Impact on health-related quality of life of the addition of bevacizumab to first-line chemotherapy for ovarian cancer

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Introduction

What is the role of health-related quality of life (QoL) as an endpoint in clinical trials for patients with advanced cancer? When there is no significant difference between arms in terms of overall survival (OS) or progression-free survival (PFS), difference in QoL (and treatment tolerability) can become crucial in choosing the best treatment option. On the other hand, when the experimental arm is associated with a better outcome in terms of OS or PFS, QoL analysis can be useful to exclude the possibility that this higher efficacy is obtained at the cost of greater toxicity and impairment of QoL. Both phase III trials testing the addition of the anti-angiogenic antibody bevacizumab to first-line chemotherapy for patients with advanced ovarian cancer demonstrated a prolongation in PFS [1, 2]. Does this higher activity imply a benefit in terms of QoL due to symptom improvement, or, conversely, is it associated with a worsening in QoL, due to higher treatment toxicities? The two recent publications presenting the QoL analysis of the two trials [3, 4] give us some answers to this issue, answers that are particularly important given that bevacizumab is becoming part of the standard first-line treatment for ovarian cancer.

Summary of the two publications

In the ICON-7 trial [2, 4], patients were randomized to receive either six cycles of standard chemotherapy with carboplatin and paclitaxel alone or with bevacizumab (7.5 mg/kg), given intravenously with chemotherapy and then continued as maintenance, for up to 54 weeks. In this trial, QoL was measured by the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire-core 30, and the primary QoL measure was the global QoL at the end of bevacizumab treatment (week 54) [4]. Overall, the trial randomized 1528 patients, and about 90% in both arms completed baseline QoL questionnaires, while the proportion of patients with QoL data after 54 weeks was 66% in the bevacizumab group and 51% in the control arm.

The mean global QoL score at 54 weeks was higher in the standard chemotherapy group than in the bevacizumab group (76.1 vs. 69.7 points, Δ 6.4 points, 95% confidence interval [CI] 3.7–9.0; $p<0.0001$). The authors concluded that maintenance with bevacizumab seems to be associated with a small but clinically significant decrement in QoL compared with standard treatment, and that the trade-off between the prolongation of PFS and the quality of that period of time needs to be considered in clinical practice when making treatment decisions [4].

In the GOG-218 double-blind, placebo-controlled trial [1, 3], patients were randomized to six cycles of chemotherapy with carboplatin/paclitaxel alone (arm 1), or chemotherapy with concurrent bevacizumab 15 mg/kg (arm 2), or chemotherapy with concurrent bevacizumab followed by maintenance bevacizumab for further 16 administrations, one every 3 weeks (arm 3). In this trial, QoL was measured by the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI), administered before cycles 1, 4, 7, 13, and 21; and 6 months after completing study therapy [3]. Of the 1873 patients randomized, 1747 (93.3%) provided valid baseline QoL assessment and 86.8%, 83.2%, 76.1%, 66.4%, and 59.3% completed valid follow-up assessments prior to cycle 4, 7, 13, 21, and 6 months follow-up, respectively. The two arms with bevacizumab added to chemotherapy reported lower FACT-O TOI scores compared to the control arm, mainly during chemotherapy (at cycle 4), when patients receiving bevacizumab reported 2.72 points (98.3% CI: 0.88–4.57; effect size = 0.18) and 2.96 points (98.3% CI: 1.13–4.78; effect size = 0.20) lower scores in arm 2 and arm 3, respectively, than patients in arm 1. The difference in QoL scores between arm 1 and arm 3 remained statistically significant up to cycle 7, but there

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were no statistically significant differences between arms 1 and 3 during the maintenance phase. Authors concluded that the small QoL worsening observed during chemotherapy in patients receiving concurrent bevacizumab did not persist during maintenance bevacizumab [3].

Methodological comment

In 1996, the American Society of Clinical Oncology (ASCO) published a special article about the outcomes of cancer treatment for technology assessment and cancer treatment guidelines [5]. In that paper, QoL (that is a '*patient outcome*' and not a simple '*cancer outcome*') was already considered an important endpoint. Members of the Outcomes Working Group emphasized that '*the choice between alternative treatment approaches often involves a trade-off between length and quality of life; survival alone may not answer the question of whether gains in survival justify the toxicity*' [5]. This consideration should be applied also for the evaluation of bevacizumab in the first-line treatment of ovarian cancer.

