Survival, quality of life and breast cancer

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Summary

In recent years, evaluating quality of life (QoL) has become increasingly important as an additional measured outcome in cancer clinical trials, in particular in the field of breast cancer. This paper, after a general introduction to the present debate on the methodological issues involved in QoL evaluation, reviews results and open questions regarding the use of this measure in surgical, adjuvant and metastatic studies.

Key words: adjuvant treatment, breast cancer, metastatic disease, quality of life, surgical treatment

Introduction

Breast cancer (BC) is the most common cancer among European women with more than 200,000 new diagnosed cases and more than 60,000 deaths every year. In the last century, we witnessed the development of several treatment options ranging from surgery to radiotherapy and chemotherapy, and from hormonal therapy to palliative care. BC randomised clinical trials (RCT) have traditionally evaluated the efficacy of new interventions by using indicators of life prolongation (survival) or disease control (response). More recently, clinicians, BC patients and their associations, and health policy makers have all become increasingly more interested in Quality of Life (QoL) outcomes. QoL is recognised as a more comprehensive assessment of treatment effects, as it accounts for the subjective evaluation of patients' social and physical functioning, psychological well-being and health perception. Moreover, the introduction of patients' points of view is considered a further step towards a more comprehensive humanistic approach to cancer treatment [1].

This trend is well documented in medical literature by the increasing number of BC studies reporting QoL results. We carried out a MEDLINE search, using 'quality of life', 'breast cancer' in the title and abstract for different periods of years. Concerning the BC articles published, the proportion of studies including 'quality of life' was 0.18% (10 of 5396) between 1971 and 1980, 0.86% (128 of 14731) between 1981 and 1990 and 2.17% (621 of 28516) between 1991 and 2000.

In 1999, Tao and Ganz [2] discussed the conceptualisation and the definition of QoL, the different approaches to measuring QoL in BC patients, the properties of generic and specific instruments available and, finally, the contributions of QoL in BC research studies. They demonstrated that the research in this field is strong, a fact that should allow an easy and useful integration of QoL outcomes in contemporary RCT and research studies.

Despite this state of affairs, the assessment of QoL in BC, as well in the treatment of other cancers, is still controversial for several reasons:

- The definition of QoL is frequently debated among experts. Leplege and Hunt discussed the lack of a valid and robust conceptualisation of QoL and the difficulties of finding a universal definition of the concept [3]. In particular, they underlined some discrepancies between the prevalent discourse of what QoL instruments are supposed to measure – the objective health status filtered by the patients subjective perception of health – and what they actually do measure – a model of health and illness that is mainly the product of the medical point of view.

- Most of the criteria suggested actually concern the intrinsic characteristics of the instruments, in particular their reliability, validity and responsiveness [4]. No recommendations have been proposed about how to interpret QoL results from BC trials. Finally, applying QoL research under less than optimal conceptual and empirical conditions can lead to dilution of its potential contribution to clinical decision making.

- Among researchers and clinicians, a QoL outcome is often considered as an ancillary end point. Patient-oriented measures were often considered to have a minor role in the evaluation of treatment and, for this reason, little attention is paid to the recruitment of patients for QoL assessment and to applying the right methodological approaches. Nevertheless QoL measures are included as a ther-
apapeutic efficacy end point in several studies, and may assist the pharmaceutical companies in the regulatory process and in the marketing of their products.

Moreover, despite the continuing debates about the objectives to be measured and how to measure them, there are indications that the present situation may change:

• Some scientific societies have set up working groups to debate the role of using such evaluation techniques in clinical research, and authoritative reports have been published in leading journals. In 1996, the American Society of Clinical Oncology published the deliberations of the Outcomes Working Group regarding the guidelines for patient outcomes, defined as measures of the effect of treatment on the patients e.g., survival, toxicity and quality of life [5].

• Several sets of guidelines intended to serve as starting points for discussion on the use of pharmacoeconomic data to support claims have been drafted by a subdivision of the Food and Drug Administration (division of Drug Marketing, Advertising and Communications). They all contain statements and recommendations on the QoL issue.

• Finally, the use of measures based on the patient’s perception in clinical trials is one way of introducing the patient’s point of view into clinical research and increases continuously their involvement in medical-decision making.

