High Dose Chemotherapy and Hematopoietic Stem Cell Transplantation: A Study of Treatment Preference in Patients with Rheumatoid Arthritis and Rheumatologists

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ABSTRACT. ***Objective.*** Patients with intractable rheumatoid arthritis (RA) may benefit from treatment with high dose chemotherapy followed by rescue with autologous hematopoietic peripheral blood stem cell transplant (HSCT). We investigated whether the risks of this approach are acceptable to patients with RA and rheumatologists and whether risk taking by patients was associated with disease characteristics, socioeconomic variables, and/or personality traits.

Methods. A survey in the outpatient clinic was conducted among 2 cohorts of 45 (cohort A) and 51 (cohort B) RA patients with active disease. Patients received information about the potential benefit of HSCT (2/3 chance of a good clinical response, 1/3 no response) and treatment related morbidity and mortality. Cure was assumed not to be a realistic perspective. Cohort A was asked to choose between their own disease state for an indefinite time or HSCT. Nonparametric tests were performed to evaluate putative predictive factors that led patients to accept transplant related mortality (TRM): swollen joint count, tender joint count, visual analog scale (VAS) measures of disease activity and pain, erythrocyte sedimentation rate, Health Assessment Questionnaire (HAQ), socioeconomic variables, RA Quality of Life Questionnaire (RAQoL), and the Life Orientation Test. Cohort B was asked to consider a worst case scenario with respect to their disease activity. The minimal duration of benefit was assessed, given a TRM of 0.01% and 2%. To evaluate treatment preference of physicians, 96 Dutch rheumatologists responded to a hypothetical clinical case analogous to the interviews with RA patients. The minimum duration of benefit was assessed, given a TRM of 2% and the maximal TRM acceptable to rheumatologists if duration of benefit was 2 years in 2/3 patients.

Results. In cohort A, 5 of 45 patients were willing to accept risk of death. VAS disease activity ($p = 0.006$), VAS pain ($p = 0.021$), and HAQ ($p = 0.05$) were significantly higher in patients willing to accept risk of death. Religiosity ($p = 0.093$), a higher Ritchie Articular Index ($p = 0.096$), and low quality of life (by RAQoL) ($p = 0.133$) showed trends toward risk taking. In cohort B, 22 of 50 patients (44%) were willing to accept a risk of TRM related to HSCT. For the 22 patients the median required duration of benefit given a TRM of 2% was 5 years (range 1–15). Physicians also required a median duration of benefit of 5 years.

Conclusion. We evaluated risk taking in patients with RA and physicians based on a realistic perspective in which the tradeoff between short term risks and possible longterm benefit of HSCT was investigated. Based on current efficacy data for HSCT (2 years improvement in 2/3 patients), half the patients would accept the current TRM of 2%, based on registry results. Patients willing to accept TRM had higher VAS disease activity, VAS pain, and HAQ. Doctors were more willing to accept mortality in the treatment of RA. (J Rheumatol 2002;29:1653–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS AUTOIMMUNE DISEASES PATIENT SATISFACTION
IMMUNOSUPPRESSION TREATMENT OUTCOME
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High dose chemotherapy followed by hematopoietic stem cell transplantation (HSCT) is a new treatment modality for patients with refractory rheumatoid arthritis (RA). At present more than 50 patients with RA have undergone this therapy. Remissions up to 3 years have been reported[1], although failures have been observed as well[2,3]. In a multicenter study in the Netherlands, 12 patients were treated with HSCT. Of these 12 patients, 8 had a favorable

response, 4 did not[4]. These results are in accord with data from other studies comprising 51 patients (JA Snowden, Royal Hallamshire Hospital, Sheffield, UK; data not shown) with a good response reported in 2/3 patients. These patients accepted the toxicities associated with HSCT such as nausea, vomiting, alopecia, and febrile neutropenia, and the risk of transplant related mortality (TRM), at the time estimated to range from 1 to 10%. Because of these risks, not all eligible patients in our institute gave informed consent. Of 26 eligible patients, 14 gave consent to this treatment modality with potential morbidity and mortality. Twelve patients chose continuation of conventional therapy, which is less intensive and less hazardous, but also potentially less effective.

