Measure of outcomes in epithelial ovarian cancer patients with platinum-sensitive relapse candidate for secondary cytoreductive surgery and/or chemotherapy in a real-world scenario.

A retrospective, multicenter study:

RECOVeR (RECurrence OVarian cancer Real life) study

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1.0 Background

The current standard of care for platinum-sensitive recurrent ovarian cancer (ROC) consists of a combination of secondary cytoreductive surgery (SCS) alongside the backbone of platinum-based chemotherapy on the main international guidelines [1,2].

Retrospective and meta-analysis data showed that complete gross resection (CGR) followed by adjuvant chemotherapy gives a prognostic benefit when compared to chemotherapy alone [3,4].

Considering randomized controlled trials (RCTs), the Desktop III trial using the AGO score as an eligibility criterion applied a rigorous patients' selection and was able to reveal a significant survival benefit, both in overall (OS) and progression-free survival (PFS), in the cytoreductive surgery arm when compared to the no surgery arm. Especially, the CGR was affirmed as the strongest positive prognostic factor with a 61.9 months of median OS in this specific subset of patients [5].

In line with these findings the SOC-1 trial, selecting patients with a combination of i-MODEL and PET-CT scan, found a significantly longer PFS in the SCS group while OS results still need to be accrued [6].

Conversely, the GOG 213 failed to demonstrate a significant advantage of surgery over platinum-based chemotherapy both in PFS and OS. In a subgroup analysis, however, CGR appeared to positively impact PFS [7].

Nevertheless, these three RCTs, although better clarifying the role of SCS, have left some open issues. The *BRCA* mutation status and the tumor's molecular characterization are contributing to reshape the definition of platinum-sensitivity, so that the correlation between SCS and the patient/tumor genetic profile is now more pressing than ever [8].

In fact, in the RCTs the *BRCA* analysis was not reported on GOG 213 and Desktop III, while only 75 patients out of the 357 enrolled were profiled for the germline *BRCA* mutation in the SOC-1 trial

[5,6,7]. In addition, in the past few years maintenance therapy with anti-angiogenic therapy (Bevacizumab) and Poly (ADP-ribose) Polymerase (PARP) inhibitors has overwhelmingly emerged as the standard of care [9,10,11,12], but only the 4.9% of patients in Desktop III and approximately the 10% in SOC-1 benefited from PARPi therapy, while the 84% of patients in GOG 213, the 23% in DESKTOP III and the 1% in SOC-1 received to bevacizumab maintenance therapy [5,6,7].

2.0 Rationale & Innovation

So far, there are no definitive evidence about the role of SCS versus chemotherapy alone when stratifying patients for mutational status or maintenance therapy.

Marchetti et al. in a retrospective series of 126 platinum sensitive ROC patients demonstrated a significantly longer post-recurrence survival (PRS) in *BRCA*wt patients who underwent complete surgical cytoreduction compared to the no surgery group while the same advantage was not shown in the *BRCA*mut class [13]. The same authors, demonstrated how SCS increased both time to first subsequent treatment (TFST) and PRS in *BRCA*mut platinum sensitive ROC patients candidate for olaparib maintenance after platinum-based chemotherapy [14].

There is no updated and shared guidance defining the "ideal" candidate for SCS, and both AGO score and iMODEL are based on clinical, biochemical or imaging features lacking the genetic and molecular substrate of the disease. Moreover, there is scant literature data on the real-life application of the SCS. Therefore, this study aims to better describe the characteristics of patients for which secondary surgery or sole chemotherapy is done in a real-life scenario.

3.0 Study Objectives and Endpoints

3.1 Primary Objective

To evaluate outcome of secondary cytoreductive surgery (SCS) and chemotherapy alone and the use of PARPi or Bevacizumab maintenance therapy in a real-world scenario of platinum sensitive ROC whose *BRCA*/HRD mutational status was available.

3.2 Primary Endpoint

To evaluate the oncological outcomes as measured by progression-free survival (PFS) and post-recurrence survival (PRS) in a matched series of ROC patients who underwent SCS or chemotherapy alone stratified by *BRCA* and/or HRD mutational and by PARPi or Bevacizumab maintenance therapy.

3.3 Secondary Objectives

- To describe the clinical/genetic characteristics of patients undergoing SCS or chemotherapy alone;
- To describe the characteristics of SCS, and its outcome in terms of complete gross resection (CGR);
- To describe intra- and postoperative complications occurring within 30 days from SCS and time to chemotherapy.

3.4 Secondary Endpoints

- All items considered in the following paragraph 5.0 will be summarized to illustrate clinical and genetic features and tabulated according to the treatment received (SCS or chemotherapy alone);
- The relative frequency of CGR will be calculated as the ratio between the number of CGR obtained and the total number of patients who underwent SCS and tabulated according to patients characteristics;
- Intra e post-operative complications will be graded according to Clavien-Dindo and CTCAE classifications.

4 Study Design

The proposed study will be a MITO (Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies) retrospective, multicenter, observational study aimed to evaluate survival and clinical outcomes of patients diagnosed with platinum-sensitive relapse of epithelial ovarian cancer who were tested for *BRCA* mutation and/or homologous recombination status using the HRD test in a real-world scenario. The coordinating center is the Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome.

