

Mental adjustment to cancer and survival of patients admitted for allogenic hemopoietic stem cell transplantation: a prospective cohort study

Krankheitsverarbeitung und Überlebenszeit von Patienten unter allogener hämatopoietischer Stammzelltransplantation: eine prospektive Kohortenstudie

Abstract

Objective: The Mental Adjustment to Cancer Scale (MAC scale) has evolved to a standard measure in the field of psycho-oncology. In this context an attitude called "fighting spirit" gained much attention as a coping style. Some reports suggest that coping efforts as measured by the MAC scale are predictive for survival of breast cancer patients. We explored the predictive power of the MAC scale by using a sample of patients with haematological malignancies undergoing allogenic hemopoietic stem cell transplantation (HSCT).

Methods: Between 9/1999 and 12/2001 127 patients were administered the MAC scale prior to HSCT. Follow-up data of overall survival and event-free survival were obtained in December 2003 and analyzed using Cox-regression models.

Results: At the time of the follow-up, 68 patients had died (overall survival), 75 patients had experienced a relapse or had died (event-free survival). We failed to find significant results for the MAC subscales with and without adjustment for prognostic factors.

Conclusion: In the special situation of patients facing HSCT the MAC scale seems not to be of predictive value. In general, with respect to survival the empirical evidence is not very convincing.

Keywords: survival, psychological response, coping, neoplasm, stem cell transplantation

Zusammenfassung

Zielsetzung: Die Mental Adjustment to Cancer Scale (MAC-Skala) hat sich im Feld der Psychoonkologie zu einem Standardmessinstrument entwickelt. In diesem Zusammenhang gewann ein als "fighting spirit" bezeichneter Bewältigungsstil breite Aufmerksamkeit. In manchen Studien wurde berichtet, dass mit der MAC-Skala erfasste Krankheitsverarbeitungsweisen mit späterer Überlebensdauer korreliert sind. Wir untersuchten die Vorhersagekraft der MAC-Skala in einer Stichprobe von Patienten mit hämatologischen Erkrankungen, die sich einer allogenen hämatopoietischen Stammzelltransplantation (HSZT) unterzogen.

Methode: Zwischen 9/1999 und 12/2001 bearbeiteten 127 Patienten die MAC-Skala vor Durchführung der HSZT. Ein Follow-up im Hinblick auf Überlebenszeit erfolgte im Dezember 2003. Die Überlebenszeitdaten wurden mit Cox-Regressionsmodellen evaluiert.

Ergebnisse: 68 Patienten waren verstorben, 75 Patienten waren verstorben oder erlitten Rezidiv. Es wurden mit und ohne Adjustierung bezüglich medizinischer Prognosefaktoren keine signifikanten Zusammenhänge einer der MAC-Subskalen mit der allgemeinen und der krankheitsfreien Überlebenszeit gefunden.

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Fazit: In der speziellen Situation vor HSZT scheint die MAC-Skala keinen Vorhersagewert für die Überlebenszeit zu haben. Jedoch gilt auch allgemein, dass die empirische Evidenz in dieser Hinsicht nicht überzeugend ist.

Introduction

The introduction's first part addresses the background of the development of the Mental Adjustment to Cancer Scale (MAC scale) that internationally gained wide attention. We assume that this development would not have taken place if the intriguing idea of a *fighting spirit* prolonging survival time for cancer patients had not been raised. In the second part we outline our interest and the background of our study.

In 1972, Greer and colleagues started studying a total of 62 women diagnosed with early breast cancer. Based on clinical interviews they discovered that those patients who had a fighting attitude or were in denial had an advantage with respect to survival time. This advantage was confirmed in 5, 10, and 15 year follow-ups [1], [2]. Subsequently, this research group developed the Mental Adjustment to Cancer Scale (MAC scale) as a questionnaire, which correlated reliably well with the clinical ratings [3]. This questionnaire assesses how the patients cope with the cancer experience. It evaluates five dimensions: fighting spirit (FS), helplessness/hopelessness (HH), anxious preoccupation (AP), fatalism (F), and avoidance (A). This instrument found wide international attention and is in use in several languages, e.g. Chinese [4], French [5]; German [6], Greek [7]; Italian [8]; Japanese [9]; Swedish [10]). In the field of psycho-oncology the MAC scale seems to have advanced towards a standard measure. It is in use not only to assess coping styles but serves to evaluate the outcome of psychosocial interventions [11], [12] as well.