Patients' preferences are of prime concern in weighing the benefits and side effects of HSCT in the treatment of RA. Little knowledge exists on the considerations of patients confronted with different treatment options (treatment preference). In a survey of a heterogeneous group of patients with RA it was concluded that patients were willing to accept a mortality of 19% if cured[5]. In another study, it was concluded that risk taking was associated with the extent of disability measured by the Health Assessment Questionnaire (HAQ)[6]. However, neither study employed a realistic scenario. It is appreciated that cure is not a realistic scenario in the treatment of severe RA and that in addition to TRM, morbidity may also be a major factor affecting treatment preference. We have attempted to describe a realistic scenario in order to investigate whether the risks of this approach are acceptable to patients with RA. Further, we assessed whether risk taking was associated with disease characteristics, socioeconomic variables, and/or personality traits. In addition, we investigated the opinions of rheumatologists with regard to mortality and duration of benefit for a chronic disease such as RA.

MATERIALS AND METHODS

Patient survey. The study consisted of a survey in the outpatient clinic and clinic of the Department of Rheumatology, Leiden University Medical Center, a tertiary referral center. The protocol was approved by the Ethics Committee. All patients provided written informed consent. Eligibility criteria were as follows: (1) established diagnosis of RA according to American College of Rheumatology (ACR) criteria[7], (2) active disease necessitating change of disease modifying antirheumatic drug (DMARD) therapy, (3) age 18–70 years, and (4) Steinbrocker class II or III[8]. Exclusion criteria were severe comorbidity and insufficient knowledge of Dutch language. The treating physician asked patients whether they were willing to participate in the treatment preference survey by a trained investigator. A total of 100 consecutive RA patients with active disease enrolled. All interviews were performed by one trained investigator (SDM). To evaluate patients' attitudes to HSCT versus conventional therapy, the treatment preference (TP) or tradeoff was assessed[9,10]. Patients received oral and written information about the potential toxicity and benefits of HSCT. It was explained that the treatment burden included hospitalization totaling 5 weeks including recovery in isolation, alopecia for at least 6 months, blood transfusions, diarrhea, nausea, vomiting, a risk of infection, fever, and infertility and early menopause for women. A more intensive followup was necessary so patients would be visiting the outpatient clinic once every month during the first year after HSCT. It was emphasized that there was a risk of death. The clinical effect, based on recent data[4], was explained to the patient as at least 50% decrease in (1) disease activity (indicated by severity of joint swelling and tender joints), (2) pain, (3) fatigue, (4) morning stiffness, and (5) functional disability. It was explained that 2 out of 3 patients would obtain a favorable response and one would not, and that cure was unlikely.

Two cohorts (A and B) were interviewed. Cohort A served to evaluate the relationship between disease characteristics and risk taking. Cohort B served to determine maximally accepted mortality and minimal duration of benefit. Therefore Cohort A was asked to impersonate the disease as they actually experienced it and to choose between either permanent continuation of their own disease state or HSCT with a TRM of 0.01%, but a 2/3 chance of marked gain in quality of life. Cohort B was asked to consider a worst case scenario with respect to disease activity. In order for patients to impersonate such a disease course they were given disease characteristics of patients who had undergone HSCT in our own study population [assessed by HAQ, RAND-36[11,12], and Arthritis Impact Measurement Scale (AIMS)]. This cohort was also asked to choose between continuation of conventional treatment and HSCT, given a TRM of 0.01%, corresponding to the treatment related mortality of DMARD. In case patients made a choice for HSCT they were asked what then their minimal duration of benefit should be, given a TRM of 2%, as a realistic TRM for HSCT in the treatment of RA. To enable patients to conceptualize TRM, patients were not only given this information in writing but also in a pictogram. Next, patients were asked what their maximal accepted TRM was, given a duration of benefit of 2 years in 2/3 patients (considered a realistic prognosis for HSCT in the treatment of RA), and their maximal TRM given a duration of benefit of 2 years in all patients.

Several questionnaires were administered — the HAQ (range 0–3) was used to study patients' functional well being and disability; the Life Orientation Test (LOT; see Appendix)[13] was used to measure patients' optimism and pessimism. Patients were asked to indicate their degree of agreement with statements such as, "In uncertain times, I usually expect the best," and "I hardly ever expect things to go my way," using a 5 point response scale ranging from 0 (strongly disagree) to 4 (strongly agree) (maximum score 24). Of the 6 items that are scored (4 are so called "fillers"), 3 are keyed in a positive direction and 3 are keyed in a negative direction. After reversing the scoring for the negatively worded items, item scores were totaled to yield an overall optimism score, with high scores representing greater optimism.

