Gynecologic Oncology 131 (2013) 437–444

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Quality of life of advanced ovarian cancer patients in the randomized phase III study comparing primary debulking surgery versus neo-adjuvant chemotherapy

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HIGHLIGHTS

- Institutions with good QOL compliance have higher optimal debulking rates and better survival outcomes.
- QOL compliance within a clinical trial is not independent from the clinical care.
- Institution seems to be a prognostic factor for QOL compliance.

ARTICLE INFO

Article history:
Received 10 May 2013
Accepted 15 August 2013
Available online 27 August 2013

Keywords:
Ovarian cancer
Quality of life
Patient-reported outcomes
Phase III trial
Gynecologic oncology

ABSTRACT

Objective. The EORTC 55971 trial compared primary debulking surgery (PDS) versus neo-adjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). The impact of both treatment arms on quality of life (QOL) is reported.

Methods. Patients with stages IIIc or IV ovarian cancer completed the EORTC QLQ-C30 before treatment, at the third and sixth cycle of chemotherapy, and at 6- and 12-month follow-up.

Results. Data of 404 patients ($N = 201$ PDS arm; $N = 203$ IDS arm) were included in the QOL analysis. Between treatment arms no statistically significant differences were found in any of the QOL functioning scales. Patients showed a clinically relevant improvement (>10 points) on the global health/QOL, role functioning, emotional functioning and social functioning scales during and after treatment independent of the type of treatment. Clinically relevant differences from baseline to the follow-up assessments were noted for fatigue, pain, insomnia, appetite loss, constipation, diarrhea indicating symptom control in both treatment arms. Institutions with good QOL compliance were associated with better outcomes. There was a statistical significant difference in the overall debulking status with 39.9% optimal debulking surgery in institutions with good QOL compliance compared to 19.9% in institutions with poor QOL compliance ($p = 0.0011$). Overall survival (median 32.30 versus 23.29 months; $p = 0.0006$) and progression free survival (median 12.35 versus 9.92 months; $p = 0.0002$) were also significantly better.

Conclusions. Survival and QOL after NACT followed by surgery was similar to survival and QOL after PDS followed by chemotherapy. However, institutions with good QOL compliance had better survival outcomes.

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0090-8258/$ – see front matter
http://dx.doi.org/10.1016/j.ygyno.2013.08.014

Introduction

Ovarian cancer is the gynecological cancer with worst survival [1]. Due to inadequate screening tools and a lack of early clinical symptoms the majority of women are diagnosed with FIGO stage IIIC or IV disease. The majority of these patients develop a relapse within the first 5 years after initial diagnosis and only 20–25% of cases are cured [2]. The standard treatment for patients with advanced ovarian carcinoma was at the time of performing this trial primary cytoreductive surgery aiming to remove all visible tumor tissue, followed by chemotherapy with paclitaxel/carboplatin [3–5]. Optimal debulking surgery (all lesions ≤1 cm) prior to chemotherapy is associated with an improvement in overall survival [6–10]. Van der Burg found in patients who could not undergo primary cytoreductive surgery that three courses of platin-based chemotherapy prior to interval surgery lengthened progression-free and overall survival [11]. Since then neoadjuvant chemotherapy has been proposed to reduce the burden of disease in patients with bulky disease primarily [8,12–14]. Although innovative treatment regimens in clinical trial settings do not always result in substantial differences in survival, these treatments can improve quality of life (QOL) of patients by reducing tumor burden and ascites. Patients with advanced disease frequently experience a variety of treatment- and disease-related side effects which may diminish their QOL. Patient-reported QOL has been recommended as an endpoint in clinical trials. The National Cancer Institute and the Food and Drug Administration mandated that the treatment goals should not only focus on survival but also on QOL [15]. Numerous clinical trial protocols have included QOL as a secondary endpoint but until now only a few publications reported QOL outcomes in phase III ovarian cancer trials [16–19].

The EORTC Gynecological Cancer Group trial (GCG protocol 55971) comparing neo-adjuvant chemotherapy (NACT) versus primary debulking surgery (PDS) in stage IIIC or IV ovarian cancer included QOL as a secondary endpoint. The median overall survival was approximately 30 months in both treatment arms [20]. The study demonstrated that NACT followed by interval debulking surgery (IDS) was not inferior to PDS followed by chemotherapy. This article reports the QOL outcome of this randomized clinical trial.

