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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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Abbreviations:

1. Adolescent and Young Adult (AYA**)**
2. Germ Cell Tumor (GCT)
3. Malignant Ovarian Germ Cell Tumor (MOGCT)
4. Malignant Germ Cell Tumor International Consortium (MaGIC)
5. United States (U.S.)
6. United Kingdom (U.K.)
7. Clinical Trial Organizations (CTOs)
8. Children's Oncology Group (COG, United States, Canada and Australia)
9. United Kingdom Children's Cancer Study Group (UKCCSG)
10. Children's Cancer and Leukaemia Group (CCLG, United Kingdom)
11. Gynecologic Oncology Group (GOG, United States)
12. International Federation of Gynecology and Obstetrics (FIGO)
13. International Germ Cell Cancer Collaborative Group (IGCCCG)
14. Cisplatin, Etoposide, Bleomycin once weekly (BEP)

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RESEARCH ARTICLES.
Articles should represent original and in-depth studies involving any aspect of clinical or laboratory investigation.
Abstract: structured under headings (Background, Procedure, Results, and Conclusions. Length should be 250 words or less.
Length: 4000-word maximum (excludes title page, Abstract, References, Tables, Figures, and Legends.)
References: 40 or fewer
Figures/Tables: The number combined should be not be greater than 6 (excluding supplemental material). Tables and figures should not simply repeat information in the text.
Supplementary Material: No Limit.

15. Cisplatin, Etoposide, Bleomycin once per cycle (PEb or pediatric BEP)
16. High Dose Cisplatin, Etoposide, Bleomycin once per cycle (HD-PEb)
17. Carboplatin, Etoposide, Bleomycin once per cycle (JEb)
18. Carboplatin, Etoposide (JE)
19. Alpha-fetoprotein (AFP)
20. Beta-human chorionic gonadotropin (β-hCG)
21. Lactate Dehydrogenase (LDH)
22. Event-free survival (EFS)
23. Overall survival (OS)
24. Years (y)
25. Versus (vs.)
26. Second malignant neoplasm (SMN)

Abstract

Background:

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, adolescents and young adult women) for advanced-stage dysgerminoma.

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 1983-2009. 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 years(y) (range=6-46y). The median follow-up was 10.3y (range=0.17-21.7y). The five-year event-free survival (EFS_5) and overall survival (OS_5) was 94.1% (95%CI,0.88-0.97) and 96.6% (95%CI,0.91-0.99) respectively. Survival outcomes were comparable between carboplatin-(EFS_5=96.0% (95%CI,0.85-0.99), OS_5=96.0% (95%CI,0.85-0.99)) and cisplatin-(EFS_5=93.2% (95%CI,0.83-0.97)), OS_5=96.6% (95%CI,0.87-0.99)) based regimens. Across three age groups, comparison of

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the EFS_5 (<11y=100%, 11-25y=91.4% (95%CI,0.82-0.96), >25y=97.1% (95%CI,0.81-0.99)) and OS_5 (<11y=100%, 11-25y=95.7% (95%CI,0.87-0.99), >25y=97.1% (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.

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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.

Methods

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. 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 2) or International Federation of Gynecology and Obstetrics (FIGO) stage IC-IV (Appendix 3).[18] 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=10800 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.

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 1. 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) tested "JEb" = carboplatin 600 mg/m^2/cycle (area under the curve (AUC), 7.9 mg/mL per minute), etoposide 360 mg/m^2/cycle, and bleomycin 15 Units/m^2/cycle, administered every 21 days.[7] In GOG 0078, the adult "BEP" regimen consisted of cisplatin 100 mg/m^2/cycle, etoposide 500 mg/m^2/cycle, and bleomycin 30 Units weekly (Days 1, 8, 15), administered every 21 days.[10] In GOG 0090, the adult "BEP" regimen consisted of cisplatin 100 mg/m^2/cycle, etoposide 500 mg/m^2/cycle, and bleomycin 60 Units/m^2/cycle (20 Units/m^2/dose on Days 1, 8, 15), administered every 21 days.[9] In CCLG, the "PEb" (pediatric BEP) regimen (GC1) consisted of cisplatin 100 mg/m^2/cycle, etoposide 360 mg/m^2/cycle, and bleomycin 15 Units/m^2/cycle, administered every 21 days.[8] In COG, the "PEb" (pediatric BEP) regimen (INT-0097, Arm II) consisted of cisplatin 100 mg/m^2/cycle, etoposide 500 mg/m^2/cycle, and bleomycin 15 Units/m^2/cycle, administered every 21 days.[13, 15] The COG trial (INT-0097, Arm I) tested high-dose cisplatin 200 mg/m^2/cycle, etoposide 500 mg/m^2/cycle, and bleomycin 15 Units/m^2/cycle, administered every 21 days.[13, 15]