The RA-specific Quality of Life instrument (RAQoL) was used for assessing quality of life[14,15]. Respondents were asked to answer 30 items with a yes/no response format according to their agreement with the statements. All items were scored with 0 (no) or 1 (yes), yielding a range from 0 to 30. Higher score indicated a poorer quality of life.

Patients' pain VAS (0–10) and disease activity VAS (0–10) were recorded. A physical examination was performed to assess total swollen joint count (SJC, range 0–44) and Ritchie Articular Index (RAI, range 0–78). The erythrocyte sedimentation rate (ESR) was performed at the same time. Based on these data the 4-variable disease activity score (DAS) was calculated[16].

Other data collected were: age (years), sex, disease duration (years), erosive disease (yes/no), number of previously used DMARD, rheumatoid factor positivity (yes/no), joint arthroplasty (yes/no), comorbidity (yes/no), prednisone use (yes/no), previous participation in clinical trials (yes/no), history of adverse side effects of antirheumatic medication (yes/no), labor force status, marital status, parenthood (yes/no), religion (yes/no), and level of education (1 to 8; from elementary school only to academic degree).

To assess whether patients who were willing to accept a certain TRM differed from patients who were not, the Mann-Whitney U test was performed with respect to disease associated, socioeconomic indicators and/or personality traits.

Physician survey. A total of 96 Dutch rheumatologists attending a continuing education course in January 2001 participated in responding anony-

mously to a clinical case using a computer based voting system. The case concerned a 50-year-old female patient with active erosive RA, refractory to DMARD, including (combination therapy with) methotrexate and tumor necrosis factor (TNF) blocking therapy. Three questions were asked, analogous to the interviews of patients with RA, except that the questions were put in multiple choice format with 8 alternatives. Answers ranged from "I would never propose HSCT to RA patients" to "I would accept > 20% TRM." The first question was if physicians considered HSCT a treatment option for the described patient, if 2 out of 3 patients had a chance of a clinically meaningful response (> ACR 50% response[17]) for 2 years and if TRM was 0.01%. The second question was what the minimal duration of benefit should be given a TRM of 2% and clinical improvement in 2/3 patients. The last question related to the maximal accepted TRM when the duration of benefit was 2 years in 2/3 patients.

RESULTS

Patients. Demographic details and measures of disease activity of cohorts A and B are summarized in Table 1. Cohort A was formed from September 19 to October 24, 2000, cohort B from October 26, 2000, to February 26, 2001. Entry criteria for the 2 cohorts did not differ. Two patients failed to comprehend the numerical information given by the investigator and were excluded from the study. Cohort B patients had slightly more active disease than Cohort A with respect to swollen joint count ($p = 0.018$, Mann-Whitney U test) (Table 1). There was a marked difference between Cohort A and B ($p < 0.001$, Mann-Whitney U test) in the number of patients that were willing to accept a TRM of 0.01% given a favorable response in 2/3 patients for 2 years (Table 1). Cohort A was used to examine a potential relationship between risk taking and patient data. Table 2 shows disease characteristics and personality traits for patients who were and those who were not willing to undergo HSCT. VAS pain, VAS disease activity, and HAQ scores were significantly higher in patients who were willing to accept the TRM for treatment of RA. A reduced quality of life, measured by the RAQoL, and the quality and quantity of painful joints, measured by the RIA, were lower in patients who were not willing to accept HSCT.

There were no significant differences in other disease characteristics or patient data such as age, sex, disease duration, joint arthroplasty, erosive disease, comorbidity, number of previously used DMARD, previously participated in clinical trials, presence of rheumatoid factor, prednisone usage, labor force status, parenthood, marital status, religion, level of education, previous adverse side effects of DMARD, and the LOT score, between patients who were and those who were not willing to undergo HSCT.

Patients' views of acceptable risk (Cohort B) are shown in Table 3. Forty-four percent of the patients were willing to accept 0.01% mortality given a 2/3 chance of marked gain in quality of life. The minimal desired duration of benefit given a TRM of 2% and a favorable response in 2 out of 3 patients was 5 years (median). If the duration of a favorable response was set at 2 years, the acceptable mortality

Table 1. Characteristics of Cohorts A and B.

