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The EORTC QLQ-HDC29: A supplementary module assessing the quality of life during and after high-dose chemotherapy and stem cell transplantation

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ABSTRACT

High-dose chemotherapy followed by haematopoietic stem cell transplantation can be associated with high physical and emotional distress levels and reduced quality of life. Systematic prospective measurement of impact of therapy on patient quality of life can aid treatment choices and provide better patient information.

We describe the development of a high-dose chemotherapy questionnaire module to supplement the European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30). Phases 1–3 of module development were conducted in United Kingdom, Germany, Austria and Norway, according to EORTC QOL Group guidelines. Forty-eight quality of life (QOL) issues were generated from the literature searches and interviews with health care professionals ($n = 24$) and patients ($n = 92$). This produced a 50 item provisional module. Further testing in 169 patients resulted in the QLQ-HDC29 module, containing 29 items, conceptualised into six multi-item scales and eight single items.

The EORTC QLQ-C30, supplemented by QLQ-HDC29 will provide a comprehensive QOL measure for the international clinical trials of high-dose chemotherapy.

1. Introduction

High-dose chemotherapy (HDC) with haematopoietic stem cell transplantation (HSCT) has been applied increasingly during the past 20 years in a variety of clinical situations. The latest European Group for Blood and Marrow Transplantation (EBMT) activity survey reported that in 2003, there were 21,028 first HSCT (66% autologous and 34% allogeneic) and 4179 additional re- or multiple transplants reported from 597 centres in 42 European countries.[1] Main indications were lymphoma (55%; 93% autologous), leukaemia (31%; 78% allogeneic) and solid tumours (9%; 92% autologous).

Allogeneic HSCT has been established as the standard consolidation therapy with curative potential in acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) in first or subsequent remission according to patients

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(cyto)genetic profile and risk of relapse.[2,3] However, the benefit of allogeneic HSCT is considerably offset by complications following transplantation, including graft-*versus*-host disease and toxicity of HDC and radiotherapy.

HDC with autologous HSCT represents standard care in multiple myeloma,[4,5] relapsed Hodgkin's disease[6] or relapsed aggressive non-Hodgkin's lymphomas[7] in younger patients. HDC is experimental in other types of malignant lymphomas including chronic lymphocytic leukaemia (CLL). HDC may be beneficial in patients with solid tumours,[8,9] but is generally regarded as experimental.

Initially, bone marrow was the primary source of stem cells for HSCT. Prospective randomised studies confirmed the advantage of peripheral blood compared to bone marrow as a stem cell source both in malignant lymphoma and solid tumours.[10,11] Today, peripheral blood is the main source of stem cells for autologous HSCT. In allogeneic HSCT, the change in the stem cell source from bone marrow to peripheral blood began later and proceeded more slowly. In 2003, 65% of all allogeneic HSCT were peripheral blood derived, although a debate on differences in acute and chronic graft-*versus*-host disease following either source of stem cells is still ongoing.[1]

HDC is associated with significant immediate, intermediate and long-term toxicity. Many of the toxicities from chemotherapy are dose dependent and HDC requiring stem cell transplantation can impair the subjective quality of life more than lower dose regimens during the treatment period and in the long term. The use of total body irradiation (TBI) as a part of high-dose therapy can have an additional negative impact on patients' functioning. Over recent years a significant number of studies examined the short and long-term impact of HSCT on functioning and quality of life (QOL). High-dose treatment and HSCT are associated with high physical and emotional distress levels and reduced quality of life.[12,13] In the long term, studies reported overall good functional level in HSCT survivors, in spite of problems with emotional well-being, increased fatigue, sleep problems, and sexual dissatisfaction.[14–16] Compared with healthy controls, physical and social functioning is still worse.[17] Some studies show that physical recovery occurs earlier than psychological recovery.[18,19] Up to 65% of patients report fatigue and sleeping disorders and these symptoms may persist for several years following SCT.[20–23] Recently, neuropsychological deficits have been investigated in patients undergoing HSCT.[24,25] Problems with memory or attention can be found in nearly 20% of patients in the first year after HSCT.