The idea of a *fighting spirit* has spread and was broadly discussed in the relevant literature, both inside and outside academia. Especially in the non-academic world the findings of Greer and his group fostered the idea that being positive enough all the time and keeping up your fighting attitude, you can beat cancer with your mind. But this idea raised fear for several patients that they undermine their perspectives if they do not sustain positive thinking and maintain their fighting spirit irrespective of their actual situation. What was assumed as beneficial could become a source of distress following feelings of guilt or failure.

In 1999, Watson and colleagues [13] published the results of a prospective study that was intended to replicate the earlier findings of Greer and colleagues [1], [2]. In this impressive study with sound methodology, 578 women with early-stage breast cancer were followed up for at least five years. Women were aware of their diagnosis and were enrolled 4-12 weeks after diagnosis. The outcome measures were overall survival and event-free survival controlled for known prognostic factors. They

could not confirm the hypothesis of a connection between fighting spirit and survival but identified a statistical significant relation between the dichotomized MAC subscale helplessness/hopelessness (HH) and event-free survival (adjusted hazard ratio (HR) 1.55, 95%-CI = 1.07-2.25). The association between overall survival and HH reached only a weak tendency (adjusted HR 1.30, 95%-CI = 0.84-2.00). Most recently Watson et al. [14] report on their findings of the 10-year follow-up with results for HH and survival (event-free survival: adjusted HR 1.53, 95%-CI = 1.11-2.11, overall survival: adjusted HR 1.34, 95%-CI = 0.95-1.89) comparable to their initial findings [13]. With respect to the above mentioned pressure to maintain a fighting attitude Watson et al. [13] concluded that their "findings suggest that women can be relieved of the burden of guilt that occurs when they find it difficult to maintain a fighting spirit" (p. 1335).

Since more than twenty years, our research group has a special interest in the field of coping with bone marrow transplantation/hemopoietic stem cell transplantation (HSCT) [15], [16], [17], [18], [19]. The idea that a fighting attitude would be beneficial to adjust to cancer and survival was still a common hypothesis, even though a convincing empirical basis was still lacking. In a first exploratory study focusing on patients with leukaemia undergoing allogenic bone marrow transplantation that were recruited in the period from 1990 to 1995 our group found empirical support for a possible link between coping strategies (labelled "fighting spirit") and survival using the Ulm Coping Manual (UCM) [19], [20], [21]. Raters had to evaluate audio-taped interviews based on the definitions of coping strategies given in the UCM. This procedure is quite time consuming opposed to a self assessment questionnaire as the MAC scale.

When we started to design the present investigation in 1997 the results of the Watson et al. study [13] were not published, but we were determined to explore the MAC scale in our study group.

The possible link between psychological factors and the survival rate was and still is a subject of intensive controversies [22], [23], [24], [25], [26] in general as well as in the field of hemopoietic stem cell transplantation (HSCT) [19], [27]. Beside the studies by Watson and colleagues [13], [14] no other prospective study using the MAC scale as measure has shown convincing associations to survival time. Three descriptive studies are relevant for this topic in the field of HSCT [28], [29], [30]. Andrykowski et al. [28] found that higher levels of MAC subscale AP were associated with shorter survival time in a sample of 42 BMT-patients and a median follow-up period of approximately two years, but found no significant results for the other MAC subscales. Jenkins et al. [30] studied 29 patients pre BMT, and compared deceased patients and those still living after one and six months

and Murphy et al. [29] compared 16 out of a sample of 42 patients undergoing BMT with FS as the predominant coping style to the other 26 patients reporting other predominant coping styles. In both studies, they could not find an association between MAC scale and the survival rate. Methodological shortcomings [27], the small numbers of participants of these studies, and the heterogeneity of results did not offer an empirical basis for a hypothesis testing approach for our study. Therefore, the aim of our study is to explore whether there exist any links between coping styles as measured by the MAC scale administered before performing allogeneic HSCT and survival thereafter.

Patients and methods

The study was approved by the ethics committee of Ulm University. Inclusion criteria were being eighteen years of age or older, fluency in German and having been scheduled for the first allogeneic peripheral blood stem cell or bone marrow transplantation. At hospitalization, patients were informed about the study, that participation in the study was voluntary and that nonparticipation would have no impact on their treatment in the unit. Prior to the investigation, written informed consent was obtained from the patients and questionnaires were administered. They were answered before HSCT. A follow-up of two years was planned for each patient.