To show the complexity of assessing QoL in BC treatment, three examples are discussed below.

Surgical treatment of breast cancer

Mastectomy (either radical or modified) was the predominant treatment of stage I and II BC for almost a century. In the last two decades, breast conserving therapy (BCT) has become the preferred method of treatment, since it has become clear that more aggressive local treatment did not improve survival and that failure was more often due to systemic dissemination of the tumour before surgery. Furthermore, mammographic screening has shifted the diagnosis towards smaller tumours. The local control of disease, the prognostic information and a good cosmetic result are the main end-points of surgical treatment.

The strategy in BCT is to remove the tumour surgically and to use moderate doses of radiation therapy to eradicate any residual cancer. Six prospective RCTs [6-11] have compared mastectomy with BCT for stage I and II BC, and during a follow-up period of up to 18 years, none of them showed significant differences in overall or disease-free survival between the two treatments. No significant differences in the risk of recurrence in the treated breast or chest wall after mastectomy was observed in five of the six RCTs. In the National Cancer Institute trial, a higher local failure rate was reported in the BCT arm, a finding possibly attributable to the fact that negative margins were not required for study entry. These results have been confirmed in a meta-analysis [12]. Partially based on such information, it was concluded at the National Consensus Conference on the treatment of early-stage BC in 1990 [13] that “BCT is an appropriate method of primary therapy for the majority of women with stage I and II BC, and may be preferable because it provides survival outcomes equivalent to those achieved by total mastectomy and axillary dissection while preserving the breast”.

A careful selection of patients and a multidisciplinary approach are important for the choice of the best local treatment. To accomplish this, an estimate of the risk of local recurrence after BCT or mastectomy must be balanced against the expected cosmetic outcome, an evaluation of the patient’s desires and expectations, and any medical contraindications to the chosen procedure. It is also important to discuss with the patients the risks and the benefits of both forms of treatment so that the woman can evaluate the impact of this choice on her psychological adaptation, body image and sexuality and, in one word, on her QoL.

Between 1981 and 1995, 40 different studies evaluated the impact of BCT on the QoL of patients. Three articles [14-16] reviewed these studies with respect to the methodological issues and results obtained. Unfortunately, all these reviews underlined the fact that most of the articles suffer from: a) small sample size and several methodological inconsistencies, such as variability in methods of assigning treatment, mostly chosen by the patients with randomisation being the exception, b) definition of QoL that tends to cover a broader range of social, psychosocial and economic issues, c) use of ad hoc instruments developed for the specific study instead of well-known standardised and validated questionnaires. Moreover, the time elapsed since surgical treatment varied among studies from a few weeks to five years or more. The results obtained show a lack of substantial benefit resulting from BCT; however, all the reviews found that BCT provided some benefits for body/self-image, while no significant differences were observed for psychological, marital-sexual, social adjustment and cancer-related fears and concerns.

Adjuvant treatment of breast cancer

At present, clinicians have a wide choice of adjuvant regimens for BC, ranging from hormonal regimens to aggressive polychemotherapy regimens. Because in this setting patients are healthy and only at risk for a disease relapse, decision-making about adjuvant treatment involves weighing the expected therapeutic effect of each specific regimen against potential side effects, in order to determine the probable net benefit. More than one hundred RCTs have evaluated the efficacy of adjuvant treatment based on classical survival end points. Furthermore, thanks to an enormous
laborative Group, EBCTCG), a systematic meta-analysis of virtually all RCTs begun worldwide before 1990 is yielded accurate estimates of the benefits of adjuvant treatment in terms of quantitative improvement of disease-free survival and of survival [17-18]. From the latest data of the EBCTCG overview, we know that six onths of adjuvant polychemotherapy decrease, on average, the annual odds of recurrence and death by 1.5% and 15.3%, respectively. Correspondingly, the Lministration of tamoxifen for five patients ith node-positive oestrogen receptor positive tumours duces the annual odds of relapse and of death by 43% id by 28%, respectively.

