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Quality of life assessment and research in the EORTC (European Organisation for Research and Treatment of Cancer)

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Abstract: Quality of Life (QOL) assessment and research within the European Organisation for Research and Treatment of Cancer (EORTC) has become increasingly important over the past 25 years, starting already in 1979 with the founding of the EORTC Quality of Life Group (EORTC QLG), and QOL has become part of many cancer clinical trial protocols in different ways. This paper briefly presents an overview of QOL within the EORTC, the development of the QLQ-C30 instrument, the construction of specific modules, issues of cross-cultural validation and translation, and the various other activities of the QLG and the Data Centre Quality of Life Unit (QLU). The article also includes key findings from selected QOL studies published by the EORTC, highlighting this large international clinical trial organisation's contribution to this field of oncology.

Keywords: Cancer – Quality of life – Clinical trials – EORTC – QLQ-C30

The EORTC quality of life group

The formation of the Quality of Life Group (QLG) dates back to 1979, when a group of dedicated physicians and researchers met during a NCI-EORTC cancer drug symposium in Brussels to discuss the topic of « Quality of Life » in cancer medicine. An European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Study Group was founded and held its first meetings in Marseille and Amsterdam. The proceedings of these early workshops already included a number of topics that set the scene for developments that would come in forthcoming years, such as theoretical considerations of quality of life, measurement of quality of life in cancer patients, and management of psychological stress in cancer patients. Subsequent meetings consolidated the group's assessment strategies and the development of the new instrument, later known as EORTC QLQ-C30, in various European and non-European languages. In 1988, a report on the first EORTC quality of life field study #15861, studying the properties of the newly developed instrument in lung cancer patients, already included 373 patients from 21 institutions in 15 countries. In 1987, the EORTC Monograph on Quality of Life was published [1], and in the following years formal subcommittees for module development and liaison work were created. The first EORTC Guidelines for module development were published, followed by translation guidelines [4, 10]. Project groups for QOL in various areas started working and finally in 1993 the results of the big international field studies with the EORTC QLQ-C30 were published, making the instrument and its psychometric properties available to the scientific community [2]. In 1994, the Quality of Life Unit (QLU) at the EORTC Data Centre in Brussels began work and the first manual in the series of « blue books », the QLQ-C30 scoring manual, was published, followed by an atlas of norms in 1996 [16]. The construction of the item bank followed, along with the professional treatment of the growing number of QLQ-C30 translations and the multiplying number of modules [8]. The series of « blue books » now comprise: Scoring Manual QLQ-C30, Reference Values Manual, Translation Guidelines, Module Development Guidelines, Guidelines for Assessing QOL in EORTC Clinical Trials, Item Bank Guidelines.

QOL core instrumenT QLQ-C30

By 1993 the EORTC QLG had completed the development and validation of the QLQ-C30 core instrument. It was designed to be cancer-specific, multidimensional, self-administered, for use in cross-cultural settings and in conjunction with additional tumour- or treatment-specific modules. The 30 items on a four- or seven-category answer format cover five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global QOL scale. A number of single items address dyspnoea, loss of appetite, insomnia, constipation, diarrhoea, and financial impact of the disease. Instrument development continues and currently a

shortened version of the QLQ-C30 for use in palliative care (PAL 15) has been built employing computerized adaptive testing (CAT) [18].

QLQ-C30 modules

The QLQ-C30 was meant to be a short core instrument for general use with cancer patients and to be supplemented by additional modules addressing tumour- and/ or treatment-specific issues. Modules should either assess symptoms from a specific tumour site or special side-effects from treatment or additional QOL domains not represented in the core (e.g., fatigue, sexuality, etc.). With the aim of assessing patients' response to treatment and tumour burden longitudinally, comparisons between treatment groups should be made possible within clinical trials. Meanwhile, many other groups have adopted this so-called « modular approach ». QLG guidelines and procedures have been developed to ensure the quality of module development and cover four phases through to completion of a module. In phase 1, relevant QOL issues are identified. In phase 2, items and possible scales are designed. In phase 3, the module is re-tested. Phase 4 concerns international psychometric testing for reliability and validity, usually within field studies with over 400 patients and in a larger number of European countries. Currently, well over a dozen modules are available in different phases of development concerning not only site-specific issues (breast, prostate etc.), but also QOL areas (fatigue, information, etc.) and special treatment situations (e.g., high dose chemotherapy).