Patients

From September 1999 until December 2001, 230 patients were admitted for allogeneic HSCT at the BMT units of the University Hospitals of Ulm and Tübingen, Germany. Of them, 31 did not fulfill the inclusion criteria, eight were not approached in time, and one patient did not proceed to HSCT. Of the remaining 190 patients, 140 (73.7%) agreed to participate in our psycho-social study. Our analysis is restricted to data of 127 patients with a complete data set of target variables (eight questionnaires with missing values, five patients without the necessary physicians' assessments). Of these patients, 59% were male, and 80% lived with a partner. The average age was 41 years (range 18-61 years, SD = 11.2). Most of them had been diagnosed with acute (50%) or chronic (22%) leukaemia. 34% of the patients received their stem cells from bone marrow, others from peripheral blood. 91% received HLA-identical transplants. After transplantation, nearly 3 out of 10 patients relapsed, and 53% of all patients died during the follow up period.

Methods

To measure the psychological response we used the Mental Adjustment to Cancer Scale [31]. This instrument is a 40-item questionnaire addressing reactions of patients on having cancer. Items are given as statements, and patients assess their agreement using a 4-point

Likert-scale (1 = definitely does not apply to me, 2 = does not apply to me, 3 = applies to me, 4 = definitely applies to me). Each item is assigned to exactly one of the five subscales. Scores for the subscales are calculated by adding up the answers of the assigned items. Following are examples for items:

- fighting spirit (FS): "I firmly believe that I will get better";
- helplessness/hopelessness (HH): "I feel that life is hopeless";
- anxious preoccupation (AP): "I suffer great anxiety about it";
- fatalism (F) "I've left it all to my doctors";
- avoidance (A; single item scale): "I don't really believe I had cancer".

Prognostic factors

There is currently no system available to help characterize the prognosis for haematological diseases in general. For CML, for example, such an index was proposed [32], but this index is not transferable to acute leukaemia without making some changes to it. Other recently suggested prognostic indices, e.g. for lymphomas [33] or comorbidity [34], weren't available when we started recruiting, so we did not determine these indices in our study.

With respect to the diversity of potential risk factors, we looked for a global indicator for prognosis and decided to use the transplanting physician's expertise. From an earlier study performed in Ulm, we knew that physicians' assessments ascertained before transplantation were highly predictive for long term outcome [35]. After admission to hospital, we asked the physician for an assessment of the patient's prognosis using a 6-point scale (1 = very good, 6 = very poor). To replicate the earlier findings, we checked the prognostic validity of this assessment by using Cox regression and Kaplan-Meier survival analysis methods. Again, as in the former study, the physician's assessment was highly predictive of survival ($p < .001$): relative risk = 1.48 (95%-CI = 1.22-1.80), i.e. an increase of 1 point on the scale is associated with an approximately 50% increased risk to die.

Statistical analyses

Two strategies to evaluate the MAC scale were suggested by Watson et al. [13]. First, we looked for the predominant response from the subscales FS, HH, F, and AP via calculating z-scores for each scale and looked for the subscale with the highest z-score. This subscale is the patient's predominant response. If all z-scores are negative, the patient is classified as having no predominant response. The second evaluation used the calculation of cut-off scores for all five subscales. The subscales are dichotomized at the mean plus one standard deviation to differentiate cases from non-cases. This criterion results in skewed distributions but has to be seen as "the standard" in this context.

Usual descriptive statistics were calculated. Following the procedures of Watson et al. [13] survival times were evaluated for all questionnaire subscales subjecting the corresponding groups (predominant responses; cases vs. non-cases for all five MAC subscales) as categorical covariates to Cox-regression analyses with and without adjustment for physician's prognosis as continuous covariate. However, with respect to the skewed distributions of the dichotomized MAC subscales we will explore the results using the MAC subscale scores as continuous covariates, too.

Two outcomes were examined by Watson et al. [13]: overall survival and event-free survival. Overall survival defines events as cases of death irrespective of the specific cause of the death. Event-free survival means survival without relapse and focuses on the time from the specific starting point to the point when a relapse was diagnosed or, if no relapse occurred, the patient had died.

In our study survival time was calculated as time from date of HSCT until date of event. If no event was registered, the case was considered as censored and survival time was calculated as time from HSCT until censoring. For censored cases, the date of the most recent documented visit in the hospital was used for calculation. Analyses were performed by using the software package SPSS for Windows (Release 11.0.1., 15 Nov 2001; Chicago, Ill.: SPSS Inc.).

Results

We checked the available records in December 2003. Sixty-eight patients had died. *Overall survival* therefore refers to 68 events. Median follow-up time was 2.54 years (inter-quartile range 2.1-3.2) for censored cases, and 0.53 years (0.26-1.09) for cases. Of the 38 patients with a relapse post HSCT, 31 died. The seven patients who had relapsed and were alive at follow up represent events when looking at relapse-free (event-free) survival, thus resulting in 75 events. For the outcome *event-free survival* median follow-up time was 2.51 years (inter-quartile range: 2.0-3.2) for censored cases, and 0.45 years (0.18-0.97) for cases.

