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Systematic or Meta-analysis Studies

Health-related quality of life assessment in contemporary phase III trials in advanced colorectal cancer

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ABSTRACT

Background: Health-related quality of life (HRQOL) is often used as an endpoint in cancer clinical trials. We assessed the frequency and correlates of HRQOL use in phase III trials in advanced colorectal cancer.
Methods: We searched PubMed for phase III trials published between January 1998 and December 2014, as well as for companion papers reporting on HRQOL separately. We excluded papers reporting on correlative biology or prognostic factors in isolation from the main trial results, as well as trials on supportive care and on local therapy.
Results: We retrieved 111 trials that enrolled a total of 61,531 patients in 241 trial arms. HRQOL was reportedly used as an endpoint in 40 trials (36%), in all but two as a secondary endpoint. There was a significant decrease in the use of HRQOL, with frequencies of 46% in trials published between 1998 and 2006, and 27% between 2007 and 2014 ($P = 0.04$). Trials with HRQOL as endpoint were significantly larger than trials without such endpoint. Formal statistical comparisons involving HRQOL parameters were reported in 36 of 40 trials (90%) with HRQOL assessment, with a significant difference between arms found in 14 (39%), six of which favoring the experimental arm. HRQOL gains were usually accompanied by improvements in efficacy endpoints, but were not related to the number of patients or chemotherapy line.
Conclusions: HRQOL has been formally assessed in about one-third of recent phase III trials in advanced colorectal cancer, with a significant gain in HRQOL in about 40% of cases. It is questionable whether HRQOL results may largely help select between competing treatments. This assumption may be one of the reasons for the apparent decreased use of HRQOL as an endpoint in phase III trials in this disease.

Introduction

Cancer poses an enormous burden on society, both in well- and less economically developed countries. Based on GLOBOCAN estimates, about 14.1 million new cancer cases and 8.2 million deaths from cancer occurred in 2012 worldwide [1]. Colorectal cancer (CRC) is one of the most prevalent types of cancer in the world, particularly in developed countries. According to GLOBOCAN, it is the third most common malignancy in men and second in women, estimated to cause 694,000 deaths in 2012 globally [1]. CRC incidence and mortality in the Western world has decreased over the past decade, probably as a consequence of wider use of screening, earlier detection of symptomatic disease and more effective therapy [2,3]. Within this period, the 5-year survival rate for CRC has increased from 51% to 65%; but still half of the patients will eventually develop metastasis and most of them will succumb to their disease [4]. Since advanced CRC remains incurable for most patients, the chief therapeutic goal is palliation, aiming at prolongation of survival, with improving or maintaining good quality of life and symptom control. The design and interpretation of phase III trials in advanced CRC has changed within the past decades: the use of OS as the primary endpoint has decreased, whereas the use of PFS has increased [5].

It is now widely recognized that cancer and its therapy affect not only patients' health, but also their quality of life [6,7]. Health related quality of life (HRQOL) is a multi-dimensional concept that has been developed and is widely used as an outcome measure for cancer patients' care. This method is particularly devised for patients with advanced cancer, as they are more likely to have

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symptomatic disease. In general, HRQOL assessment instruments measure five quality of life dimensions: physical, role, cognitive, emotional, and social functioning. HRQOL assessment has many potential utilities and implications for clinical practice and research, and its assessment has become an important secondary objective in cancer clinical trials. This assessment may provide understanding and information on how HRQOL influences cancer patients' lives and treatment strategies [8–10]. The impact of treatment on HRQOL is best addressed in the context of randomized clinical trials [9–11]. The primary objectives of these trials are generally related to the efficacy of interventions measured by standard outcomes, such as overall survival (OS) and progression-free survival (PFS). Nevertheless, more attention has recently been paid to improving the way patients live during and after anticancer treatment [12,13]. It is believed that assessment of HRQOL can facilitate choosing between alternative treatments interventions, particularly if they show similar survival outcomes. However, the question of whether HRQOL assessment contributes significantly to provision of better cancer care remains a matter of debate.

Given the perceived importance of HRQOL assessment, our objective in this study was to analyze HRQOL results in contemporary phase III trials in advanced CRC, in an attempt to further our understanding of the actual role of HRQOL assessment in this setting.