Given these estimates of survival benefit, is QoL assessment a relevant end point in this context? Clearly, an assessment might be irrelevant when evaluating potentially curative treatment which is unlikely to have y important toxic effect. Polychemotherapy, however, is provided, on average, a smaller impact on the rivial end point, while showing toxicity. The availability of QoL data in such a context may thus be useful cause it can: a) inform patients about what to expect om their treatment, b) describe QoL differences beeen treatments, c) provide an additional baseline earse with potential prognostic significance, d) inform clinicians about their patients' experinces with xities, e) indicate situations in which psychosocial terventions might be useful, and f) document patient syping with diagnosis and treatment. Unfortunately, ly few RCTs have reported data on QoL. The reason twofold. First, RCTs of adjuvant therapy usually volve many centres, even across different countries, d the evaluation of QoL by the administration of a icific questionnaire may be difficult. Second, RCTs usually take many years to complete and, although any organisations have introduced QoL as an outcome measure in their trials, we have to wait a few years, efore there is a pronounced increase in trials reporting L results.

Thus two main questions remain open: which is the st way of measuring and assessing QoL within the amework of RCTs and how to integrate this information with the survival information in order to evaluate risk benefit from treatments given in the adjuvant ting. As far as measurement of QoL is concerned, any instruments have been developed, each one ith own advantages and limitations [19].

At present, the major contribution to our understand ng of the use of QoL studies in the adjuvant setting of C comes from the data published by the International reast Cancer Study Group (IBCSG). Using single-item human analogue self-assessment scales and a psychometric questionnaire for emotional well-being, they have ensured QoL changes during and after the adjuvant eraopy of patients enrolled in two large international CTs [20]. Their results show that CMF-based adjuvant entment leads to a measurable decrement in QoL, but is effect is transient and minor compared with the process of adaptation to the disease. Furthermore, it indicates that after completion of adjuvant chemotherapy, the patient's QoL returns at least to baseline. This latter finding has been confirmed by a survey in which the QoL of BC survivors was seen to resemble that of healthy women, irrespective of the type of adjuvant treatment received, tamoxifen, chemotherapy, chem+ tamoxifen [21].

In order to integrate QoL information with survival data, the IBCSG has developed a new statistical technique, known as Quality-adjusted Time without Symptoms and Toxicity or Q-TwiST; this is a natural extension of the Quality-Adjusted Life Year (QALY) to include censored data [22]. Briefly, it consists of a 'partitioned' survival analysis in which time spent on therapy and time spent after disease relapse is discounted by a quality coefficient (utility coefficient), with values ranging from 0 to 1, based on the patient's relative perception of their QoL during these two time periods. Results can be reported as a function of all possible combinations of utility coefficients (threshold analysis). Empirically, however, it has been estimated that patients tend to put a high value on the utility coefficient for time in adjuvant chemotherapy [23], indicating a willingness to accept this treatment even for a small to modest potential survival benefit. Using the Q-TwiST method, Gelber et al. carried out a meta-analysis to assess the quality-adjusted benefits of adjuvant CMF versus no therapy in node-positive patients aged 49 years or younger [22]. The results of the meta-analysis endorse the benefits of CMF in this setting, even in the extreme hypothetical case of a relative QoL equal to zero during the treatment. Of course, in situations in which the survival effect of chemotherapy is smaller, the Q-TwiST analysis may yield different results. For instance, a similar meta-analysis aimed at assessing the Q-TwiST benefit of adding chemotherapy to tamoxifen for post-menopausal patients showed no significant advantage for the chemo-endocrine treatment as compared to tamoxifen alone [24]. As a trend to higher Q-TwiST values over time was evident in that study, we predict that, as follow-up matures, Q-TwiST benefits will become evident for the combination therapy.

In summary, based on the available data, adjuvant CMF chemotherapy for early BC seems to live only mild and temporary effects on the patient's QoL. Patient preferences seem to favour the use of adjuvant chemotherapy even for potentially small survival advantages. However, further data are required in order to make quality-adjusted comparison between different kinds of chemotherapy (CMF vs. anthracycline-based vs. taxane-based) with or without tamoxifen administration.

