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Is carboplatin-based chemotherapy as effective as cisplatin-based chemotherapy in the treatment of advanced-stage dysgerminoma in children, adolescents and young adults?

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HIGHLIGHTS

- Patients with pure ovarian dysgerminoma have excellent survival outcomes regardless of the age or stage at diagnosis.
- Fertility-sparing surgery should be encouraged in the frontline management of dysgerminoma, when feasible.
- In this analysis, carboplatin is not shown to be inferior to cisplatin-based chemotherapy in the treatment of dysgerminoma.

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ABSTRACT

Objective. Dysgerminoma is the most common malignant ovarian germ cell tumor (GCT) with peak incidence during adolescence and young adulthood. Current standard of care for patients with disease that has spread outside of the ovary (advanced-stage) utilizes platin-based chemotherapy regimens. The study objective was to compare clinical outcomes between platin-based (carboplatin versus cisplatin) strategies across all age groups (children < 11 years (y), adolescents = 11–25 y and young adult women > 25 y) for advanced-stage dysgerminoma.

Abbreviations: AYA, adolescent and young adult; GCT, germ cell tumor; MOGCT, malignant ovarian germ cell tumor; MaGIC, Malignant Germ Cell Tumor International Consortium; U.S., United States; U.K., United Kingdom; CTOs, Clinical Trial Organizations; COG, United States, Canada and Australia, Children's Oncology Group; UKCCSG, United Kingdom Children's Cancer Study Group; CCLG, United Kingdom, Children's Cancer and Leukaemia Group; GOG, United States, Gynecologic Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IGCCCG, International Germ Cell Cancer Collaborative Group; BEP, cisplatin, etoposide, bleomycin once weekly; PEb or pediatric BEP, cisplatin, etoposide, bleomycin once per cycle; HD-PEb, high dose cisplatin, etoposide, bleomycin once per cycle; JEb, carboplatin, etoposide, bleomycin once per cycle; JE, carboplatin, etoposide; AFP, alpha-fetoprotein; β-hCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase; EFS, event-free survival; OS, overall survival; y, years; vs., versus; SMN, second malignant neoplasm.

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Malignant germ cell tumor international consortium (MaGIC)

Methods. The Malignant Germ Cell Tumor International Consortium (MaGIC) pooled data from six GCT trials (3 = pediatric, 3 = adult) conducted internationally by pediatric and gynecologic oncology clinical trial organizations (CTOs) between 1983 and 2009. Newly diagnosed patients, with advanced-stage (FIGO IC–IV) dysgerminoma, who received either carboplatin- or cisplatin-based chemotherapy were eligible for analysis.

Results. 126 eligible patients were identified; 56 patients (38 = pediatric, 18 = adult) received carboplatin-based and 70 patients (50 = pediatric, 20 = adult) received cisplatin-based chemotherapy. Mean age was 20 y (range = 6–46 y). The median follow-up was 10.3 y (range = 0.17–21.7 y). The five-year event-free survival (EFS_5) and overall survival (OS_5) was 0.94 (95%CI, 0.88–0.97) and 0.96 (95%CI, 0.91–0.99) respectively. Survival outcomes were comparable between carboplatin-(EFS_5 = 0.96 (95%CI, 0.85–0.99), OS_5 = 0.96 (95%CI, 0.85–0.99)) and cisplatin-(EFS_5 = 0.93 (95%CI, 0.83–0.97), OS_5 = 0.96 (95%CI, 0.87–0.99)) based regimens. Across three age groups, comparison of the EFS_5 (<11 y = 0.1, 11–25 y = 0.91 (95%CI, 0.82–0.96), >25 y = 0.97 (95%CI, 0.81–0.99)) and OS_5 (<11 y = 0.1, 11–25 y = 0.95 (95%CI, 0.87–0.99), >25 y = 0.97 (95%CI, 0.81–0.99)) did not demonstrate any statistically significant differences in outcomes.

Conclusions. Patients diagnosed with dysgerminoma have an excellent OS, across all ages, even in the context of metastatic disease. Data from three large CTOs supports the investigation of carboplatin-based regimens in the frontline treatment of all patients with advanced-stage dysgerminoma to minimize treatment-related toxicities.

1. Introduction

Dysgerminoma is the most common histological subtype of all the malignant ovarian germ cell tumors (MOGCT). Although it can occur during childhood, it is most frequent during adolescence and young adulthood, with a peak incidence at 15–19 years of age [1]. Dysgerminoma is exquisitely radio- and chemo-sensitive. Although radiation therapy is effective, it is no longer recommended as frontline therapy due to the risk of second malignant neoplasm (SMN), premature ovarian failure, and a significant impact on fertility despite contralateral ovarian shielding [2].