Tables 1 and 2 summarize the results for the Cox regression analyses (with and without adjustment for prognosis) for the predominant response and the five dichotomized MAC subscales and for both focused outcomes: overall survival and event-free survival, respectively. No significant results are found. All reported 95%-confidence intervals include the hazard ratio 1.0 expressing the same risk for both groups. There may be a slight trend for the MAC subscale avoidance (A) showing a decreased risk if the patient fully agrees to the item "I don't really believe I had cancer", a trend that is more pronounced in the case of overall survival.

Our explorative analyses with MAC subscale scores as continuous covariates do not result in remarkable differences compared to the results already reported; therefore we abstain from reporting these numbers. The trends for the MAC scale A that were mentioned above clearly weaken.

Table 1: Number of events (deaths), totals, death rate and results for Cox regression analyses for MAC scales and overall survival (hazard ratios with 95%-CI) for n=127 patients (68 events)

		deaths	total	death rate (%)	unadjusted hazard ratio	adjusted* hazard ratio
MAC scale						
PR	none	9	17	53	1.00	1.00
	FS	25	46	54	0.92 (0.43-1.97)	1.11 (0.51-2.39)
	HH	10	17	59	1.26 (0.51-3.11)	1.41 (0.57-3.50)
	AP	13	24	54	1.02 (0.44-2.40)	1.16 (0.49-2.73)
	F	11	23	48	0.76 (0.31-1.83)	0.79 (0.33-1.92)
FS	≥58	59	109	54	1.00	1.00
	<58	9	18	50	1.06 (0.52-2.13)	0.96 (0.47-1.93)
HH	<10	59	110	54	1.00	1.00
	≥10	9	17	53	1.10 (0.55-2.22)	1.22 (0.61-2.51)
AP	<21	59	109	54	1.00	1.00
	≥21	9	18	50	1.15 (0.57-2.31)	1.26 (0.62-2.55)
F	<18	55	102	54	1.00	1.00
	≥18	13	25	52	0.91 (0.50-1.67)	1.03 (0.56-1.91)
A	<4	60	105	57	1.00	1.00
	=4	8	22	36	0.50 (0.24-1.05)	0.54 (0.26-1.13)

MAC scale: PR predominant response; FS fighting spirit; HH helplessness/hopelessness; AP anxious preoccupation; F fatalism; A avoidance for prognosis

Table 2: Number of events (relapse or death), totals, event rate, and results for Cox regression analyses for MAC scale and event-free survival (hazard ratios with 95%-CI) for n=127 patients (75 events)

		events	total	event rate (%)	unadjusted hazard ratio	adjusted hazard ratio
MAC scale						
PR	none	11	17	65	1.00	1.00
	FS	30	46	65	0.94 (0.47-1.88)	1.17 (0.58-2.37)
	HH	10	17	59	0.98 (0.42-2.31)	1.08 (0.46-2.55)
	AP	13	24	54	0.83 (0.37-1.87)	0.95 (0.42-2.14)
	F	11	23	48	0.59 (0.26-1.36)	0.62 (0.27-1.43)
FS	≥58	63	109	58	1.00	1.00
	<58	12	18	67	0.80 (0.43-1.49)	0.72 (0.39-1.34)
HH	<10	65	110	59	1.00	1.00
	≥10	10	17	59	1.09 (0.56-2.13)	1.18 (0.60-2.31)
AP	<21	66	109	61	1.00	1.00
	≥21	9	18	50	0.97 (0.48-1.94)	1.03 (0.51-2.06)
F	<18	62	102	61	1.00	1.00
	≥18	13	25	52	0.75 (0.41-1.37)	0.81 (0.45-1.49)
A	<4	65	105	62	1.00	1.00
	=4	14	22	64	0.59 (0.30-1.15)	0.66 (0.34-1.29)

MAC scale: PR predominant response; FS fighting spirit; HH helplessness/hopelessness; AP anxious preoccupation; F fatalism; A avoidance for prognosis

Discussion

We assessed the patients' psychological response to their disease and treatment by using the established MAC scale for a sample of 127 patients facing HSCT, and evaluated overall and event-free survival post HSCT as outcomes. A physician's assessment of the prognosis, which proved to be highly predictive for survival, served as a variable to statistically control somatic risk factors. With respect to frequency distributions and cut-off scores on the MAC subscales, our results are quite similar to those reported by Watson and colleagues [13], [14]. We did not find any relationships between predominant psychological response or any single MAC subscale and event-free or overall survival. With respect to HH we could not confirm the findings of Watson et al. [13], [14]. The range of the confidence intervals (HR) for HH is nearby between halving and doubling the risk. There is no obvious trend towards a better survival by less HH in our sample.