Attrition of patients during follow-up, with a high number of missing questionnaires, can be a methodological problem for the QoL analysis [6]. Patients receiving first-line treatment for advanced ovarian cancer have a better short-term prognosis than several other solid tumours (such as lung cancer or gastric cancer), and the attrition rate in this setting is not expected to be dramatic. As expected, the proportion of patients completing QoL questionnaires declined over the observation period in both trials, but at an acceptable level. The issue of missing data would have been particularly relevant if the attrition rate had been different between the treatment arms because this could create a bias and compromise the correct interpretation of the observed result. However, this was not the case in the two randomized trials considered, because the attrition rate, although not negligible, was similar in the different treatment arms.

As a general rule of interpretation of QoL results, it should be emphasized that a statistically significant result is not necessarily clinically relevant. In the GOG-218 trial, there was a statistically significant worsening of QoL score during the first period of treatment, but the authors emphasize that the difference was small and not clinically meaningful. On the other hand, the worsening in the global QoL score in the ICON-7 trial was judged to be clinically meaningful. The difference between statistical significance and clinical relevance should always be discussed, particularly when the small observed difference is in favour of the experimental treatment, and this applies not only to interpretation of QoL results but also to other efficacy endpoints.

In summary, the addition of bevacizumab to first-line che-

Table 1. Main differences between the two randomized phase III trials testing the addition of bevacizumab to first-line chemotherapy in women with advanced ovarian cancer

	ICON-7 trial [2, 4]	GOG-218 trial [1, 3]
Type of trial	Open-label (2 arms)	Double-blind, placebo-controlled (3 arms)
Bevacizumab schedule	Bevacizumab 7.5 mg/kg, every 3 weeks, for 17–18 administrations: concurrent with chemotherapy (cycles 1–6 or 2–6) + 12 more administrations	Bevacizumab 15 mg/kg, every 3 weeks, for 5 administrations (cycles 2–6 of chemotherapy) or for 21 administrations (cycles 2–6 of chemotherapy + 16 more administrations)
QoL instrument	EORTC QLQ-C30	FACT
Primary QoL measure	Global QoL (items 29 and 30 of EORTC QLQ-C30) after 54 weeks [4]	FACT-O TOI before cycles 4, 7, 13, and 21; and 6 months after completing study therapy [3]
Number of randomized patients	1528	1873
Number of patients with baseline QoL questionnaire	1375	1747

EORTC QLQ-c30, European Organisation for Research and Treatment of Cancer quality-of-life questionnaire-core 30; FACT-O TOI, Functional Assessment of Cancer Therapy-Ovary Trial Outcome Index; QoL, quality of life.

motherapy was associated with a long-term worsening in QoL in the ICON-7 trial, judged to be small but clinically relevant, and with a transient, small worsening during the chemotherapy phase in the GOG-218 trial, judged to be not clinically meaningful. Is this slightly different result between the two randomized trials simply due to chance? At least three comments should be made about the differences between the two trials (Table 1). Firstly, the two trials used two different instruments for the evaluation of QoL: the EORTC questionnaire in the ICON-7 trial, and the FACT-O questionnaire in the GOG-218 trial. Both instruments are valid, reliable and sensitive, and have been widely used in many trials [7]. Secondly, the global QoL score in the EORTC questionnaire, despite the name 'global', is not a sum of the different questionnaire items, but is based on two questions related to the well-being and the global status of the patient during the last week of treatment. On the contrary, the FACT-O TOI is a score obtained by the sum of three different subscales (physical, functional and ovarian), from 26 questions. Thirdly, the GOG-218 trial was double-blind and placebo-controlled, so all patients (both those assigned to bevacizumab and those assigned to placebo) experienced the repeated visits to the hospital: in other words, the comparison between arms does not account for the worsening in QoL due to repeated hospital access and intravenous administrations. Conversely, the ICON-7 trial was open-label, and patients assigned to the experimental arm compiled the final QoL questionnaire after 1 year of continuous, q3w administrations, whilst patients in the control arm completed the questionnaire after a long treatment-free interval, following the completion of only 6 cycles of chemotherapy. These differences could contribute to explain the different results between the two studies.

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