Statistical Analysis

Event-free survival (EFS) was defined as the time from date of enrollment on study; to the date of disease relapse or progression, diagnosis of a SMN, death, or last follow-up, whichever occurred first. A patient without an event was censored at last follow-up. For each of the two patients who relapsed during observation after initial complete resection, EFS was defined as the time from the date chemotherapy was first administered to the date of disease relapse or progression, diagnosis of a SMN, death, or last follow-up, whichever occurred first.

Overall Survival (OS) was defined as the time from date of enrollment on study; to the date of death, or last follow-up, whichever occurred first. Patients who died, regardless of the cause, were considered to have experienced an event; otherwise, the patient was censored at last follow-up. For each of the two patients who relapsed during observation after initial complete resection, OS was defined as the date chemotherapy was first administered; to the date of death, or last follow-up, whichever occurred first. Survivor functions for EFS and OS were estimated using the Kaplan-Meier method.[19]

The patient characteristics considered in the exploratory analyses described below were calculated at the relevant date (i.e. date of enrollment on study or date chemotherapy was first administered) for each patient. Ninety-five percent confidence intervals (95% CI) for the Kaplan-Meier estimates at specified time points were calculated with the complementary log-log transformation.[20] The effects of various factors (age at

diagnosis, stage at diagnosis, AFP at diagnosis, year treated and type of treatment received) on the risk for experiencing an event or death were estimated with relative risk regression.[20] Possible association between risk of EFS event and prognostic factor was assessed using the two-sided log rank test. Characteristics associated with p-values ≤ 0.05 were considered significantly associated with the risk of an EFS event. All analyses were conducted with Stata 13.1 (StataCorp, College Station, Texas).

Results

Patient Characteristics

The MaGIC database identified 126 eligible patients with newly diagnosed, COG/CCLG stage II-IV or FIGO stage IC-IV, pure ovarian dysgerminoma treated with platin-based chemotherapy (Figure 1). Fifty-six patients (38=pediatric, 18=adult) received carboplatin-based and 70 patients (50=pediatric, 20=adult) received cisplatin-based chemotherapy regimen. The mean age in the cohort was 20 years (y) (range, 6-46y). The majority of the patients included in the analysis were between the age of 11-25y (57.1%); 12.7% were <11y of age and 30.2% were over the age of 25y. The age distribution was comparable between the COG (median 12y, range=6-16y) and CCLG (median 13y, range=7-16y) trials. As expected, the median age was higher in the GOG trials (median 25y, range=7-46y). The distribution of age was similar between those treated with carboplatin- vs. cisplatin-based regimens. The mean pre-operative AFP and beta-human chorionic gonadotropin (β-hCG) at diagnosis were 597 ± 2306.5 ng/mL (range, 0-10,800 ng/mL) and 6.4 ± 2 IU/L (1-9 IU/L) respectively. The mean lactate dehydrogenase (LDH) at diagnosis was 3260 ± 6772 units/L (range, 24-27,447 units/L). Laterality was

not reported in 76 (60.3%) patients. Of the remaining patients, 48 (38.1%) had unilateral disease and 2 (1.6%) had bilateral disease. Staging distribution was as follows; COG/CCLG stage II (3.2%), III (30.9%), IV (5.5%), FIGO stage IC (11.9%), II (5.6%), III (31%), IV (4%). Staging information was not reported in 10 (7.9%) patients. Patient characteristics are summarized in Table 2.

Prognostic Parameters

Risk of event was evaluated in a univariate analysis in Appendix 4. The comparisons of risk of an EFS event and the risk of death across the 25 years did not demonstrate significant differences in our patient cohort. Neither age (p-value=0.27) nor treatment regimen (p-value=0.42) were significantly related to outcome. Similarly, AFP at diagnosis (p-value=0.87) and era of treatment (p-value=0.87) did not correlate with outcomes. The only variable that was significant was stage; however, there were only five patients with FIGO stage IV disease, hence, the confidence intervals are very broad. The small number of EFS and OS events observed in this cohort precluded the evaluation of any associations between risk for an EFS event and patient characteristics in a multivariate analysis.

