Explorative Study on the Predictive and Prognostic Value of Early Complete Metabolic Response By FDG-PET–CT During Neoadjuvant Chemotherapy in Patients With Advanced Ovarian Cancer

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Abstract
The role and optimal duration of neoadjuvant chemotherapy (NACT) in advanced ovarian cancer is debated. The use of PET/CT after 3 cycles of NACT as a determinant of pathological response, PFS and OS was studied in 50 patients treated with a total of 6 cycles. Complete metabolic response by PET/CT allows to identify patients who benefit from extending the duration of NACT and with a better outcome.

Background and Aim: Early complete metabolic response (e-CMR) by fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) during neoadjuvant chemotherapy (NACT) in advanced ovarian cancer (AOC) could have predictive and prognostic value. The present explorative study prospectively investigated changes of dual-time FDG-PET, at baseline and after 3 cycles of NACT in patients who were not candidates for upfront debulking surgery by comparing with standard serum cancer antigen 125 (CA-125) monitoring.

Patients and Methods: Fifty consecutive patients with AOC were treated with 6 cycles of carboplatin/paclitaxel before surgery. FDG-PET and serum CA-125 were evaluated at baseline and after 3 cycles. e-CMR and early complete biochemical response (e-CBR) were defined as the normalization of the maximum standardized uptake values and serum CA-125 levels, respectively. Results: e-CMR and e-CBR were observed in 34% and 38% of patients, respectively. At the end of NACT, an optimal pathologic response (pR) and optimal surgery with no residual tumor (R0) were achieved in 23 (46%) and 26 (52%) patients, respectively. E-CMR and e-CBR positive predictive value was 88% and 84% for pR and 88% and 89% for R0, respectively. Median progression-free survival and overall survival were 13.8 and 28.1 months, respectively. At multivariate analysis, e-CMR, but not e-CBR, showed an independent prognostic value with regard to both progression-free survival and overall survival.

Conclusions: e-CMR may predict pR and R0 surgery obtained at the end of NACT and identify patients a favorable long-term outcome.

Introduction
Two-thirds of patients with ovarian cancer have disease at presentation.1 Although an upfront surgical approach is the first treatment op-
tertiary life expectancy.\textsuperscript{2,3} Neoadjuvant chemotherapy (NACT), defined as the administration of chemotherapy before any surgery, is making headway as an alternative approach when upfront optimal cytoreduction cannot be achieved.\textsuperscript{6} The concept of NACT followed by interval debulking surgery (IDS) after 3 or more cycles has emerged and is now being widely used.\textsuperscript{7-12} However, a meta-analysis including a large series of heterogeneous phase I-II studies reported that NACT was associated with inferior overall survival compared to initial cytoreductive surgery and that survival was negatively affected with increasing number of chemotherapy cycles prior to interval surgery.\textsuperscript{19}

Recently, the 2 strategies were prospectively compared by the European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group\textsuperscript{20} in a large phase III randomized trial. The study showed that NACT followed by IDS was not inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian cancer. For patients who are candidates for NACT followed by IDS, the optimal chemotherapy duration has not yet been defined. At the moment, 2 duration models can be suggested: the first entails 2-3 cycles followed by IDS and subsequently 3-4 additional cycles of chemotherapy, and, the second entails 5-6 NACT cycles followed by a definitive surgical intervention.\textsuperscript{21}

The availability of a dynamic test that predicts optimal sensitivity to cytotoxic treatment could allow us to tailor the NACT duration in patients with advanced ovarian cancer (AOC) who were unsuited to upfront aggressive surgery. During NACT, the test changes should identify early those patients who have a high chemosensitive tumor and who could be selected for postponement of debulking surgery with a high likelihood of obtaining an optimal pathologic response (pR) and optimal surgery. CA-125 is currently the most widely used tumor marker for AOC, and serial level determinations during chemotherapy are useful for assessing treatment response.\textsuperscript{22,23} However, recent guidelines by an expert international panel have indicated that the prognostic information supplied by CA-125 up to the start of the third course of chemotherapy is not accurate enough to manage individual patients.\textsuperscript{25}

Several researchers have shown that fluoro-18 fluorodeoxyglucose positron emission tomography (FDG-PET) may play a role in predicting patient response and outcome to chemotherapy for many solid tumors\textsuperscript{24-28} and lymphomas.\textsuperscript{29} However, only a few small studies so far have investigated the usefulness of FDG-PET in predicting response to NACT and patient outcome in gynecologic cancer.\textsuperscript{30-33} Recently, we reported that patients with AOC who present normalization of maximum standardized uptake value (SUVmax) by FDG-PET after 3 cycles of NACT have a high likelihood of benefiting from 3 additional cycles to obtain a pR and to receive optimal surgery.\textsuperscript{24,28} The present explorative study, which is part of a larger study project named the “Arianna 2 project” has prospectively investigated the predictive and prognostic value of dual-time FDG-PET, at baseline and after 3 cycles of NACT, in patients who were not candidates for upfront debulking surgery by comparing that value with standard serum CA-125 monitoring.