The cases included in our analysis must be consecutive and comply with the following inclusion/exclusion criteria:

4.1 Inclusion criteria

- Patients over 18 years of age
- Initial diagnosis of moderate/high-grade ovarian, fallopian tube, or peritoneal cancer
- Diagnosis of first recurrent platinum-sensitive moderate/high-grade ovarian, fallopian tube, or peritoneal cancer
- Patients who underwent secondary cytoreductive surgery or chemotherapy alone
- Available *BRCA* and/or HRD testing

4.2 Exclusion criteria

- Patients judged unable to undergo SCS and/or chemotherapy
- Borderline ovarian tumors and non-epithelial ovarian cancer
- Low-grade/mucinous tumours
- Platinum-refractory or platinum-resistant tumor relapse (tumor recurrence within 3 or 6 months from the start of primary chemotherapy)

- Unavailable *BRCA* and/or HRD testing
- Unavailable follow-up data

5.0 Methods and Procedures

This will be a MITO multicenter collaborative study with the Fondazione Policlinico Universitario A. Gemelli, IRCCS of Rome as the coordinating center.

Only women with first recurrent epithelial ovarian/fallopian tube/peritoneal cancer and whose *BRCA*/ MyChoice HRD testing are available, will be included. Demographic characteristics and clinical data regarding histopathology and treatments will be extracted.

All the parameters in the AGO score or in the i-MODEL will be collected, namely, FIGO Stage at diagnosis, residual disease at first surgery, ECOG-performance status, presence/estimated volume of ascites at recurrence, platinum-free interval (PFI) and Ca125 level at recurrence. The recurrence is assessed by physical examination, CA125 serum levels, and/or radiologic evidence (computed tomography -CT-scan or FDG-PET/CT scan). Data from staging laparoscopy will be collected if available.

The following imaging data will be collected: site of recurrence (peritoneal; parenchymal; lymph-nodal; mixed), and type of recurrence (“single” site recurrence; "oligometastatic", i.e. up to three nodules; "multifocal/diffuse carcinomatosis", i.e. more than three nodules or wide peritoneal spread).

Residual disease at the end of SCS will be considered and complete cytoreduction is defined as no visible residual disease. The complexity of surgical procedures will be graded according to the surgical complexity score by Aletti et al. [15].

Perioperative complications and time to chemotherapy will be registered in the SCS group. In particular, data about intra- and postoperative complications occurring within 30 days from surgery will be retrieved, and surgical morbidity will be classified according to Clavien-Dindo and CTCAE classifications [16].

Patients should have received follow up according to clinical practice with a general clinical and gynecological examination, including six monthly transvaginal ultrasonography, CA125 serum levels, CT scan, for the first three years after second-line chemotherapy.

Survival analysis will be performed in a propensity-matched population. PFS will be calculated from the date of first recurrence diagnosis to the date of second recurrence or death, whichever came first. PRS will be calculated from the date of first recurrence diagnosis to the date of death or censored at the last follow up.

6.0 Statistical Analysis

Given the retrospective nature of the study and the purely descriptive primary objective, no formal hypotheses are considered and we estimate to reach a sample size of about 400 patients. A first analysis will be made on the entire series of consecutive patients fulfilling the selection criteria.

Continuous variables will be tested for normality assumptions using the Kolmogorov-Smirnov test and reported as median, range and interquartile range if the normality is not respected; if it is means and standard deviations will be calculated. Categorical variables will be summarized as absolute frequencies and percentages. The distribution of categorical variables between groups will be compared with chi-square test or Fisher's exact test according to the expected minimum cell frequencies while differences in quantitative items between groups will be analysed with the Student's t-test or Mann-Whitney test, as appropriate. A logistic regression model will be applied to determine the effect of independent clinic-pathological variables on the choice of performing a SCS or not in a real-world scenario.

Because of the non-randomized nature of the study design and the potential allocation biases rising from the retrospective comparison between the groups (SCS vs. chemotherapy alone), a propensity score-matched analysis will be applied to balance clinical factors which could predict receiving one or the other treatment.

Matching will be based on the variables resulting associated with the treatments at a multivariable approach.

Survival curves will be calculated using the Kaplan–Meier method. Log-rank test will be used to compare survival between groups. Multivariable survival analysis will be performed with Cox regression model and will include all variables with $p \leq 0.10$ in univariate analysis. All p-values will be 2 sided and a $p < 0.05$ will be considered statistically significant. No adjustment for multiple comparisons will be made and results will be considered in an hypotheses generating approach.

Statistical analysis will be carried out using IBM Statistical Package for Social Science software, Version 25, and R-Studio 0.98.1091 software.

7.0 Ethical Implications and Risks & Benefits for Patients

The study will be conducted following the "Declaration of Helsinki" and according to the regulations in force in the Lazio region, Italy. Retrospective analysis of data from patients who meet the inclusion and exclusion criteria of this study does not pose any risk to the patients themselves. These have already received the appropriate surgical and medical treatment for their disease per current international guidelines. The benefits of our analysis potentially concern all future patients with recurrent epithelial ovarian cancer. We aim to move towards a more personalized treatment thanks to the integration of patient's molecular characteristics and the integration of maintenance therapy.

8.0 References

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