Patient Details	Cohort A, n = 45		Cohort B, n = 50	
	Mean	Range	Mean	Range
Age, yrs	56	35–65	54	24–70
Sex, M:F	14/31		20/30	
Duration RA, yrs	14	0–39	10	0–48
Erosive disease, %	87		80	
RF, %	82		74	
TSJC	19	2–40	24	6–42
Ritchie TJC	17	1–46	20	0–60
ESR, mm/h	32	1–119	30	1–103
VAS pain	3.9	0.4–9.4	4.7	0.1–9.7
VAS disease activity	4.1	1.2–8.0	4.7	0.2–9.2
Four variable DAS	4.3	1.5–7.5	4.7	1.6–8.0
HAQ	1.2	0–2.75	1.3	0–2.88
Patients using prednisone, %	18		30	
Patients currently working, %	27		32	
Patients with children < 18 yrs, %	24		42	
Patients married, %	87		88	
Patients with joint arthroplasty, %	20		18	
Patients experiencing adverse side effects of DMARD, %	62		60	
Patients with religious conviction, %	56		56	
Accepts HSCT as a treatment for RA (%)	5/45 (11)		22/50 (44)	

RF: rheumatoid factor positive patients, TSJC: total swollen joint count (range 0–44), Ritchie TJC: Ritchie tender joint count (0–78), ESR: erythrocyte sedimentation rate, DAS: Disease Activity Score [= $(0.54 \times \sqrt{\text{Ritchie articular index}}) + (0.065 \times \text{number of swollen joints}) + (0.33 \times \text{LN ESR}) + (0.0072 \times \text{patient} \times \text{disease activity VAS})$], HAQ: Health Assessment Questionnaire, DMARD: disease modifying antirheumatic drugs, HSCT: autologous stem cell transplantation.

Table 2. Mean disease and personality related factors of RA patients who were either willing to accept TRM in the treatment of RA (yes to HSCT) or were not (no to HSCT), given a transplant related mortality of 0.01%. Differences were calculated with the Mann-Whitney U test.

	Yes to HSCT, n = 5		No to HSCT, n = 40		p, Mann–Whitney U Test
	Mean	Min–Max	Mean	Min–Max	
Age, yrs	57	52–67	57	31–70	0.303
Disease duration, yrs	7	1–18	14	0–39	0.575
Ritchie articular index	25	16–35	16	1–46	0.096
Total swollen joint count	21	18–29	19	2–40	0.814
ESR, mm/h	22	1–47	33	1–119	0.492
VAS pain	6.0	5.3–7.6	3.7	0.4–9.4	0.021
VAS disease activity	6.3	5.0–7.2	3.8	1.2–8.0	0.006
Four variable DAS	5.7	4.5–7.6	4.7	1.6–9.3	0.406
HAQ	1.7	1.5–2.13	1.1	0–2.75	0.050
LOT	21	18–22	22	12–30	0.827
RAQoL	18.5	16–20	12.8	0–26	0.133

HSCT: autologous stem cell transplantation, ESR: erythrocyte sedimentation rate (mm/h), VAS: visual analog scale, DAS: Disease Activity Score [= (0.54 × √Ritchie articular index) + (0.065 × number of swollen joints) + (0.33 × LN ESR) + (0.0072 × patient × disease activity VAS)], HAQ: Health Assessment Questionnaire, LOT: Life Orientation Test, RAQoL: rheumatoid arthritis–specific quality of life instrument.

Table 3. Treatment preference — patients' and doctors' opinions regarding risk taking for RA therapy. Doctors were more willing to accept mortality in the treatment of RA than patients (p = 0.001, Mann-Whitney U test). The minimally desired effectiveness of HSCT did not reach significance (p = 0.089, Mann-Whitney U test).

	Patients			Doctors	
Willing to accept TRM of 0.01 % if 2/3 patients had a favorable response for 2 years	22/50 (44.0%)			87/96 (90.6%)	
	Median	Mean	Range	Median	Range
Minimal desired duration of benefit when TRM was set at 2% and 2/3 patients had a favorable response, yrs	5	6.4	1–15	5	0.50– ≥ 5
Acceptable mortality if 2/3 patients had a favorable response for 2 years, %	0.1	0.44	0.01–2.0	1.0	0.01–13.0
Acceptable mortality if all patients had a favorable response for 2 years, %	0.1	3.4	0.01–50	—	—

dropped to 0.1% (mean 0.44%). If all patients had a favorable response (instead of two-thirds), the mean accepted mortality rose to 3.4%.