Patients and Methods

Patients

Women with newly diagnosed histologically proven advanced FIGO (International Federation of Gynecology and Obstetrics) stage IIIc or IV ovarian or peritoneal carcinoma not suitable for optimal debulking surgery (postsurgical residual disease being zero) were eligible for this study. Histologic diagnosis and the feasibility of optimal resection were assessed at baseline by open laparoscopy. The inclusion criteria were age older than 18 years; histologic diagnosis of epithelial ovarian or peritoneal carcinoma; hematologic, renal, hepatic, and cardiac function adequate for platinum- and taxane-based chemotherapy. The exclusion criteria were Karnofsky Performance Status lower than 70, pregnancy, history of other malignancies (except for nonmelanoma skin cancer and in situ cervical carcinoma) in the past 5 years. Patients with contraindications for surgery or with uncontrolled diabetes were also excluded. Physical examination, computed tomography (CT), and trans-vaginal sonography were performed on all patients at baseline, every 3 cycles, and upon completion of NACT. The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Treatment

The patients received 6 cycles of carboplatin (AUC5) plus paclitaxel (175 mg/m\textsuperscript{2}), administered at 3-week intervals. All the patients were reassessed for surgery at the end of NACT, the target being to achieve no postsurgical residual disease (R0). A total anterior hysterectomy plus bilateral salpingo-oophorectomy, radical omentectomy, and appendectomy were the minimum resections performed in all optimally operated patients. Apart from that, removal of any metastatic peritoneal nodule, superficial liver resections, bowel resection, and splenectomy were performed whenever required. Lymphadenectomy was not routinely performed and was reserved for patients with no intraperitoneal residual disease and radiologically or clinically suspect lymph nodes.

FDG-PET Imaging

FDG-PET with CT was carried out at baseline, after 3 cycles, and at the end of NACT. FDG was produced in the radiopharmacy of the nuclear medicine unit of our hospital by standardized synthesis techniques. All the tests were performed by using a hybrid PET-CT scanner (Discovery LS; GE Medical System, Waukesha, WI). FDG-PET–CT was carried out by standard procedure.\textsuperscript{35} The patients had been in fasting condition for at least 6 hours, and the baseline blood glucose level was <120 mg/dl in all patients enrolled; FDG was administered intravenously at the dose of 5.3 MBq/kg; imaging acquisition started 60-70 minutes after radiotracer injection. To minimize bladder activity, the patients were asked to urinate just before image acquisition.

PET data were acquired for 4 minutes per bed position, then 35 images were reconstructed after CT data nonuniform attenuation correction; CT parameters were 120 kV, 60 mA, 0.8 seconds per tube rotation, 30-mm bed speed per gantry rotation (multislice technology enabling acquisition of 4–5-mm-thick slices per tube rotation). It was shown that CT does not release a high radiation dose onto the patient but is still efficient in distinguishing different tissues with good spatial resolution. CT images were subsequently merged with PET images to obtain an accurate localization of the FDG-PET findings. Regions of interest were drawn on the area of abnormal FDG uptake that corresponded to the tumor in the baseline scan and likewise after 3 cycles of NACT. The maximum standardized uptake value (SUVmax) was calculated by using the maximum activity val-
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uses within each region of interest on the transaxial slices with the highest radioactivity concentration normalized to the dose injected and the patient’s body weight according to the following formula: tissue concentration (MBq/mL) per injected dose (MBq) per body weight (g). All focal lesions with SUVmax higher than normal in surrounding tissue uptake (ie, >2) were considered pathologic according to revised RECIST (Response Evaluation Criteria In Solid Tumors) guideline (version 1.1).35

CA-125 Monitoring

Serum CA-125 was determined at baseline and at each chemotherapy course. CA-125 was measured at our institutional laboratory by a commercially available radioimmunoassay, which remained unchanged throughout the study period.

Assessment of Response

Histopathologic Response. In accordance with the literature on the response to primary chemotherapy in the breast36 and AOC,37-38 we considered a complete pR (pCR) to be the absence of cancer cells in surgical specimens, and minimal residual disease as a >90% partial response defined by the surgical evaluation with concomitant persistence of only small clusters or individual cancer cells in surgical specimens, as defined by the pathologist. Only patients with pCR and minimal residual disease were considered as pR, whereas all other cases were considered as nonresponding (NR).