The current standard of care for advanced-stage dysgerminoma, i.e. disease that has spread outside of the ovary, is post-operative adjuvant chemotherapy with either carboplatin or cisplatin, combined with etoposide and bleomycin. Though the advent of cisplatin-based chemotherapy in the treatment of advanced-stage dysgerminoma has led to excellent cure rates, its success has been offset by the emergence of considerable long-term treatment-related morbidity and mortality. The late effects of cisplatin-based chemotherapy have been widely reported in testicular seminoma, the histological counterpart of ovarian dysgerminoma [3]. Two of the most concerning late effects of cisplatin for young long-term survivors, are the two-fold risk of cardiovascular disease and SMN [4,5]. Other significant late effects include the risk of ototoxicity, nephrotoxicity, neurotoxicity and gonadotoxicity leading to premature ovarian failure or infertility [4–6].

To address concerns related to some of the cisplatin-induced toxicities, over the last 25 years, the United Kingdom Children's Cancer Study Group (UKCCSG) has utilized a carboplatin-based strategy in clinical trial design in an attempt to specifically minimize the acute side effects of ototoxicity and nephrotoxicity [7]. However, a comparison of the efficacy of carboplatin-based regimens with the more conventional cisplatin-based regimens remains unexamined. Given the anticipated excellent survival outcomes, even in the context of metastatic disease, there is a concerted drive to directing future research strategies towards improving the quality of survival by tailoring therapy to minimize treatment-related toxicities.

Dysgerminoma is a rare disease, and as such, has been historically difficult to study. Its study has been further hampered by the fragmentation of care between two different oncologic subspecialties: pediatric oncology and gynecologic oncology. The differences in staging systems, inclusion criteria for enrollment on clinical trials, and treatment regimens across various pediatric and adult clinical trials, nationally and internationally, have complicated the interpretation of clinical trial results. To overcome these limitations, the Malignant Germ Cell Tumor International Consortium (MaGIC), comprising members of the Children's Oncology Group (COG; United States (U.S.), Canada and Australia), Gynecologic Oncology Group (GOG; U.S.) and UKCCSG later renamed as Children's Cancer and Leukaemia Group (CCLG; United Kingdom (U.K.)), merged 25 years of clinical trial data on pediatric, adolescent and young adult (AYA) germ cell tumors (GCTs). Although some trials used a cisplatin-based regimen, and other trials used a carboplatin-based regimen, the pooling of the clinical trial data was justified by a comparison of previously published results that indicated similar outcomes [7–17]. We conducted an analysis of the MaGIC database to assess whether a difference in outcomes could be detected between patients treated with cisplatin-based versus (vs.) carboplatin-based regimens, controlling for other known risk factors including age.

2. Methods

2.1. Patient population

Patients in the MaGIC database with newly diagnosed, pure ovarian dysgerminoma with advanced-stage disease were included in the analysis (n = 126). Patients with mixed GCT that included dysgerminoma were excluded. All ages were eligible for the analysis; children <11 years, adolescents 11–25 years and young adult women >25 years. Chemo-naïve patients with stage I disease, who recurred on active surveillance, and were subsequently treated with chemotherapy (n = 2) were included in the analysis. Advanced-stage disease was defined as either COG/CCLG stage II–IV (Appendix S2) or International Federation of Gynecology and Obstetrics (FIGO) stage IC–IV (Appendix S3) [18]. Although COG/CCLG stages I and IV are comparable to FIGO stages IA/IB and IV respectively; COG/CCLG stages II-III are not comparable to FIGO stages IC, II, or III (Appendix S2 and S3). Due to irreconcilable differences in staging systems within each cooperative group, patients with staging based on COG/CCLG and FIGO were analyzed separately.

Of the 126 patients included in the analysis, three patients had pre-operative alpha-fetoprotein (AFP) levels at diagnosis that exceeded the expected level for pure ovarian dysgerminoma (AFP = 3509, AFP = 9922, AFP = 10,800 ng/mL). We reviewed the pathologic reports and confirmed that each patient was recorded as a pure ovarian dysgerminoma. We performed a sensitivity analysis that excluded these 3 patients to examine the impact on outcome.

2.2. Clinical trials

Six (GC1, GC2, INT-0097, GOG 0078, GOG 0090, GOG 0116) of the ten clinical trials in the MaGIC data set included patients with dysgerminoma; details of each trial are summarized in Table 1 and Appendix S1. The pathology of all patients enrolled on each of these clinical trials underwent a central pathologic review. One adult trial (GOG 0116) tested "JE" = carboplatin 400 mg/m^2/cycle, and etoposide 360 mg/m^2/cycle, administered every 28 days [11]. In CCLG, (GC2)

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