Methods

Trial eligibility

We selected eligible trials using PubMed, with the medical subject headings 'colorectal neoplasms' and 'drug therapy', as well as the filter 'randomized controlled trials'. We then manually searched for all phase III trials on systemic anticancer therapies for advanced CRC published between January 1, 1998, and December 31, 2014. We only included trials whose main results had been published in the study period. We also searched for companion papers reporting on HRQOL separately, by using the names of the first and last author of each main paper. We excluded papers reporting on correlative biology or prognostic factors in isolation from the main trial results, randomized phase II trials, trials on supportive care alone and on local forms of therapy, trials with patients treated both in adjuvant fashion and for metastatic disease, and papers reporting combined analyses of two or more separate trials already retrieved in the main search. We did not attempt to control for publication bias, since our aim was to assess trials that are more likely to influence clinical practice given their publication in widely read journals.

Data collection and analysis

For each eligible trial, we abstracted its general characteristics and data on the use of endpoints. When not explicitly stated in the publications, we considered the primary endpoint as the one used for sample-size calculation or the endpoint first cited in the 'Methods' or 'Results' section of papers. With regard to the use of HRQOL parameters as endpoints in the trials, we first attempted to identify any mention of HRQOL data collection during the trial or, when no such mention was found, the existence of a companion paper on HRQOL. If only symptoms were assessed, without formal use of HRQOL instruments, we did not consider such a trial to use HRQOL as an endpoint. When HRQOL was used as a trial endpoint, we collected data on the instruments used, assessing whether there was formal statistical comparison between trial arms and considering the results of such comparisons as reported by investigators. We considered a significant difference between arms to be present if there was any statistically significant difference for any of the HRQOL parameters analyzed. A significant difference between symptom scores was considered only when the assessment of such symptoms had been done using HRQOL instruments. We compared categorical and continuous variables between variously defined groups of trials using Fisher's exact test and the Mann-Whitney test, respectively, with a two-sided significance level of 5%.

Results

Characteristics of the phase III trials

We retrieved 111 phase III trials that were eligible for analysis (a complete list of these trials is available upon request). Forty-eight trials were published between 1998 and 2006, and 63 between 2007 and 2014. A total of 61,531 patients were enrolled in 241 trial arms. These trials randomized a median of 428 patients in total (range, 55–2397), and a median of 191 patients per arm (range, 28–1199). Ninety-six trials had two arms, 12 had three, two had four, and one had five arms. Sixty-nine trials compared chemotherapy regimens exclusively (in some cases with biomodulators, such as interferon or levamisole), 37 assessed at least one targeted agent (usually in combination with chemotherapy), four compared a targeted agent with best supportive care (BSC), and one compared chemotherapy with BSC. Trial therapy was administered in the first line in 86 trials, in subsequent lines in 24 trials, and for one trial the information on treatment line was not provided.

Use of HRQOL endpoints

HRQOL was reportedly assessed in 40 (36%) trials [14–52]. The summary characteristics of these trials are shown in Table 1, and their more detailed relevant features are displayed in Table 2. Except for two trials (including one with another co-primary endpoint), HRQOL was always a secondary endpoint. There was a temporal trend with regard to use of HRQOL endpoints: between 1998

Table 1
Summary characteristics of 40 phase III trials reporting on HRQOL outcomes in advanced colorectal cancer published between 1998 and 2014.

Characteristic	*N* (%) or value
Journal of publication	
Journal of clinical oncology	18 (45%)
Lancet	8 (20%)
New England journal of medicine	5 (13%)
Annals of oncology	4 (10%)
British journal of cancer	1 (3%)
Cancer	1 (3%)
Clin colorectal cancer	1 (3%)
Int J cancer	1 (3%)
J cancer res clin oncol	1 (3%)
Year of publication	
1998–2006	23 (58%)
2007–2014	17 (42%)
Line of therapy	
First	30 (75%)
Subsequent/unknown	10 (25%)
Number of patients	
Median	496
Range	55–2135
Type of therapy	
Chemotherapy alone	26 (65%)
Targeted therapy ± chemotherapy	10 (25%)
Targeted therapy vs best supportive care	3 (8%)
Chemotherapy vs best supportive care	1 (3%)