Outcomes

The five-year event-free survival (EFS_5) and overall survival (OS_5) for all patients who received chemotherapy (n=126) was 94.1% (95% CI, 0.88 to 0.97) and 96.6% (95% CI, 0.91 to 0.99) respectively (Figure 2). Survival probabilities by age, stage and treatment regimen are summarized in Table 3. Across three age groups, the comparison of the EFS_5

(<11y=100%, 11-25y=91.4% (95% CI, 0.82 to 0.96), >25y=97.1% (95% CI, 0.81 to 0.99)) and OS_5 (<11y=100%, 11-25y=95.7% (95% CI, 0.87 to 0.99), >25y=97.1% (95% CI, 0.81 to 0.99)) did not demonstrate any statistically significant differences in outcomes.

Both the EFS_5 and OS_5 for all patients with COG/CCLG stage II-IV disease was 93.8% (95% CI, 0.82 to 0.98). The EFS_5 and OS_5 for all patients with FIGO stage IC-IV was 95.0% (95% CI, 0.85 to 0.98) and 98.2% (95% CI, 0.88 to 0.99) respectively. Excluding the 10 patients in whom staging information was not reported, an analysis of children, adolescents and young adults (n=116) was conducted to compare locoregionally advanced-stage disease without metastatic disease (COG/CCLG stage II-III or FIGO stage IC-III) vs. advanced-stage disease with metastatic disease (COG/CCLG stage IV or FIGO stage IV). The EFS_5 (COG/CCLG II-III=92.9% (95% CI, 0.80 to 0.98) vs. COG/CCLG IV=100%) and OS_5 (COG/CCLG II-III=92.9% (95% CI, 0.80 to 0.98) vs. COG/CCLG IV=100%) demonstrates excellent outcomes even in the context of metastatic disease. Similarly, EFS_5 (FIGO stage IC, II, III=98.0% (95% CI, 0.87 to 0.99) vs. FIGO stage IV=60% (95% CI, 0.13 to 0.88) and OS_5 (FIGO stage IC, II, III=98.0% (95% CI, 0.87 to 0.99) vs. FIGO stage IV=100%) demonstrates overall excellent outcomes. The comparatively low EFS_5 in FIGO stage IV patients is attributable to the small number of patients (n=5) in our cohort. Regardless of the staging system utilized (COG/CCLG vs. FIGO), patients with advanced-stage dysgerminoma had excellent outcomes.

Of the 126 patients, 27 were treated on COG trials, 23 on CCLG and remaining 76 were treated on GOG trials. Two of these 126 patients received JEb after demonstrating disease recurrence during active surveillance following initial surgical resection. The remaining 124 patients received adjuvant carboplatin- or cisplatin-based chemotherapy (JEb=17, JE=37, BEP=39, PEb=18, High Dose-PEb (HD-PEb)=13). None of the patients in our cohort received radiation therapy. The EFS_5 and OS_5 were comparable between carboplatin-(EFS_5=96.0% (95% CI, 0.85 to 0.99), OS_5=96.0% (95% CI, 0.85 to 0.99)) and cisplatin-(EFS_5=93.2% (95% CI, 0.83 to 0.97), OS_5=96.6% (95% CI, 0.87 to 0.99)) based chemotherapy regimens, in advanced-stage dysgerminoma, across all age groups (Figure 2, Table 3). For those patients who received chemotherapy and did not experience an event, the median follow-up was 10.3 years (range=0.17-21.7 years). The hazard ratio for an event in patients treated with carboplatin-based regimens was 0.51 (95% CI, 0.10 to 2.65) vs. 1 in patients treated with cisplatin-based regimens; p-value=0.42 (Appendix 4).

In the sensitivity analysis that excluded the 3 patients with AFP levels at diagnosis that exceeded the expected level for pure ovarian dysgerminoma, as expected, the inclusion or exclusion of these 3 patients did not impact the survival probabilities, hence these 3 patients were included in the final analysis.

Events

The characteristics of the patients who experienced an event are summarized in Table 4. Seven patients experienced an event; only one patient was alive at the last follow up. Of

the 7 events, two patients experienced death as the first event without any reports of disease progression. Two events were observed in patients who received carboplatin-based chemotherapy (JE=1, JEb=1), whereas five events were observed in patients who received cisplatin-based chemotherapy (BEP=3, PEb=2). All events (five relapses and two deaths as first event) occurred within the first 52 months after initial treatment, with a median of 4.2 months. Data regarding site(s) and stage of relapse, attempted salvage strategies and cause of death were not collected as part of any of the clinical trials contained in the MaGIC database.