Most of this research is done in cross-sectional single centre studies, including survivors after treatment and there are relatively few studies investigating QOL prospectively in clinical trials during treatment and in the long term.[26,27] The United Kingdom MRC AML10 trial indicated, in a large cohort, an adverse impact of bone marrow transplantation on professional and leisure activities, and worse sexual and social relationships.[28] More specific assessment and replication of such data are required to clarify any reconsideration of treatment strategies, based on QOL data.

The aim of this study was to develop a treatment-specific quality of life (QOL) questionnaire to supplement a widely used core measure (EORTC–QLQ C30),[29] in order to assess treatment-specific side-effects/co-morbidity and additional QOL dimensions (emotional, social and family issues) for patients with malignancies treated with high-dose myeloablative treatment with HSCT, including allogeneic/autologous bone marrow transplantation (Auto-BMT/Allo-BMT) or peripheral stem cell transplantation (PSCT).

The module was targeted to cover time during the treatment (usually in-patient) and up to 6 months post-treatment (usually out-patient). In addition, the module was tested in patients who had completed their transplant between 1 and 10 years earlier to assess its applicability to long-term effects.

2. Materials and methods

2.1. Study design

The development of the provisional module was according to guidelines published by the EORTC QOL Group[30] (http://www.eortc.be/home/qol/Manuals.htm, 12.06.2001). The module development process has four distinct phases (see Table 1), aimed at ensuring validity and reliability.

Phase IV of the module development process consists of psychometric testing and will be carried out on questionnaire data collected in future clinical trials.

2.2. Phase I: generation of QOL issues

Relevant QOL issues/themes for patients treated with HSCT were identified by the Medline literature searches (from 1984 to 1996), Cancerlit and Psychlit, using the MeSH headings 'quality of life', psychosocial', 'psychological' combined with 'bone marrow transplant', 'PSCT', 'high-dose chemotherapy', 'dose-intensive chemotherapy'. Additional articles on high-dose chemotherapy with HSCT in the major oncology and haematology textbooks were reviewed with the aim of creating a list of known side-effects and complications of the treatment that may affect QOL. Existing questionnaires assessing QOL aspects in patients treated with HSCT were identified and reviewed for relevant issues.

A list of issues was compiled and presented to health care professionals, treating and supporting patients with HSCT, from several European countries and with different professional backgrounds (physicians, nurses, psychologists). Using a semi-structured interview the relevance of each issue (*i.e.* how frequently a symptom or a complaint occurs, and the trouble it may cause) was noted and any missing issues were added to the list. The health professionals were asked to rate the issues from 1 – 'not relevant' to 4 – 'very relevant' and to select 5–10 core issues to be definitely included in the questionnaire.

The list of issues was then presented to patients from eight cancer hospitals in Europe (three in UK, two in Germany, one in Austria and two in Norway). Ethical Committee permissions were obtained. Eligible patients were (a) those receiving high-dose therapy followed by HSCT; (b) within 6 months of transplant; (c) speaking/understanding the language of the questionnaire; and (d) able to give informed consent. Patients indicated the extent to which they experienced each problem during the past week, were asked to select 5–10 issues they regarded as most important and to add any that they had experienced, but were not on the list.

Table 1 – Guidelines for development of EORTC QOL modules

Phase	Aim	Procedure
Phase 1	Generation of QOL issues relevant to the selected group of patients	1. Literature search 2. Semi-structured interviews with health care professionals and patients 3. Quantitative and qualitative data analysis 4. Combination of results from interviews to produce a list of issues
Phase 2	Construction of the issues into a provisional questionnaire	1. Consultation with the EORTC QOL group Item Bank database for existing items 2. Construction of new items – items are worded to be compatible with the QLQ-C30 response categories 3. Translation of provisional questionnaire according to EORTC QLG guidelines
Phase 3	Testing of the provisional questionnaire for acceptability and relevance	1. Patient completion of questionnaire and interview 2. Quantitative and qualitative data analysis 3. Modification of questionnaire 4. Formal development report reviewed by EORTC QLG
Phase 4	International field testing	Psychometric testing of reliability, validity and sensitivity to change of the questionnaire

2.3. *Phase 2: construction of provisional questionnaire*

The selected issues were constructed into items according to the following criteria: (a) questions should be compatible with EORTC QLQ-C30 response categories 'not at all', 'a little', quite a bit' and 'very much'; (b) questions compatible to the 1-week time frame of EORTC QLQ-C30 wherever possible; and (c) questions should refer to states (*i.e.* ongoing) rather than to changes.