Patients and methods

The EORTC GCG 55971 trial is a randomized phase III study with overall survival as the main endpoint and secondary endpoints being progression-free survival, toxicity and QOL. The trial design and the results of the primary endpoint have been published previously [20]. Patients were eligible if they had a biopsy-proven stage IIIC or IV epithelial ovarian carcinoma. Fine needle aspiration cytology was allowed under strict inclusion criteria, WHO performance status of 0 to 2 and no other malignancies or disabling disease which would contraindicate primary surgery or platinum-based chemotherapy. All patients provided written informed consent before randomization. The local ethics committee of each participating center approved the study. Patients were randomly assigned to primary debulking surgery followed by at least six cycles of platinum based chemotherapy (PDS arm) or three cycles of neo-adjuvant platinum-based chemotherapy followed by interval debulking surgery and three additional courses of platin-based chemotherapy (NACT arm). Randomization was done centrally at the EORTC headquarters using a minimization technique to stratify for institution, method of biopsy, tumor stage (IIIC-IV), and preoperative tumor size.

Quality of life assessment

QOL was assessed using the EORTC QLQ-C30 core questionnaire version 3. The QLQ-C30 consists of a global health status/QOL scale, multi-item functional scales and symptom scales, and a scale regarding financial difficulties. The QLQ-C30 has been psychometrically validated and meets the standards for reliability [21]. QOL assessments were scheduled before randomization, on the last day of the third and sixth cycle of chemotherapy, and at 6- and 12-month follow-up. Data forms were subject to the standard EORTC quality assurance procedures and all patient files were reviewed by the study coordinator (IV).

Statistical analysis

The study required 498 events in order to demonstrate non-inferiority between the treatment arms in terms of overall survival. The trial had sufficient power to detect clinically meaningful differences in the QOL scales. The QLQ-C30 scales and single items were linearly transformed to 0–100 and analyzed according to the procedures recommended by the EORTC Quality of Life Group [22]. Higher scores on the functioning scales and the global health/QOL scale indicate a higher level of functioning and a better QOL. Higher scores on the symptom scales represent a higher level of symptoms or problems. A minimal clinically significant difference of at least 10 points was classified as improved or worsened on the EORTC QLQ-C30 [23]. For the functioning scales a 10-point increase between baseline and a subsequent QOL assessment indicated improvements, whereas for the symptom scales a 10-point increase indicated worsening. Questionnaire completion rates were calculated for all patients per assessment time and per treatment arm.

Logistic regression was used to identify patient characteristics related to missing data. The main QOL objective was to test whether NACT followed by IDS leads to improved QOL when compared with PDS followed by postoperative chemotherapy, based on the global health/QOL scale of the QLQ-C30. The primary analysis was performed by fitting a linear mixed model with treatment, a (linear) time effect, a time–treatment interaction as fixed effects and patient specific random effect on all randomized patients. Prior to reducing the model, the most suitable covariance structure was determined on the basis of Akaike's Information Criteria [24]. In order to account for certain potential imbalances, the analysis was repeated but with the stratification factors at randomization added as additional fixed-effect covariates: country, method of biopsy, largest tumor size, FIGO stage. Score estimates, standard errors, associated confidence intervals and resulting tests were obtained from the model, including a general overall post baseline test for no differences between the two treatment arms at all post baseline time points via an overall *F*-test statistic at the two-sided 5% significance level. Differences of at least 10 points were classified as the minimum clinically meaningful change in a QOL parameter [23]. As missing data is a problem in most QOL studies, sensitivity analyses were performed. For the primary QOL scale, explicit regression imputation was applied where imputed values were predicted from a regression model including factors related to missing data observed in this study [25].

Results

Between September 1998 and December 2006, a total of 670 patients with ovarian cancer were randomly allocated to the PDS or NACT arm. The required number of events (498) was reached with a median follow-up of 4.7 years. Overall survival and progression free survival were similar in the two groups. Detailed clinical results have been published elsewhere [20].

Quality of life: Completion and baseline scores

Compliance on all patients was too restrictive and changes to the protocol defined analysis plan were made. The data set was limited to data from institutions with the best compliance. The overall sample size ($N = 670$) was determined by the primary outcome of the trial demonstrating non-inferiority for overall survival. As such the trial was overpowered to detect clinically meaningful QOL differences between the two arms. Therefore reducing the sample size to 400 patients was deemed acceptable. The following selection criteria were