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Secondary cytoreductive surgery in patients with isolated platinum-resistant recurrent ovarian cancer: A retrospective analysis

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HIGHLIGHTS

- SCS prolongs time to progression up to 4th line of chemotherapy in isolated platinum-resistant recurrent ovarian cancer.
- SCS in independent predictor of longer post-relapse survival in isolated platinum-resistant relapsed ovarian cancer

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ABSTRACT

Objective. To analyze the impact of secondary cytoreductive surgery (SCS) on survival outcome in a retrospective series of isolated platinum-resistant recurrent ovarian cancer.

Methods. We evaluate a consecutive series of 268 ovarian cancer patients with platinum-resistant relapse. Isolated recurrence was defined as the presence of a single nodule, in a single anatomic site, and was observed in 27 cases (10.1%). In all women the presence of isolated relapse was assessed at radiological evaluation, and surgically confirmed in the SCS group.

Results. Among the 27 patients with isolated recurrence, 16 (59.3%) received chemotherapy alone, and 11 (40.7%) complete SCS followed by non-platinum based chemotherapy. No significant differences were observed in the distribution of baseline clinico-pathological characteristics, pattern of recurrent disease, duration of PFI, and type of salvage chemotherapy between the two groups. In the SCS group, 6 patients (54.5%) showed isolated peritoneal relapse and 5 women (45.4%) showed isolated lymph nodal recurrence, and were treated with peritonectomy and lymphadenectomy, according with site of relapse. Two post-operative complications (18.2%) occurred: asymptomatic lymphocele and groin wound dehiscence. SCS significantly prolonged median time to first progression (12 months vs 3 months; p-value = 0.016), median time to second progression (8 months vs 3 months; p-value = 0.037), and post-relapse survival (PRS) (32 months vs 8 months; p-value = 0.002). Residual tumor at 1st surgery ($X^2 = 5.690$; p-value = 0.017), duration of PFI ($X^2 = 5.401$; p-value = 0.020), and complete SCS ($X^2 = 4.250$; p-value = 0.039) retains independent prognostic role for PRS in multivariate analysis.

Conclusions. SCS prolongs PRS compared to chemotherapy alone in isolated platinum-resistant recurrent ovarian cancer.

Introduction

In the last decade, relevant advancements have been achieved in the management of recurrent ovarian cancer. In particular, even if randomized clinical trials are still lacking, meta-analysis of several retrospective series strongly suggests that secondary cytoreductive surgery (SCS) is able to prolong survival in women with platinum-sensitive recurrent disease [1–3]. In this context, the benefit of SCS seems particularly relevant in patients with isolated relapse [4,5]. In fact, the limited number of surgical procedures required in these women to achieve complete debulking is associated with a lower risk of major complications [4,5]. Furthermore, the introduction of minimally invasive approaches may further reduce SCS-related morbidities [6–8].

On the other hand, in women experiencing platinum-resistant relapse, regardless of the extension and pattern of disease presentation, salvage chemotherapy represents the only recommended therapeutic option [9]. However, recently published studies reported comparable survival outcomes in women with platinum-sensitive and resistant recurrent disease treated with SCS in combination with hyperthermic

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intraperitoneal chemotherapy (HIPEC). These data suggest that a room may exist for secondary debulking, even in women with chemoresistant relapse [10,11]. Among them, the subgroup of patients with isolated platinum-resistant disease may represent the clinical setting in whom SCS may ensure a survival benefit, without relevant morbidity.

For these reasons, we conducted a retrospective study aimed at evaluating both surgical complications, and post-relapse survival, in a consecutive series of ovarian cancer patients with isolated platinum-resistant relapse treated with SCS versus chemotherapy alone.

Patients and methods

Patients' demographics, surgical, post-operative and follow-up data were obtained from the electronic database of our Gynecologic Oncology Unit. All data were retrospectively collected and analyzed for the purpose of the present study, and all women gave a written informed consent for their data to be collected and analyzed for scientific purpose. The Institutional Review Board approved the study.

In all patients, the pattern of recurrence was recorded and classified as previously described [12]. In particular, isolated relapse was defined as the presence of a single nodule, in a single anatomic site at radiological examination. From 2006, PET/CT scan was introduced in the routine clinical practice of our Institution, and all women showing recurrent disease at conventional CT-scan were submitted to further evaluation with PET/CT scan.

In all cases, PET/CT (when available) and CT-scan findings were submitted to a rejoined evaluation, and the site of recurrent disease was defined in the context of multidisciplinary meetings.

As widely accepted, platinum free interval (PFI) was defined as the time elapsed between the end of primary platinum-based chemotherapy and first recurrence, and all women showing a PFI $\leq$6 months were classified as platinum resistant.