Metabolic Response. SUVmax obtained after the third cycle of chemotherapy were compared with baseline SUVmax, which was considered the reference value upon which to obtain the percentage reduction (ΔSUVmax). Thus, an ΔSUVmax equal to 0% meant no change in tumor, SUVmax and ΔSUVmax equal to 100% meant that tumor SUVmax during treatment became equal to normal surrounding tissue uptake (values <2). This result was defined as early complete metabolic response (e-CMR). If multiple metastatic tumors were present in a patient, then the lesion with the lowest change in FDG uptake was used for analysis on the rationale that the metastatic tumor with the worst response would determine survival.

In a previous study, the threshold value of the ΔSUVmax, with highest positive predictive value (PPV) taken to detect pR was 100%.36 A specialist specifically trained in nuclear medicine (P.C. or S.F.) performed the analysis of PET data. Analysis of PETs was performed with no knowledge of the CT or other clinical test results.

Biochemical Response. Akin to FDG-PET, CA-125 after 3 cycles was compared with the baseline value and the percentage reduction was calculated (ΔCA-125). ΔCA-125 equal to 0% meant no change in serum CA-125 and ΔCA-125 equal to 100% meant that serum CA-125 was below the normal range (values <35 U/mL). Thus, early complete biochemical response (e-CBR) corresponded to normalization of the serum marker after 3 cycles.

Statistical Analysis

FDG-PET and CA-125 changes (ΔSUVmax and ΔCA-125) after 3 cycles of NACT were analyzed in correlation with histopathology specimens by subdividing the patients into pR or NR. We calculated the accuracy, sensitivity, specificity, and positive predictive value (PPV) and negative predictive value of a ΔSUVmax and ΔCA-125 threshold of 100% after the third cycle of NACT as successfully identifying pR. The same cutoff was used to analyze progression-free survival (PFS) and overall survival (OS). PFS was measured from the date of NACT initiation to the first documented date of progression, or death, whichever occurred first. OS was measured from the date of NACT initiation to the date of death. PFS and OS rates were estimated by means of the Kaplan-Meier method, and comparisons were made by means of the log-rank test. Multivariate analysis was performed according to the Cox proportional hazards model. All P values refer to the Wald test of Cox proportional hazards regression. Ordered categoric variables were coded as continuous variables. All tests were 2-sided and were performed at a 5% level of significance by using SPSS for Windows, version 13.0 (SPSS Inc, Chicago, IL).

Results

Fifty consecutive patients with AOC were enrolled from November 2004 to June 2008. The main characteristics of the patients are listed in Table 1. A baseline histologic diagnosis was obtained by open laparoscopy in all cases except 4 patients who underwent explorative laparotomy (2 cases) or transparietal biopsy (2 stage IV cases). Forty-eight (96%) patients completed 6 cycles of NACT, whereas 2 patients with stage IV disease stopped the treatment after 5 cycles due to disease progression and poor treatment compliance, respectively.

Histopathologic Response

Thirteen (26%) of 50 patients did not have surgery because of clinically progressive disease6 or clinical disease unchanged7 at the end of NACT, and were considered NR. Of 37 operated patients, 23 presented pR and 14 did not reach the criteria for pR definition and were classified as NR. Hence, of the total 50 patients, the pR rate was 46%, 5 (10%) and 18 (36%) patients reached pCR and minimal residual disease, respectively, whereas the NR rate was 54%.

The goal of no macroscopic residual tumor after surgery was achieved in 26 (52%) patients, including all 23 patients with pR and 3 additional patients who were NR who were converted to residual tumor equal to zero. Postsurgical residual disease ≤1 and >1 cm in the largest diameter was found in 7 and 4 patients, respectively.

Metabolic and Biochemical Response

Baseline SUVmax was abnormal in all patients (median, 11.5; range, 3.1-32). After 3 cycles, it significantly decreased (P = .003) and reached a median value of 3 (range, <2-21). Seventeen (34%) patients obtained e-CMR. All patients with pR had ΔSUVmax > 50% (median, 100%; range, 51%-100%). By contrast, the 27 patients classified as NR had ΔSUVmax values widely scattered between 0% and 100% (median, 33%). The predictive values in terms of identifying pR and R0 surgery by e-CMR are reported in Tables 2 and 3. For both endpoints, the PPV was equal to 88%.