Physicians. Ninety-six of 107 rheumatologists completed the whole questionnaire. Sixty percent of respondents were male, 27.8% were employed at a university affiliated hospital. Age, sex, or academic affiliation did not influence risk taking by rheumatologists. Eighty-seven of 96 considered HSCT a realistic therapeutic option for their patients, given a TRM of 0.01% and a favorable response for 2 years in 2/3 patients. The median duration of benefit given a TRM of 2% was 5 years, the same response as from patients (Figure 1A). The maximal accepted TRM when the duration of benefit was 2 years in 2/3 patients is shown in Figure 1B. There was a significant difference between accepted mortality for patients and doctors: a median of 1% versus 0.1% for patients (Table 3).

DISCUSSION

We investigated patients' and rheumatologists' preferences for HSCT or continued conventional treatment in the therapy of RA employing a realistic risk/benefit scenario. We evaluated 2 cohorts of patients (A and B) to study 2 issues. Patients with active RA were interviewed to analyze (1) factors that were related to risk taking (Cohort A) and (2) risk estimation regarding treatment related mortality and required duration of benefit (Cohort B). Patients were informed about the potential benefits of HSCT (2/3 chance

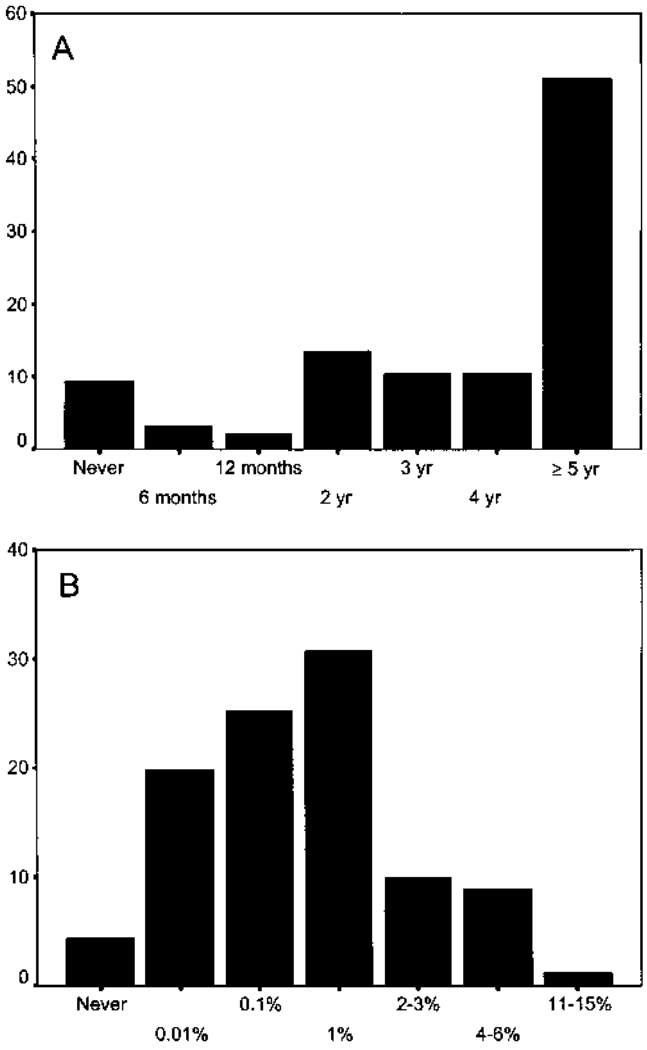

Figure 1. A. Minimally required duration of benefit reported by rheumatologists given a transplant related mortality (TRM) of 2% and a clinical improvement in 2/3 patients. Y axis: the percentage of physicians. X axis: the accepted TRM. B. Maximal accepted TRM reported by rheumatologists, given duration of benefit of 2 years in 2/3 patients. Y-axis: the percentage of physicians. X-axis: the accepted TRM.