Existing items were harmonised to ensure comparability of data across the modules. This was done using the EORTC QOL Item Bank.[31] The Item Bank comprises all existing EORTC QOL questionnaires items and their translations, organised by themes, with identification of the original module and all other modules, containing this item.

2.4. *Phase 3: testing of the provisional questionnaire: acceptability and relevance*

This phase identified problems relating to the wording and clarity of items and determined the need for adding or deleting items. The provisional module was tested in additional patients from participating countries. In addition, a third group of patients who were treated between 8 months and 10 years earlier was added in order to determine the suitability of the module for assessing late effects.

Patients were asked to complete the EORTC QLQ-C30 and the high-dose module indicating if they found any questions annoying, confusing, upsetting or intrusive, and if so, they were asked to re-phrase the question. Patients were asked whether any questions were irrelevant or whether there were additional issues not included in the module. Finally, patients were asked to select 5–10 most important issues that in their opinion should definitely be included.

2.5. *Data analyses and criteria for item selection*

The results from Phase 1 and Phase 3 interviews were analysed using descriptive statistics: (1) mean score for each item; (2) range of responses; (3) prevalence (number of patients who experienced each complaint, *i.e.* who scored 2, 3 or 4, divided by the total number of patients who completed that item, multiplied by 100); and (4) the proportion of patients or professionals prioritising the issue. In Phase 1, items were selected using the following criteria:

- mean score at least 2.0;
- range of responses at least two points, *i.e.* 1–3 or 2–4;
- prevalence ratio at least 50%;
- at least 15% of patients or professionals prioritising the item.

Items were retained if they met at least three out of these four criteria. Items that met only two criteria were considered borderline and included only if they were rated as particularly important for a subgroup of patients (*i.e.* in-patients or out-patients, auto-HSCT or allo-HSCT). Items that met two or less criteria were discarded. The data were analysed for the whole sample as well as separately for the two main treatment modalities groups (auto-HSCT and allo-HSCT) and for in-patients and out-patients. The scores were considered in conjunction with patient comments made during interviews.

In Phase 3, mean scores, range, prevalence and priority ratings were calculated. Cut-off points to retain items were as follows:

- mean score at least 1.5;
- range at least two points;
- prevalence ratio >30%;
- priority given by at least 15% of patients.

Items meeting at least three of those four criteria were retained, those meeting two criteria were retained only where considered appropriate for subgroups of patients (auto-HSCT and allo-HSCT; in-patients and out-patients). Decisions for retaining or deleting items were made in conjunction with patient comments during the interviews.

Comments on difficulties with comprehension due to wording or language were taken into consideration. The final wording was achieved using a consensus methodology, where all co-authors considered the data on comprehensibility and then agreed on appropriate re-wording.

3. Results

3.1. *Phase 1: generation of issues*

Thirty-six articles on QOL and psychosocial issues during and immediately after the transplant were identified. Twenty-six were original studies and 10 were reviews. Ten questionnaires were identified that assess QOL aspects relevant to the period of active treatment with HDC and HSCT and these were reviewed. A list of 120 relevant symptoms/issues/co-morbid conditions was compiled and summarised into the following domains:

- physical (57 issues subdivided into side-effects and complications – gastrointestinal, pain, skin, sensory, constitutional, endocrine, catheter related, self-care and fatigue);
- psychological (26 issues on mood changes, fears about the future, adjustment to treatment, enjoyment, cognitive function);
- social (20 issues on employment, family and sexuality);
- spiritual (12 issues);
- satisfaction with care (5 issues).

