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Adjuvant chemotherapy does not improve disease-free survival in FIGO stage IC ovarian granulosa cell tumors: The MITO-9 study

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HIGHLIGHTS

- No clear evidence of benefit from adjuvant therapy in stage I patients has been demonstrated.
- Surgical staging seems to be an independent prognostic factor.
- In our study no difference in DFS between stage IC patients administered adjuvant therapy versus no treatment.

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ABSTRACT

Objective. Evidence-based management of granulosa cell tumors of the ovary (GCT) has been not yet standardized: surgery, including fertility-sparing procedures for young women, has been traditionally the standard treatment; on the other hand, chemotherapy has been used for treatment of advanced and/or recurrent disease. However, very limited experience, has been selectively focused on the role of adjuvant chemotherapy in stage IC patients. The objective of this retrospective study was to assess the efficacy of first line postoperative chemotherapy in patients with stage IC treated at the Italian Centers involved in the MITO (Multicenter Italian Trials in Ovarian cancer) Group.

Patients and methods. A retrospective multi-institutional review of patients with GCT of the ovary at FIGO stage IC treated or referred to MITO centers was conducted. Surgical outcome, pathological findings and follow-up data were analysed. Kaplan–Meier and Cox proportional hazards analyses were used to determine the predictors factors for disease free survival.

Results. A total of 40 patients with primary GCT of the ovary at FIGO stage IC were identified. The median follow-up period was 96 months (range 7–300). At multivariate analysis, surgical treatment outside MITO centers and incomplete surgical staging were independent poor prognostic indicators for recurrence; adjuvant chemotherapy did not retain significant predictive value for recurrence.

Conclusions. This study raises the question about the value of adjuvant chemotherapy in stage IC GCT: a comprehensive evaluation of a larger series is urgently needed in order to characterize stage IC substages who can be spared treatment toxicity.

Abbreviations: GCTs, granulosa cell tumors; BEP, bleomycin, etoposide and cisplatin; FIGO, International Federation of Gynecology and Obstetrics; MITO, Multicenter Italian Trials in Ovarian cancer; DFS, disease free survival; OS, overall survival; TTR1, time to first recurrence; TTR2, time to second recurrence; TT3, time to third recurrence; yr, year.

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1. Introduction

Granulosa cell tumors (GCTs) are rare gynecological malignancies which arise from the sex-cord stromal cells of the ovary, and are characterized by an indolent behaviour with relapse occurring many years after initial diagnosis and treatment [1,2].

Surgery, including fertility-sparing procedures for young women, currently represents the standard treatment of this disease [3,4]. Chemotherapy with bleomycin, etoposide and cisplatin (BEP) combination has been traditionally used for treatment of advanced and/or recurrent disease not amenable to be optimally managed by surgery [5]. As far as the adjuvant setting is concerned, the role of chemotherapy and radiotherapy still remains controversial [6–8]; given the rarity of these neoplasms and their typical indolent behaviour [9,10], it is unlikely that a randomized study focused on adjuvant versus no adjuvant chemotherapy in early stage disease, would be ever carried out. As far as the available data are concerned, BEP combination is administered in the adjuvant setting [6,7]; however, the combination carboplatin/paclitaxel has become more and more accepted as a less toxic alternative to BEP [8]; in this context, the ongoing Phase II randomized GOG0264 is recruiting patients with advanced or recurrent sex cord-ovarian stromal tumor, randomized to BEP versus carboplatin/paclitaxel with the primary outcome measure represented by the 10-year progression-free survival (www.clinicaltrials.gov).

As a result, practice is highly variable, and despite some scientific Societies and the National Comprehensive Cancer Network guidelines suggest administration of adjuvant treatment for high risk stage I patients, definition of "high risk" disease remains to be established [11–13]. The lack of clear evidence of benefit from adjuvant therapy, and the risk of chemotherapy-related adverse effects and toxicities [14,15], make treatment decisions difficult. In particular, among stage I, earlier lines of evidence as well as more recent long term follow up studies have reported higher relapse rate and shorter disease-free survival in stage IC compared to stage IA disease [6,9,10,16]. These observations have resulted in considering ruptured stage IC with high mitotic index as high risk GCTs, thus advocating the need of adjuvant chemotherapy administration in this subset of disease. However, very limited experience, if any, has been selectively focused on the role of adjuvant chemotherapy in stage IC patients [6,10,16,17]; moreover, the adoption of the revised FIGO staging of epithelial ovarian cancer also for staging of GCTs opens new perspectives for a better definition of prognosis of stage IC disease, which now encompasses three different substages according to increasing risk of relapse (stage IC1 = intra-operative cyst rupture; stage IC2 = pre-operative cyst rupture/presence of tumor on ovarian surface; stage IC3 = malignant cells in the peritoneal washing) [18].