It seems that the findings of Watson et al. [13], [14] for the MAC subscale HH cannot be transferred to the field of HSCT. This result may have been caused by the different interview settings. Women with early-stage breast cancer who were diagnosed one to three months before inclusion into the study had quite a good prognosis compared to patients facing allogenic HSCT. This fact is clearly reflected by the survival rates in both studies. In the Watson et al. [13], [14] study, 23% and 38.2% of the women had died during the five and 10 years of follow-up respectively, compared to 53% in our study with a considerable shorter follow-up period. When facing HSCT, the patients already had passed a significant period of challenges to cope with. Most of them had suffered from other stressful therapies (in most cases chemotherapy), and now they had given informed consent to a life-threatening treatment. One could speculate that those patients who exhibit pronounced helplessness/hopelessness during the first time after diagnosis are less likely to proceed to the point when HSCT becomes a concrete option. Provided that we administer the MAC scale quite

early in the course of their disease, perhaps the MAC subscale HH could be of predictive power. Unfortunately we don't have such a baseline measure. A task for further research could be to explore the pathways leading to HSCT and the internal and external factors influencing the decisions on this way.

The MAC subscale avoidance (A) reflects denial that was identified as beneficial by Greer et al. [1], [2]. Could it be a sign of adaptive coping when facing the challenge of HSCT patients say "I don't really believe I had cancer"? Is it the ability to deny one's diagnosis in such a situation that serves as a resource leaving mental capacities to deal with the demands of the imminent challenges? But we should not overstress the statistics. At last we only found a slight trend that probably is a finding by chance. For the BMT setting, it seems to be unlikely that the MAC scale can predict survival after transplantation. Maybe an alternative version of the MAC scale could be more successful as shown by Osborne et al. [36] for breast cancer patients. They used a rescaled Australian version that is comprised of six scales. Two scales referred to fighting spirit, namely "fighting spirit - minimizing the illness" and "fighting spirit - positive orientation to the illness". In their explorative study on 61 women with early breast cancer, they found a significant association between survival and the subscale "fighting spirit - minimizing the illness", but not for the subscale "helplessness/hopelessness" which is identical to the original HH. Prior to considering consequences from the findings of Osborne et al. [36], their results have to be replicated in a hypothesis testing study. But for breast cancer patients the results with the MAC scale are heterogeneous. Recently, Goodwin et al. [37] did not find any significant associations between the MAC subscales and survival in n=225 patients. Based on clinical ratings Greer and colleagues [1], [2] discovered "fighting spirit" and "denial" as predictive. In their attempt to replicate these findings using the MAC scale Watson et al. [13] identified HH but neither FS nor avoidance (denial). Their finding of HH being a predictor, that holds in their 10-years follow-up [14], must be seen as an empirically grounded hypothesis. Maybe all other studies were underpowered, but to avoid misleading interpretations of a possible chance finding by Watson et al. [13], [14] a hypothesis-testing replication is necessary.

We focused on survival times but should bear in mind that originally, the MAC scale was not intended as a measure to predict survival. Identifying such relations would contribute towards answering the question "What is good coping?" But "good coping" should not be restricted solely to survival. This outcome is one of several others as for example quality of life, suffering from treatment-related side effects, or resuming one's professional activities.

In summary, with respect to survival, at date the empirical evidence for a predictive value of the MAC scale is not very convincing. Further investigations with the MAC scale should have a clear hypothesis testing approach.

Notes

Conflicts of interest: None declared.

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Erratum

The methods section of this article outlines a description of the Mental Adjustment to Cancer Scale that follows the original English version. Now, it was brought to our attention that the wording of the German version that we used to anchor the response categories does not completely parallel the original. Therefore this addendum is needed.

The original English version gives these anchors: 1 = definitely does not apply to me, 2 = does not apply to me, 3 = applies to me, 4 = definitely applies to me.

The German version in the translation by Hubertz et al. that we used gives these anchors: 1 = trifft gar nicht zu, 2 = trifft etwas zu, 3 = trifft überwiegend zu, 4 = trifft vollständig zu.

If we assume equal distances the verbal anchors of the English version might be translated to the numbers -1.5 / -0.5 / +0.5 / 1.5 and our German version to 0 / +1 / +2 / +3. The difference between both scales seems to be a shift to the positive side in the German version.

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