Treatment of metastatic breast cancer

Despite metastatic BC (MBC) being considered an incurable disease, about 15% of these patients can achieve complete remission (CR) with systemic treatments such
as chemotherapy and hormonal therapy. Overall median survival after relapse has been reported to be 18 to 24 months, but a small fraction of patients (1–3%) can remain disease-free for 5 to 10 years or more, thus having long-term survival [25, 26]. New therapeutic strategies, such as high-dose chemotherapy with stem-cell support, have been used in the attempt to increase CRs and consequently the number of long-term survivors. The efficacy of such approaches has, however, not been sufficiently demonstrated; further evidence is needed from RCTs to allow a wide use of high-dose chemotherapy in clinical practice. Therapeutic strategy in MBC should not disregard the fact that the end points of therapies are eminently palliative and that the least toxic treatments offering the best therapeutic index should be used.

Some very broad indications concerning the type of treatment are recently suggested by Fossati et al. [27] in a systematic review where overall survival, response rate, and toxicity were considered. Regarding overall survival, polychemotherapy and chemohormonal therapy given at full doses or for longer periods obtained better results than mono-chemotherapy and therapy given at lower doses for shorter periods. There were no differences in survival between schemes with or without anthracyclines, while doxorubicin-based chemotherapy provided a marginally statistically significant survival advantage versus epirubicin-based regimens. There were no differences in survival between the compared endocrine therapies, even though toxicity profiles were very different; therefore hormonal therapy should be tailored for every patient on the basis of therapeutic needs and expected toxicities. Although the outcomes of various treatments were often overlapping for survival, response rate and toxicity, QoL assessment was reported in only 2,995 (9.5%) of the 31,510 patients. The conclusions of the authors were that: a) low toxicity polychemotherapy is preferable and high-dose chemotherapy should not be considered for routine clinical practice, b) endocrine therapy must be chosen on the basis of risk/benefit ratio in every single patient, c) as highly significant improvement of clinical end points like survival is unlikely, RCTs in MBC should include a formal evaluation of QoL and a cost-evaluation.

In 1987, Coates showed that a strategy of continuous treatment obtained better objective results and QoL than intermittent therapy [28]. The results concerning QoL were claimed to be counterintuitive, but one has to notice that the intermittent therapy was stopped after only three cycles and not after having obtained the best response. Moreover, subjective effects of continuous chemotherapy could reflect, at least in part, a placebo effect of the treatment. Tannock et al. [29] demonstrated that full-dose chemotherapy achieved better palliation than low-dose treatment. The study considered mainly disease related symptoms and that as ‘full doses’ meant conventional doses of CMF, while low doses were unusually low dosages of the same drugs. Fraser [30] confirmed that more aggressive therapy can give better response, similar survival, and not impaired QoL compared with low dose chemotherapy, while other authors reported that every-three-week treatment is less psychologically distressing than weekly administration [31]. Studies on hormonal treatments show that, when antitumoral efficacy is equal, preference should be given to the dosage [32] or drug [33] with a higher therapeutic index. The use of some new therapies to supplement traditional chemotherapy is not associated with a worsening of QoL [34].

According to Ramirez et al. [35], the presence or absence of some subjective parameters, like dry mouth, high levels of psychological distress, pre-treatment lack of energy and breathlessness, could be even used to assist clinicians in deciding which patients should or should not be offered chemotherapy. It is widely believed that a correlation exists between objective and subjective response; however, McLachlan [36], in a study of phase II tumors in patients undergoing third-line chemotherapy, reported a rate of subjective responses (34%) higher than that of objective responses (5.5%). The authors ascribe these results to chemotherapy, supportive care, the placebo effect or a shift in frame of reference for QoL.

In conclusion, treatment of metastatic BC is almost exclusively of palliative nature. QoL assessment should give information able to assist the clinician in deciding the treatment with the most favourable therapeutic index. Unfortunately, there are many methodological studies, but few try to give clinical meaning to the information on QoL. Moreover, there is still not sufficient evidence indicating that what is being investigated with the assessment instruments reflects the actual comprehensive QoL of the patients. Therefore, we can not suggest a widespread use of instruments for QoL evaluation in clinical practice. Information from RCTs in which two treatments of comparable activity and efficacy could be evaluated and chosen on the basis of their impact on QoL parameters is important to clinicians.

References


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