Study groups

Between January 1995 and December 2011, 268 consecutive platinum-resistant recurrent ovarian cancer patients were admitted at the Gynaecologic Oncology Unit of the Catholic University of Rome, and Campobasso. Two hundred forty-one cases (89.9%) experienced diffuse relapse involving multiple anatomic sites, while 27 women (10.1%) showed isolated relapse at radiologic evaluation, and were selected for final analysis. In 121 cases (45.1%) enrolled after 2006, the extension of disease was further confirmed at PET/CT scan evaluation.

Among this highly selected cohort of patients with isolated relapse, 11 cases (40.7%) were submitted to complete SCS, which confirmed the presence of isolated recurrence. On the other hand, the remaining 16 women (59.3%) received chemotherapy alone with non-platinum compounds. In the cohort of patients showing isolated relapse, 14 cases (51.8%) received PET/CT scan: 6 (54.5%) in the SCS group and 8 (50.0%) in the chemotherapy alone group. The existence in our series of two treatment groups (SCS and chemotherapy alone) is mainly due to differences in terms of surgical radicality over time and among our surgeons, rather than to a selection based on initial disease extension, particularly considering that all cases presented isolated relapse at radiological examination.

Treatment

Among the study population, 15 patients (55.6%) received primary debulking surgery (PDS) with optimal residual disease (residual tumor, RT $\leq$ 1 cm), followed by 6 courses of platinum based chemotherapy. The remaining 12 women (44.4%) were judged not suitable for optimal debulking at primary surgical exploration and were submitted to 3–4 cycles of neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) with no residual disease. After completion of primary treatment, all women were triaged to routine follow-up procedures, with clinical examination and CA125 dosage every 2/4 months and chest/abdominal/pelvic CT scan every 3 months during the first year, or anytime in presence of symptoms or elevation of CA-125 serum levels. All cases, both in the surgery and chemotherapy group, received second-line chemotherapy with non-platinum compounds including: pegylated liposomal doxorubicin, gemcitabine, weekly paclitaxel and other investigational agents until disease progression. In the surgery group, complete SCS was always obtained in all cases. Post-operative outcome and time to start second-line chemotherapy were recorded. In no case, SCS was preceded by neo-adjuvant chemotherapy.

Statistical analysis

All study patients were followed up to the second half of 2013. The duration of post-relapse survival (PRS) was defined as the time elapsed between diagnosis of recurrence and death or date of last follow-up. Time to progression (TTP-1) was defined as the time elapsed from beginning of 2nd line chemotherapy to progressive disease; TTP-2 was calculated from beginning of 3rd line chemotherapy to progressive disease, and TTP-3 from beginning of 4th line chemotherapy to progressive disease. Data are given as median and range. Categorical variables are reported as absolute values and percentage. Baseline differences between chemotherapy and surgery groups were analyzed using the Pearson Chi-square exact test and Kruskal–Wallis test, as appropriate. Medians and life tables were computed using the product limit estimate by Kaplan–Meier method [13], and the log-rank test was used to assess the statistical significance [14]. Cox's regression model with stepwise variable selection [15] was used to analyse the role of clinical–pathological parameters, and treatment details as prognostic factors for PRS. All statistical calculations were performed using the Statistical Package for Social Sciences (Version 17.0, SPSS Inc., Chicago, IL, USA).

Results

Between January 1997 and December 2011, 268 patients with first platinum-resistant relapse after primary treatment were admitted at our Institution, and 27 women (10.1%) showed radiological evidence of isolated recurrence. Sixteen patients (59.3%) were treated with salvage chemotherapy, while 11 women (40.7%) received SCS followed by non-platinum based chemotherapy. The clinico-pathological characteristics of the investigated series have been detailed in Table 1. The vast majority of patients showed high grade serous (70.4%), advanced (92.6%) ovarian cancer. Around half of women received their primary treatment in satellite centers, without statistically significant differences between the two groups (Table 1). All cases received primary surgical exploration, and PDS with optimal residual tumor (RT $\leq$ 1 cm) was achieved in 15 of 27 patients (55.6%). Twelve women (44.4%) were judged unresectable at surgical exploration and received NACT followed by complete IDS. Furthermore, as part of primary surgical treatment, 6 women (22.2%) were also submitted to pelvic and paraaortic lymphadenectomy due to the presence of bulky lymph-nodes. The radiological evaluation (including CT-scan examination) performed after completion of primary treatment was negative for evident disease in all cases.

After a median PFI of 3 months (range 1–6), thirteen cases (48.1%) experienced isolated intra-peritoneal relapse, and 14 women (51.9%) experienced isolated lymph nodal recurrence. No significant differences were observed in the distribution of baseline clinico-pathological characteristics, type of primary treatment (i.e. optimal PDS vs NACT-complete IDS), duration of PFI (SCS = 4 months vs chemotherapy alone = 3 months; p-value = 0.780), pattern of recurrence, and type of salvage chemotherapy between the surgery and chemotherapy groups (Table 1).

A detailed description of the clinico-pathological features, surgical procedures, and post-operative complications of women treated with