3.2. *Phase 1: semi-structured interviews*

Twenty-four health professionals from UK, France, Germany and Austria were interviewed – 16 physicians (oncologists and/or haematologists), 2 psychologists and 6 nurses. Following the interviews, five issues were added (worry that blood counts will not recover, conditions in the transplant room, preparation for the high-dose treatment, pressure from patient's family to have the transplant, conflicting advice from professionals, friends, family).

Ninety-two patients were interviewed (see Table 2 for patient characteristics).

Quantitative analysis (mean scores, range, prevalence and proportions of priority ratings) of both professionals and patients interviews resulted in deletion of 77 issues. Based on patients' comments one symptom was added 'painful throat' and one psychological concern 'fear from death' was deleted, as it was upsetting for 4 patients. This resulted in a list of 48 issues, relevant for patients receiving HDC (Fig. 1). Of these 48 issues, 5 issues were relevant only for patients during hospital treatment and 5 relevant only during the recovery period.

3.3. *Phase 2: construction of provisional questionnaire*

Items (questions addressing QOL issues) were constructed from the 48 issues. A provisional questionnaire of 50 items was constructed as two issues were replaced by four items with alternative wordings. Thirteen existing items from the EORTC QOL Item Bank were used and 37 new items were created.

Table 2 – Demographic and clinical characteristics of the patient sample

Characteristic	Phase 1, N = 92	Phase 3, N = 76	Phase 3, Late effects group, N = 93
Age (years)– mean (range)	40.3 (17–68)	44.2 (20–71) SD 12.5	43.0 (20–65)
Gender			
Male	44	49	51
Female	48	27	42
Diagnosis			
ALL	7	3	30
AML	13	17	7
CML	15	6	17
CLL	2	–	–
Multiple myeloma	14	11	10
Hodgkin's disease	6	6	2
NHL	13	16	12
Germ cell tumours	2	11	5
Other solid cancers (predominantly breast)	20	6	10
Type of transplant			
Allogeneic HSCT	33	31	55
Autologous HSCT	59	45	38
Time of interviews			
During hospital treatment	46	31	
Recovery phase	46	45	
Late effects	–	–	93
Country			
UK	32	26	6
Germany	48	25	18
Norway	6	25	3
Austria	6	–	66

The draft module was reviewed for the clarity of wording and overlapping of items by 12 health professionals not participating in Phase 1 (3 from each country – UK, Germany, Norway, Austria) and by 3 patients from UK and 2 from Germany. Seven items were re-worded. At this stage the provisional module was reviewed by two members of EORTC QOL Group and subsequently translated to German and Norwegian according to EORTC QOL Group guidelines.

3.4. *Phase 3: testing of the Provisional Questionnaire: acceptability and relevance*

The EORTC QLQ-C30 and the provisional module were completed, and subsequent interviews performed with 169 consecutive patients (31 during hospital treatment, 45 – within 6 months of treatment and 93 – 1–8 years after treatment, median time – 30 months) (Table 2).

Eight items were deleted on the basis of quantitative analysis of patients interviews (low mean scores, low prevalence and low proportions of priority ratings). Eight items were excluded following patient comments of significant overlap with other items and difficulty in understanding the issue and difficulty in re-phrasing and translating. Three items