of long-lasting good clinical response), side effects such as alopecia and hospitalization, and risks of infection, bleeding and mortality. The results from Cohort A showed that most patients were risk aversive and did not accept mortality in the treatment of RA. Patients accepting mortality scored significantly worse with respect to impairment of activities of daily living (by HAQ), VAS pain, VAS disease activity, and quality of life. In Cohort B, 44% of the patients accepted HSCT with its treatment related morbidity and potential mortality. The median required duration of benefit given a TRM of 2% was 5 years (range 1–15). This is in accord with experience in our center, where 26 patients with refractory RA were asked to participate in an open study to evaluate safety, feasibility, and efficacy of HSCT. Out of 26 patients, 14 (53%) gave informed consent having been informed of a TRM of 2–5%. With regard to the opinion of rheumatologists it was shown that 91% considered HSCT a realistic therapeutic option for their patients, given a TRM of 0.01% and a good clinical response of 2 years in 2/3 of patients. The median duration of benefit given a TRM of 2% was 5 years, the same response given by patients.

We evaluated risk taking in patients with RA and physicians based on a realistic scenario by means of a patient preference method in which the tradeoff between short term risks and possible longterm gain of HSCT was investigated. The treatment preference method has been developed for both clinical and research settings and has been shown to be simple to use and meaningful to patients[9,10,18,19]. We attempted to make the patient preference as explicit as possible. We constructed 2 cohorts for different purposes to limit the amount of information given to patients individually. Patients were guided through the whole process of decision making by a trained interviewer, were asked whether the information was clear, and were confronted with inconsistencies in their responses.

With regard to the accepted mortality it must be noted that the accepted risks were less than those reported for antirheumatic therapy[20]. Fifty-six percent of patients did not accept a treatment with a mortality of 0.01%, which roughly corresponds to the mortality associated with the use of DMARD, showing that the "acceptable" level of risk was lower than the real risk of current drug therapy. Pullar, *et al* also found that the probability of death patients would accept was less than that of DMARD therapy[21]. An explanation for the risk aversion could be that patients found the morbidity associated with HSCT not worthwhile in a treatment that does not induce improvement in all patients and/or for indefinite time. Further, it has been shown that patients have difficulty understanding numerical information[22]. Patients probably do not realize that treatment with DMARD and/or TNF blocking therapy is not free of risks and bears a TRM as well. It would be of interest to investigate patients' preferences with these treatments. Our data do not support the use of intensification of the treatment regimen (e.g., by means of allogeneic transplantation or more intensive conditioning), as TRM will only increase. As reported using decision analysis, TRM markedly influences the decision to choose HSCT. It was found that with a TRM of less than 3.3%, HSCT is preferred above conventional treatment[23].

Others have also explored patients' decision making process. In a study by Thompson[24] using the standard gamble, 247 subjects with RA were asked what mortal risk they were prepared to accept to achieve a hypothetical cure[25]. It was concluded that on average, patients were willing to accept a chance of immediate death of 27% for total cure. Another study showed that on average the maximal acceptable risk decreased from 26.8% to 19.6% if

the therapeutic benefit was not total cure, but induced return to normal functioning[5]. Recently, the standard gamble method was employed in a study to establish whether the risks of HSCT are acceptable to patients with RA[6]. HSCT was defined as a curative therapy. Here it was found that risk taking was significantly related to self-assessed health status (by HAQ). However, these studies did not incorporate morbidity related to HSCT and assumed a cure for RA, which is an unlikely outcome in patients with irreversible joint damage[26]. Further, it is unlikely that HSCT will induce remissions for an indefinite period.

This study is the first to describe a realistic scenario on risk taking in the treatment of RA. The study provides evidence for the feasibility of the methods and can be used to elicit patients' preferences concerning the choice for HSCT or other risk-bearing treatments. Our study underscores the importance of patient preferences in therapeutic decision making when it comes to risk-taking therapies. As therapeutic decision making is to reflect patient preferences, clinicians require an understanding of the ways patients perceive and react to the potential risks.

APPENDIX

Items composing the Life Orientation Test (LOT)

1. In uncertain times, I usually expect the best
2. It's easy for me to relax (filler item)
3. If something can go wrong for me, it will*
4. I'm always optimistic about my future
5. I enjoy my friends a lot (filler item)
6. It's important for me to keep busy
7. I hardly ever expect things to go my way*
8. I don't get upset too easily (filler item)
9. I rarely count on good things happening to me*
10. Overall, I expect more good things to happen to me than bad.

* These items were reverse scored before scoring and analysis. Note that only 6 of the 10 items are used to derive an optimism score. Four of the items are filler items and are not used in scoring.

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