Translations and cross-cultural validity

Generally speaking, working with QOL assessment in an international environment where you find a multitude of cultures and languages represents a considerable challenge. This is particularly true within Europe, where there is quite a large number of core languages. It seems critical that QOL instruments are developed with proven cross-cultural validity and reliability and are translated accurately into other languages. These measures are extremely expensive, in terms of time and finance, especially when following stringent procedures of development and psychometric testing. Up until the mid-1990s only a limited number of translations of the QLQ-C30 and modules were available in core European languages. However, with the development of a well-documented EORTC QLG translation program in recent years, including more rigorous guidelines for translation and cultural adaptation, all available EORTC QOL instruments can now be quickly and accurately translated into the majority of languages required.

Implementing QOL in EORTC clinical trials

Once QOL research was promoted within clinical trials, the number of trials with QOL assessment in the EORTC Groups increased steadily. These are typically randomized phase III clinical trials, all with international patient accrual. Different parties are involved in implementing QOL research in EORTC clinical trials [9]. These include the EORTC Clinical Groups conducting the trial, the EORTC QOL Unit (QLU), and a liaison member from the Joint Scientific Committee of the EORTC QLG. Within the QLG, a Joint Scientific Committee was formed, consisting of members with expertise in the field of QOL and a specific disease site or treatment modality [11]. The aim of this committee is to liaise with EORTC Groups. These liaison members and/or QOL Unit members interact with EORTC Clinical Groups dedicated to a specific disease site or treatment modality, providing advice on the opportunities for implementation of QOL research in new trials. If QOL research is deemed relevant in a certain trial, the liaison member is involved in the design of the QOL study and participates in the analysis and publication. The QLU provides centralized support for the development of the QOL protocol section, reviews the content and oversees the entire developmental process. In almost all EORTC studies, QOL serves as a secondary endpoint when included in a trial. So far, QOL has been a primary endpoint only in field studies initiated by the EORTC QLG, intended to test the psychometric properties of the EORTC QLQ-C30 and disease-specific modules. One obvious challenge for the EORTC is the very different national systems used to recruit and collect QOL data from patients. Presently there are over 32 countries involved in QOL research throughout Europe and beyond. We have noted that most EORTC groups who undertake QOL studies within their clinical trials seem to have good levels of QOL data compliance. This may relate to the familiarity with using QOL tools in a research setting, and may reflect the importance of QOL assessment in a given disease site. Groups less active in terms of QOL tend to have lower compliance [21].

Guidelines for standardized data collection

Missing data has been identified as a major issue in QOL measurement in cancer clinical trials, especially in an international setting. This is a large-scale problem: institutions may differ substantially, not only in regard to cultural issues but also in terms of the logistics of patient care, and financial and personnel resources. In order to harmonize QOL data collection across all institutions, the QLU has developed standardized guidelines for QOL data collection in clinical trials, which are included in each protocol containing QOL components. These guidelines advise on questionnaire administration and data collection [6].

Collecting information on why there is missing data is important, since there is strong evidence that often QOL data is not missing at random; therefore it cannot be ignored without introducing bias [14]. In order to investigate the

reasons for missing QOL trial data, a QOL questionnaire completion module is added to each case report form (CRF), documenting if the patient has completed the QOL form at the specific visit linked to the CRF [24].

Standardization of QOL research protocol chapters

To ensure that high quality QOL studies are designed, a minimum set of standard requirements that must be addressed in any QOL study protocol has been devised. The protocol review committees review all protocol chapters extensively.