Discussion

In this study, our analysis compared newly diagnosed patients with advanced-stage pure ovarian dysgerminoma according to age and treatment regimen (carboplatin- or cisplatin-based chemotherapy). Our data demonstrates that patients with advanced-stage dysgerminoma have an excellent 5-year EFS and OS, across all age groups, with both cisplatin- and carboplatin-based strategies. We conducted this analysis particularly to assess the relative effectiveness of carboplatin- vs. cisplatin-based chemotherapy regimens in the treatment of children, adolescents and young adults with advanced-stage pure ovarian dysgerminoma. Our analysis demonstrates that carboplatin-based chemotherapy regimens are non-inferior to cisplatin-based chemotherapy regimens in the treatment of advanced-stage dysgerminoma across all age groups (children/adolescents: ≤25 years and adult: >25 years).

Over the years, results from seminal trials have highlighted the impact of carboplatin dose-response effect on the outcomes. On the UKCCSG GC2 study, testing JEb, the EFS_5 for 137 patients was 84.8% in those with COG/CCLG stage III GCT and 78.0% in those with COG/CCLG stage IV GCT.[7] The carboplatin dose in GC2 was 600 mg/m^2 per cycle (AUC 7.9 mg/mL per minute), which is significantly higher than the doses used in two large randomized studies with testicular cancer from Memorial Sloan-Kettering Cancer Center (carboplatin=500 mg/m^2 per cycle) and the Southwest Oncology Group (carboplatin=AUC 5mg/mL per minute) that reported carboplatin was less effective than cisplatin.[21] In the 1990s, the U.S. GOG conducted a clinical trial (GOG 0116) to evaluate the effectiveness of de-escalation of adjuvant chemotherapy with carboplatin (400 mg/m^2 per cycle) and etoposide (JE) without bleomycin in completely resected FIGO stages IB-III dysgerminoma.[11] However, despite favorable results (EFS=87.6% and OS=90.9%) the study was closed before completing its targeted accrual in light of the aforementioned testicular cancer data. More recently, single-agent carboplatin at a dose of AUC 10 mg/mL per minute, every 3 weeks for 3-4 cycles, was explored and found to be effective (3-year OS=96.3%, 3-year progression free survival=93.2%) in the International Germ Cell Cancer Collaborative Group (IGCCCG) good prognosis metastatic seminoma.[22] Biological similarity in behaviors and sensitivities between seminoma and dysgerminoma allow us to compare outcomes in future trial development.[23] Clinical trial data from three large clinical trial organizations, presented in this analysis, support the study of carboplatin-based chemotherapy regimen, with or without bleomycin, as the frontline treatment for all patients with advanced-stage

dysgerminoma, to minimize treatment-related toxicities without significantly compromising therapeutic efficacy.

This analysis builds on the success of the MaGIC collaboration by facilitating a comparison of a rare disease internationally, between pediatric, adolescent (COG/CCLG) and adult (GOG) groups, with 25 years of pooled data from three large clinical trial organizations. One limitation of this analysis is the disparity of staging systems in the adult and pediatric clinical trials. This limitation was overcome by analyzing the COG/CCLG and FIGO staging systems separately. The staging systems may be comparable if all relevant clinico-pathological data required to make such assignments are collected in future collaborative prospective clinical trials. Key data pertaining to surgical management, site(s) and stage of relapse, attempted salvage strategies and cause of death was not captured in the MaGIC database. Finally, the limitations related to small number of EFS events and OS events observed have been discussed previously.

In summary, results of our analysis illustrate that patients with dysgerminoma have an excellent outcome, even in the context of metastatic disease. Fertility-sparing surgery should be encouraged in the frontline management of dysgerminoma, when feasible and clinically appropriate, without compromising the prognosis.[24] Within this study and the extensive clinical data that has been collated in this disease, there is no clear evidence that carboplatin-based chemotherapy regimens are associated with an inferior outcome in comparison to cisplatin-based chemotherapy regimens. For advanced-stage dysgerminoma, irrespective of the adjuvant chemotherapy regimen used (BEP, PEb, HD-

PEb, JEb, JE), excellent outcomes are preserved across all ages. A key goal of future international collaborative trial design should be reduction in chemotherapy burden. Advances in the biologic understanding of advanced-stage dysgerminoma could potentially help identify therapeutically challenging subgroups and suggest future directions of research. To optimize not only the survival, but the quality of survival for these young patients in the AYA age range where MOGCT are most prevalent, we must consider how to best to design clinical studies to address "rare" tumors.[25] Analysis should be conducted by expected outcomes, in both seminoma and dysgerminoma, instead of the more conventional medical considerations around age and gender. International collaboration can create the platform for delivery of new trial design; to facilitate building our understanding of biological drivers which in turn can lead to optimization of therapeutic outcomes.

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