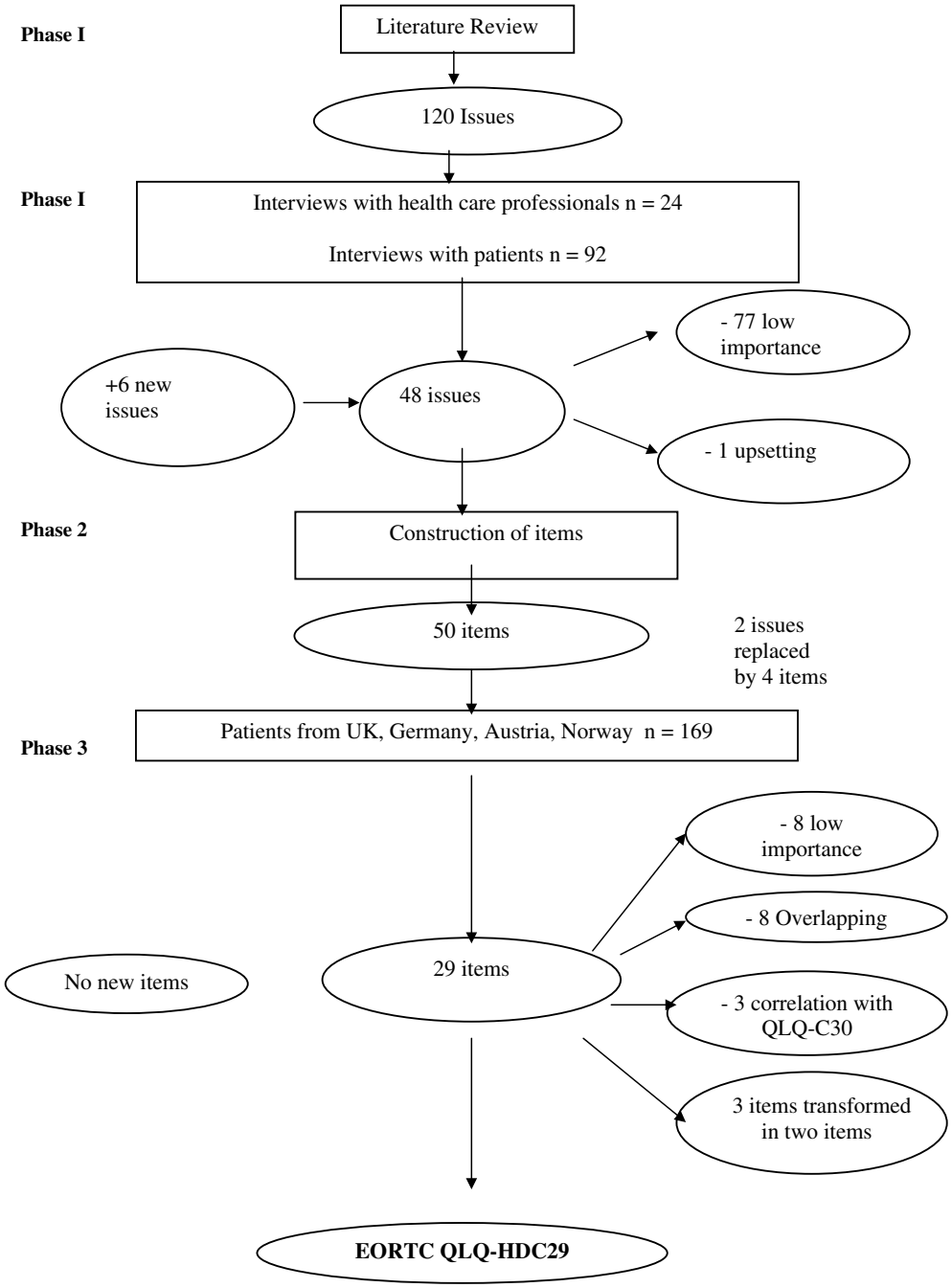

Fig. 1 – Development process of EORTC HDC-29.

(two on severe fatigue and shortness of breath) were excluded due to high correlation (*i.e.* overlap) with similar EORTC QLQ-C30 items. Three items on sore or dry mouth and throat were transformed into two items. This process resulted in retaining 28 items in the final questionnaire (Fig. 1).

Time frame for some items (family issues, worries about the future, taking regular drugs and watching closely for new symptoms) was changed from past week to past four weeks. Two items were re-phrased as their initial wording was found to be unclear. One item was made optional (concerns about ability to have children), as it was irrelevant for older patients.

No differences were found in mean scores, range of responses, prevalence ratio and priority ratings between the patients in the late effects group and the original groups of patients interviewed during and immediately after the treatment (data not shown).