Compliance monitoring

Compliance is a fundamental issue facing researchers worldwide who undertake QOL studies [15]. There are numerous published studies and systematic reviews reporting considerable difficulties in collecting QOL data [22]. Without a doubt, this problem becomes even more complex when working in an international setting. The EORTC has implemented a system of monitoring QOL compliance by means of bi-annual compliance reports. These directly specify the compliance rate by institution for each study. Where possible, these reports are presented and discussed at a group's bi-annual meeting. Discussions address ways to improve compliance, or specific reasons why certain institutions' compliance may be lower than expected. The QLU acts as a central educational resource for investigators and data managers on all aspects of QOL data collection. In future EORTC trials, a baseline QOL assessment will be mandatory to allow patients to be eligible for registration or randomization before initiation of treatment. The EORTC is considering a minimum QOL compliance level to close QOL studies where data does not meet compliance standards. This is clearly difficult, as each protocol has different aims, some emphasizing long-term compliance and others stressing mainly treatment-related compliance, depending on the expected QOL implications. In addition, over time, compliance could improve. Therefore it may be useful to establish minimum and final levels of compliance. The EORTC is pilot testing data management allocations to the monitoring of QOL studies within clinical trials. These include developing centralized dynamic reminders to investigators at each assessment point, along with a QOL schedule checklist once patients are registered. Regular reminders and clearly established time sheets aim to improve compliance. The EORTC is considering establishing a QOL Clinical Trials Implementation Committee, consisting of members of the QLG, the QLU and EORTC Data Center staff. Significant resources will be made available to members. The idea is to annually oversee levels of compliance across all groups and trials with QOL recommendations regarding specific approaches to adopt.

Analysis of EORTC studies

As the analysis of QOL studies is often a matter of debate, considerable attention is paid to both levels of missing data and patterns of patient drop out. While one QOL method will not fit all studies, several attempts have been made to standardize the way QOL data is analyzed. These include the development of standard QOL macros and, more recently, the initial development of a standard operating procedure for the analysis of EORTC QOL data.

Reporting QOL studies in EORTC clinical trials

Reporting of QOL data in cancer clinical trials has been under considerable criticism in recent years [20]. In many respects, this criticism can be justified and fairly directed at QOL research. Within the EORTC both the liaison experts and the QLU staff must be involved in the analysis and final writing of any publication containing QOL aspects, thereby helping to ensure quality. To ensure standardization across all groups and studies, the QLU is presently preparing minimum standards for the reporting of QOL studies in EORTC clinical trials. This will require as a minimum: a statement of the rationale for including QOL research in the trial, specification of the hypothesis, details of population, instruments, timing of assessments, methods of collection and analysis of data, and explicit details on compliance and methods of handling missing data, with a focus on the clinical significance of QOL results.

Selected key findings from QOL studies in EORTC clinical trials

To illustrate the value of QOL studies within the EORTC, some key findings from recently published trials are given below:

– EORTC study 26981/22981: Glioblastoma multiforme patients should undergo radiotherapy and concomitant and adjuvant temozolomide given it increases survival without any impairment to QOL when compared to radiotherapy alone [23];

– EORTC study 10961: Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide in metastatic breast cancer had the same clinical and QOL efficacy. Patients now understand the trajectory of side effects during chemotherapy assisting informed treatment decisions [5];

– EORTC study 08983: Raltitrexed and cisplatin gives better survival and similar QOL compared to cisplatin alone in malignant pleural mesothelioma patients, recommending, that in selected patients, both raltitrexed and cisplatin should be offered to patients as a treatment approach [7];

– EORTC/GELA H8 trial 20931: In supradiaphragmatic early stages Hodgkins Lymphoma patients have considerable impaired QOL years after treatment with enhanced fatigue which may need intervention post treatment [17,19].

QOL appears to offer prognostic information in many advanced diseases but may not in early stage disease [13]. There is a clear link between QOL outcomes and clinical decision-making [12].

Conclusion

In the past 25 years, the establishment of the EORTC QLG has led to an impressive development in QOL assessment and research within the EORTC. The QLQ-C30 and its modules make up one of the leading instrument systems worldwide in the QOL field, and QOL has now become a well-integrated aspect of EORTC clinical trials. The level of QOL implementation has risen dramatically over the last years. The majority of trials incorporating QOL are phase III studies. Presently all of these studies have QOL as a secondary endpoint. It is clear that in some cases the collection of QOL data requires considerable effort. This is a reflection of what has been seen worldwide and previously reported by international researchers. However, a number of approaches outlined have helped to improve the quality of QOL reporting and compliance. These include monitoring, providing feedback, education, training and planning. Ongoing initiatives will continue to improve compliance. Hopefully, in the near future, the EORTC will eradicate the problems that can plague many cancer clinical trials. The expectation is that with significant resources, time and commitment from clinicians and researchers, all EORTC QOL studies will have a significant impact on the future treatment and care of patients.

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