is patient compliance. The level of compliance was tested both prior to BMT and in a second interview which covered the inpatient period. There was no significant difference in compliance between the two groups according to the Compliance scale of the UCM.

Stage of Disease was the only hematological variable predictive of survival. This variable and recipients' HLA-compatibility with the marrow donor are the major factors influencing survival prospects from a hematological perspective[21, 22, 34]. All 52 patients of our study were genotypically matched for HLA and were therefore comparable except for Stage of Disease. Even when Stage of Disease is controlled for - as were other hematological variables such as AL, CML or treatment related variables such as GvHD-prophylaxis, radiation, chemotherapy, Karnofsky score at time of BMT and sociodemographic variables including social support and days from diagnosis to BMT - , Distraction and Fighting Spirit as coping attitudes were the only pretransplant factors predictive of improved survival.

The complex relationship between Distraction and Fighting Spirit coping suggests that an open attitude (i.e. low Distraction) towards the disease, treatment and related complications paves the way for an elevation and activation of Fighting Spirit resources. In contrast, a higher Distraction seems to draw away attention from

dealing with the challenges of the disease and treatment regime in some cases. Higher Distraction often seems to inhibit the activation of more Fighting Spirit coping. If this is the case, a higher Distraction combined with a lowered Fighting Spiritit seems to be particularly fatal. These patients have a significantly lower survival rate compared to those who display a low Distraction coping in combination with an intensive Fighting Spirit coping, no matter which Stage of Disease was given at time of transplant.

We believe that our assessment of coping strategies is more comprehensive and reflects more precisely the complex process of person-by-situation interactions[35] than those mostly employed in previous studies. Particularly the micro-analysis of the entire interview material - a sentence by sentence content analysis - obtained from the patients during the semi-structured interview is better able to identify subtle or even unconscious intentions, attitudes, and behavioral patterns of patients that allow for a comprehensive, more valid approach towards coping resources compared to subjectively obtained opinions via questionnaires[35, 36]. The result is a true, less inferential and less subjective measure of coping.

Furthermore the reliance on intensively trained psychologists as interviewers and independent, blind raters should improve the reliability and objectivity of assessment compared with studies based on patients' self-assessment.

Survival after BMT is essentially determined by events in the first year posttransplant[21,22]. We speculate that a higher Fighting Spirit, which has such a strong influence on survival, is likely to reflect personality traits which are essentially stable over time[37]. Fawzy et al. have shown that active-behavioral and active-cognitive coping strategies could be enhanced for some malignant melanoma patients by a complex psychosocial intervention program and predicted survival on a six year-follow-up basis[14]. Patients who did not increase use of such coping strategies had a poorer prognosis. Further research on this topic is needed, to determine what are enduring personality traits and what are remediable skills.

A major, still unanswered question is how does Fighting Spirit influence survival. There has been a growing interest in recent years in interactions between the brain and the immune system and the role of such interactions in modulating the development and progression of infections, autoimmune diseases and cancer[38-42]. Although no clear causal linkage can be made, immunological measures are clearly influenced by social support and mood, and psychosocial interventions may offer a putative mechanism of effect by enhancing possible resources to cope with the threat more actively[43, 45, 46, 51].

In the context of allogeneic BMT a modulating influence of psychosocial factors on immunological processes could for example affect the incidence of infections or of acute or chronic GvHD or possibly even the relapse rate via the Graft-versus-Leukemia effect. In our study survivors and non-survivors did not differ, however, with respect to the incidence of infections or GvHD. The improved survival in the high Fighting Spirit group relates entirely to a lower relapse rate, even in patients with early disease. It would be highly speculative to ascribe this lower relapse rate to a stronger GvL effect in these patients because we cannot exclude the influence of other factors with a strong influence on the risk of relapse such as cytogenetics. This aspect should be addressed in future studies.

On the other hand one might speculate if a higher Fighting Spirit attitude did significantly influence the immune system in patients of our survivor subsample thus contributing to a better survival rate. Also a more helpful psychological response like more attention towards the challenges accompanying the disease and the treatment and an activation of more Fighting Spirit coping behavior might have a direct effect on stress hormones which then might have an effect on disease progress. However, immune or endocrine parameters were not controlled for in this study. A higher Distraction coping seems to have served like a defense against dealing with the disease and the challenges caused by the extremely invasive treatment, in consequence preventing an activation of fighting resources.

The question remains why some patients distract more from their disease and the upcoming treatment burden and consequently activate less Fighting Spirit mentality than others. It could be the case that these patients may have had a more adverse career regarding prior treatments and dealing with the diagnosis and might have sensed that their outlook is less good, thus they did not show strong efforts with regard to Fighting Spirit or confronting their reality through lower Distraction. In fact none of the non-survivor subgroup expressed the importance of „Emotional Support“ received from significant others. Such coping aspects and particular forms of Fighting Spirit attitudes were expressed from survivor patients only and from none non-survivor patient prior to BMT and conditioning for transplantation[47]. However, neither were there time differences since learning about the disease by diagnosis between the survivor and non-survivor subgroups, nor were there differences regarding Stage of Disease at transplant – a significant predictor of survival chances[21, 22], as our data prove - between both subgroups. It might be that the Pre-BMT waiting period sets the course for a Fighting or a resignative attitude (i.e. Distraction). If this should be the case, the result of this study would strongly argue for an early psychological help with an onset shortly after learning about the diagnosis and long before admission to the BMT unit.

Although our study is the first to report an influence of psychosocial factors, particularly coping factors, in patients with acute and chronic myeloid leukemia undergoing allogeneic BMT, there are similar reports mainly from breast cancer and malignant melanoma studies demonstrating the positive influence of psychological support or coping responses such as Fighting Spirit or active-behavioral/active-cognitive coping on disease progression and outcome[13, 14, 48-51].

CONCLUSIONS

This study documents that beside the well known risk of advanced Stage of Disease in leukemia patients admitted for allogeneic BMT, the individual's coping style, notably intensive Fighting Spirit coinciding with lower Distraction coping, contributes to improved survival prospects post-BMT, independent of manifest biological factors.

The results of this study may be due to several methodological requirements that were addressed, which permit an intensive focus on the psychosocial variables of the study population, that relate to survival:

- patients were not assessed retrospectively but prospectively immediately after informed consent and prior to conditioning (chemotherapy and total body irradiation) for BMT
- basis for coping assessments were semi-structured interviews using trained psychological interviewers, rather than relying on patient self-report questionnaires, thus accessing coping more accurately
- ratings of interviews were carried out by well-trained psychologists, independent of the interviewers, with a satisfactory average interrater reliability of + 0.86
- the sample consisted of a relatively homogeneous hematological patient population
- the study controlled for several disease and treatment variables that could affect survival: Stage of Disease, Type of Leukemia, quality of bone marrow match, Karnofsky score at time of BMT, GvHD-Prophylaxis, radiation and chemotherapy doses, time between diagnosis and transplantation and compliance with treatment as well
- all possible sociodemographic variables were controlled for: Age, Gender, Education, Marriage and experienced Social Support

Future work on this topic should try to replicate the findings from this study before psychological intervention programs might be tested for their role in

enhancing patients' ability to activate more adequate coping resources such like less Distraction and more Fighting Spirit prior to allogeneic BMT.

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