The resulting questionnaire, consisting of 29 items, was named EORTC QLQ-HDC29 (High-dose-chemotherapy) (Table 3).

The development process and the questionnaire were reviewed and approved by three members of the EORTC QOL Module Development Committee. The module is available in English, German, Norwegian, French and Italian.

Table 3 – Content of the EORTC QLQ-HDC29 module

Gastro-intestinal side-effects sub-scale
Sore or dry mouth/throat
Difficulty swallowing
Changes in taste
Abdominal pain or cramps
Worry/Anxiety
About weight being too low
About results of examinations and tests
About that blood may not recover
About the future
Watching oneself for new symptoms
Impact on family
Felt isolated from family, friends
Disruption to family life
Distress to family
Keeping concerns from family
Body image
Hair loss
Feeling physically less attractive
Sexuality
Interest in sex
Sexual enjoyment
In-patient issues
Coping with hospital stay
Isolation
Preparation for treatment
Single items
Skin problems
Fever/chills
Urinary frequency
Aches or pains in bones
Taking regular drugs
Finishing things
Ability to have children
Experience helping to distinguish what is important in life

4. Discussion

The EORTC QLQ-HDC29 has been developed methodologically to measure physical side-effects and important emotional and family issues in patients with different malignancies, undergoing myeloablative treatment. The content of the questionnaire has been determined by the extensive literature search, by interviews with health care professionals (including doctors, nurses, psychologists) and most importantly by interviews with patients themselves. It includes the experiences of professionals and patients from four European countries and has been developed simultaneously in three European languages. This makes it possible to collect a reasonably large patient sample for a relatively rare type of treatment. In addition, it ensures that the questionnaire is comprehensive, reflects the clinical practice across Europe and is culturally acceptable.

In order to allow reliable between treatment comparisons in clinical trials, we aimed to develop a single module that will cover the side-effects of different types of treatment (autologous and allogeneic HSCT). Patients interviewed during the module development process were carefully selected to reflect different age, gender, malignant diagnoses and types of transplants. During the analysis, the results for the sub-groups were compared (data not shown) and items relevant for specific groups were retained. This vigorous procedure ensures that resulting modules can be used for different treatment modalities.

The initial intent of the module development was to measure patient experiences during and immediately after treatment. However, an increasing interest in the assessment of late effects of treatment lead us in Phase 3 to pre-test the already selected issues in patients, who have completed treatment 1–10 years before. The quantitative results and patients comments suggested that the questionnaire was well accepted by patients and reflected their experiences.

The next phase of development involves administration in a large multicultural population to provide essential data on the psychometric properties of the questionnaire. The strategy for achieving this task will be to start using the questionnaire in clinical trials in collaboration with EBMT and interested individual researchers, collect the data centrally and perform psychometric analyses.

Some weaknesses of the module development should be acknowledged. Following a rigorous procedure and developing the module simultaneously in several countries and languages meant that the study continued over several years. These were challenging times of intensive research and developments in the field of high-dose therapy, that led to confirmation of the role of treatment for some cancers and rejection for others. For example, in Phase 1 of module development a number of breast cancer patients were recruited during a period when autologous PSCT was actively studied as adjuvant treatment for high-risk breast cancer. The data from patient interviews in Phase 1 were analysed both including and excluding breast cancer patients and there were no differences in the selection of issues.

In Phase 3, the provisional module was tested in a separate group of 93 patients, treated 1–10 years earlier to evaluate suitability for assessing treatment late effects. The majority of those patients ($n = 66$) were from Austria, thus creating a potential for bias. The quantitative results of the provisional questionnaire of the Austrian patients were compared with the rest of the group, and no differences were found.

The EORTC QLQ-HDC29 can be used in conjunction with EORTC QLQ-C30 to assess treatment-specific aspects of QOL of patients participating in clinical trials of high-dose chemotherapy with autologous or allogeneic transplants, both during and after treatment. This may be of value in the longitudinal follow-up of patients, providing information about the effects of treatment on patients' lives.

Conflict of interest statement

No conflict of interest to be declared.

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