Baseline CA-125 was abnormal in all but 1 patient (median, 628 U/mL; range, 29-6000 U/mL). After 3 cycles, it decreased significantly (P = .046) and reached a median value of 90 U/mL (range, 3-4882 U/mL), and e-CBR was obtained in 19 (38%) patients. All the patients with pR had ΔCA-125 > 75% (median, 100%; range, 76%-100%). Again, as with ΔSUVmax, the 27 patients classified as NR had ΔCA-125 values widely scattered between 0% and 100% (median, 77%). The predictive value in
terms of identifying pR and R0 surgery by e-CBR response is reported in Tables 2 and 3, and the PPV was 84% and 89%, respectively.

Simultaneous normalization of both tests (e-CMR and e-CBR) in the same patient occurred in 11 patients; in these patients, the PPV of pR or R0 surgery was 100%; in contrast, when normalization occurred in only 1 of the 2 tests, the PPV decreased to 77% and 81% for pR and postsurgical R0, respectively (Table 4). If lower thresholds are taken to define metabolic response (ie, ΔSUV = 55%, according to Avril et al33) and biochemical response (ie, ΔCA-125 = 75%), the PPV is lowered still further.

PFS and OS. After a median follow-up of 42 months (range, 22-67 months), 41 (82%) patients progressed, and 32 (64%) patients died. The median PFS was 13.8 months (range, 8.4-19.2 months), and the median OS was 28.1 months (range, 17.2-39.1 months). As expected, the pR and postsurgical residual tumor significantly affected PFS and OS; in particular, patients who were pR and pathologic NRs had a median PFS of 23.5 and 10.0 months, respectively (P = .001), and a median OS of 52.6 and 19.1 months, respectively (P = .001); the patients with no residual tumor, residual tumor, and those not operated on had a median PFS of 19.0, 11.8, and 6.2 months, respectively (P = .001), and a median OS of 52.6, 22.8, and 10.0 months, respectively (P = .001).

At monovariate analysis, the patients with e-CMR by FDG-PET had a statistically higher median PFS and OS than patients who did not reach CMR (median PFS 27.2 vs. 11.7 months, P = .006; and median OS 52.6 vs. 22.8 months; P = .007) (Figure 1). By contrast, patients with e-CBR had a statistically significant higher median PFS than those who did not reach normalization of CA-125 levels (21.9 vs. 11.6 months; P = .013), but the difference was not statistically significant as concerns OS (34.6 vs. 19.9 months; P = .073) (Figure 2). Multivariate analysis of presurgical potential prognostic factors (age, stage, baseline SUVmax, baseline CA-125, ΔSUV after 3 cycles, ΔCA-125 after 3 cycles) showed that only CMR significantly affects OS (Table 5).

Discussion

In this exploratory study, we prospectively examined the predictive and prognostic value of FDG-PET changes after 3 cycles of NACT in 50 patients with AOC, which compared these results with standard serum CA-125 monitoring. Both early complete metabolic and biochemical response were able to identify patients who achieved pR (ie, PPV, 88% and 88%) and R0 surgery (PPV, 84% and 89%) with a sufficiently high PPV. Thus, in our study, FDG-PET did not show any substantial superior predictive value over classic monitoring by CA-125. However, if simultaneous normalization of the 2 tests occurred, then the PPV became 100% for both pR and postsurgical R0. These results suggest that, by using both tests, there is a high likelihood of identifying patients with chemosensitive tumors in whom the prolonging of chemotherapy up to 6 cycles would not be deleterious but actually useful in improving the antitumor effect.

Hitherto, early CA-125 normalization has rarely been used, to our knowledge, as a way of selecting patients with chemosensitive tumors and prolonging the duration of NACT. Tate et al39 reported that the CA-125 regression rate during NACT was able to separate patients into those with a good prognosis of survival and those with a poor prognosis after subsequent radical surgery, but their CA-125 regression coefficient did not correlate with pCR and postsurgical residual tumor.

As concerns the prognostic significance of e-CMR and e-CBR, we observed that patients with normalization of SUVmax or CA-125 after 3 cycles had a statistically significant higher PFS than patients who did not achieve complete response. However, when the impact of e-CMR and e-CBR on OS was analyzed, the difference proved to be statistically significant only for e-CMR. In addition, of the presurgical factors (age, stage, baseline SUVmax, baseline CA-125, ΔSUV, ΔCA-125), only early SUVmax normalization proved to be an independent prognostic factor as concerns both PFS and OS at multivariate analysis.