The objective of this retrospective study was to assess the efficacy of first line postoperative chemotherapy in patients with stage IC GCTs treated at the Italian Centers involved in the MITO (Multicenter Italian Trials in Ovarian cancer) Group.

2. Patients and methods

The Multicenter Italian Trials in Ovarian Cancer (MITO)-9 is an Italian multicenter retrospective study aiming at describing clinical characteristics and treatment strategies of rare ovarian tumors.

A series of 191 patients diagnosed with primary GCTs of the ovary were treated, or referred after primary treatment, with MITO centers from 1965 to 2008. Of these, 40 patients were diagnosed at FIGO stage IC GCTs.

Institutional Review Board approved the study. Patient data were recorded in a database that included information about age at diagnosis, clinical presentation, stage, histology, type of surgery, intra-operative findings and surgical outcome, adjuvant chemotherapy, relapse features (site and number of lesions), and treatment, as well as adequately long follow-up.

Surgery was the first treatment for all patients: fertility sparing surgery, defined as the preservation of the uterus and one ovary, was performed in young patients desiring to preserve fertility, but only in case of disease confined to one ovary.

Radical surgery, including total abdominal hysterectomy, bilateral salpingo-oophorectomy and complete tumor debulking, was the standard procedure if fertility was not an issue.

Staging was considered complete when including peritoneal washing, multiple peritoneal biopsies, omental biopsy and biopsy of any suspicious area. In case of conservative surgery, endometrial biopsy had to be carried out to rule out a concomitant uterine disease.

We used the new staging system for GCT that is the same applied for epithelial ovarian cancer; reclassification of cases according to the new staging system reports (International Federation of Gynecology and Obstetrics (FIGO) staging system, FIGO Committee on Gynecologic Oncology, 2014) [18] has been carried out by the Investigators involved in the study based on pathology reports. Specific indication for administration of adjuvant chemotherapy in stage IC GCTs are not standardized among MITO centers; therefore, the decision to administer adjuvant chemotherapy in this setting of patients was made by the attending physicians of each center after discussion with patients.

All patients were incorporated in a prolonged surveillance program with periodic clinical, serologic and radiologic follow-up at MITO centers, given the tendency of these tumors to recur several years after the initial diagnosis.

Written informed consent for anonymous publication of disease-related information is routinely obtained at MITO Institutions during the patient interview preceding surgical or chemotherapy treatment.

2.1. Statistical analysis

Descriptive statistics were used to characterize the patient population. The association between clinico-pathologic characteristics and administration of adjuvant treatment was evaluated by Fisher's exact test for proportion.

The primary objective of this study was to assess the role of adjuvant therapy on disease free survival (DFS), and overall survival (OS). DFS was defined as the time period from the date of initial diagnosis to the first observation of recurrence. OS was defined as the time from the date of initial diagnosis to the date of death of any cause.

Survival curves were calculated using the Kaplan–Meier method, and the log-rank test was used to test the statistical significance. Cox's regression model with stepwise variable selection was used to analyze in univariate and multivariate analysis the role of clinico-pathological parameters as prognostic factors for DFS. Other endpoints selected for analysis included time to first recurrence (TTR1), time to second recurrence (TTR2), and time to third recurrence (TTR3).

TTR1 was defined as the time interval from histologic confirmation of diagnosis to documentation of first recurrence; TTR2 was defined as the time interval from the start of whichever therapy of first recurrence to the documentation of second recurrence; TTR3 was defined as the time interval from the start of therapy of second recurrence to the documentation of third recurrence.

Statistical analysis was conducted using Statistical Package version 18.0 for Windows (SPSS, Inc., Chicago, Illinois). Differences were considered statistically significant at p value < 0.05.

3. Results

Clinical features and treatment details of our patients are summarized in Table 1: median age at diagnosis was 47.6 years (range: 25–76).

Presence of pelvic mass and/or abdominal distension and abdominal pain were common presenting symptoms seen in 45% and 30% of cases, respectively (Table 1). Intra-operative surgical spill (stage IC1) was documented in 16 cases (40%), while preoperative cyst rupture or presence of tumor on ovarian surface (stage IC2) were found in 10 (25.0%), and in

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