Avril et al33 carried out the only study to our knowledge on sequential FDG-PET monitoring. Their study included 33 patients with AOC who had undergone 3 cycles of NACT before receiving IDS and after surgery an additional 3 cycles of chemotherapy.
our previous observations.36 Even with this difference in the metabolic response definition, our results substantially confirm the observation of Avril et al,32 that metabolic response by FDG-PET after 3 cycles of NACT is an independent prognostic factor. Likewise, we confirm that early CA-125 normalization has no independent prognostic value, in agreement with Avril et al32 and other researchers.18,23,41

What could the position of FDG-PET be in the treatment of patients with AOC? Analysis of the results of our study suggests that, when NACT is chosen as the primary treatment, FDG-PET has a potential role in the early identification of those patients who optimally respond to NACT and who will achieve optimal surgery after completion of NACT. It means that these patients, who form 34% of our entire series (17/50), might continue to receive chemotherapy for up to 6 cycles, even if they are already candidates for IDS after 3 cycles. By contrast, a partial metabolic response (ΔSUV < 50%) after 3 cycles could guide treatment toward immediate IDS and postpone further chemotherapy cycles. In this case, an alternative chemotherapy regimen might also be considered. This assertion is quite speculative, however, and should be supported by a specifically oriented study.

Analysis of our study results also suggests that early metabolic response by FDG-PET could be an independent prognostic factor in patients with AOC. The same observation has been made in other clinical settings, including lymphomas,42 and esophageal,43 head and neck,44 rectal,45 and cervical cancers.46 The cost of two PET scans (baseline and after 3 cycles of NACT) that are needed in the hypothetical proposed strategy is certainly not comparable to the cheaper
standard monitoring of CA 125. However, our study shows that, while not offering substantial advantages in predicting pathologic response, PET is clearly superior to CA 125 for prognostic information provided. This information could become important in the planning of subsequent treatments, follow-up modalities, and management of the process of informing and/or communicating with the patient.

An important limitation of our study is its small sample size. Our results on the utilization of FDG-PET to identify individual patients who are going to respond optimally to NACT, thus affecting the
subsequent treatment options, needs to be confirmed by a larger trial. Another possible criticism is that we assume, but do not prove, that, before SUVmax normalization after 3 cycles, a further 3 cycles are necessary to achieve an pR and R0 surgery.

Another observation could be the use of carboplatin dose AUC5 and not AUC6. We don’t know any study that demonstrated superiority of the higher dose of the platinum derivative and recently the combination of paclitaxel 175 mg/m² paclitaxel i.v. over 3 h, followed by carboplatin as an i.v. infusion over 30-60 min at a dose adjusted to produce an AUC of 5-6 mg·ml/min and to repeat this every 3 weeks for six cycles was confirmed to be the first-line chemotherapy for ovarian cancer by Fourth International Ovarian Cancer Consensus Conference, the Gynecologic Cancer InterGroup.47

In conclusion, this study indicates that patients with e-CMR after the third cycle of NACT have a high likelihood of obtaining an pR and achieving R0 surgery after a total of 6 cycles. In this subset of patients, dual-time FDG-PET-TC could lead to a therapeutic option other than the one recommended today and, at the same time, may provide important information on long-term patient outcome more accurately than is provided by CA123 monitoring. Given the exploratory character of this study and its small sample size, confirmatory investigations are required.

Clinical Practice Points

● Only one small study investigated the role of FDG-PET/TC during NACT for advanced ovarian cancer (AOC) prior to surgery. The metabolic response after 1 or 3 cycles of NACT was associated with better OS than patients who did not respond. This information, however, had no impact on decision making for individual patients because all had undergone surgery after the 3rd cycle of NACT.

● In our study including 50 AOC patients, the duration of NACT was predetermined for 6 cycles before definitive surgery and the metabolic response with FDG-PET-TC was evaluated after 3 cycles. The complete metabolic response occurred in 17 patients and in 15 of them (88%), an optimal pathological response and a R0 surgery has been reached. If changes in CA 125 serum levels were also considered, all patients showing simultaneously complete metabolic and biochemical response after 3 cycles, obtained an optimal pathological response and an optimal surgery. In addition the complete metabolic response, but not the biochemical one, identifies patients with a very good prognosis (median OS 52.6 months).

● A FDG-PET/TC scan might be added in the workup of AOC patients undergoing NACT and repeated after 3 cycles. The complete metabolic response could help to identify patients with highly chemosensitive tumours in which it would be justified to extend the duration of NACT before performing the surgery. Conversely, the intervention should be provided immediately in the other patients less responsive. Given the exploratory character of our study confirmatory investigations are required.

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Disclosure

The authors have stated that they have no conflicts of interest.

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