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Comparison of Carboplatin vs. Cisplatin in the Treatment of Pediatric Extracranial Malignant Germ Cell Tumors: A Report of the Malignant Germ Cell International Consortium.

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Abstract

Purpose: To compare the outcomes of pediatric and adolescent extracranial malignant germ cell tumor (GCT) patients treated with either carboplatin and cisplatin on clinical trials conducted by Children's Oncology Group (COG) and the Children's Cancer and Leukemia Group (CCLG).

Methods: The Malignant Germ Cell International Consortium (MaGIC) has created a database of the GCT clinical trials conducted since 1983 by COG (United States, Canada, Australia), which used cisplatin-based regimens, and by CCLG (United Kingdom), which used carboplatin-based regimens. Using the parametric cure model, this study compared the overall 4-year event-free survival (EFS), stratified by age, stage, site, and the a-priori defined MaGIC 'risk' groups: standard risk ((SR) 1 (EFS>80%; age<11years) , SR2 (EFS>80%, age≥11y), and poor risk (EFS≤70%, age≥11y).

Results: Cisplatin-based therapy was used in 620 patients; carboplatin was used in 163 patients. In the overall multivariate cure model, the two regimens did not differ significantly (cisplatin: 4y-EFS 86%; 95% confidence interval (CI) 83-89% vs. carboplatin 4y-EFS 86%; 95% CI 79-90%; p=0.87). No significant differences were noted in stratified analyses by site, stage, age and MaGIC risk group: SR1 (p=0.20), SR2 (p=0.55) or PR (p=0.72) patients.

Conclusions: In these trials conducted contemporaneously, there is no significant difference in outcome observed overall, or any subset of patients, who were treated with regimens containing cisplatin vs. carboplatin These results suggested sufficient equipoise to justify a randomized trial to evaluate the effectiveness of carboplatin vs. cisplatin in the treatment of children, adolescents and young adults with standard risk GCT, which is currently underway.

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Introduction

After the landmark study by Einhorn et al. [1] in 1977, cisplatin-based therapy was rapidly accepted as standard of care for testicular cancer, and testicular cancer became "the model of a curable neoplasm" [2]. However, cure comes with the price of significant immediate and often permanent toxicities, including hearing loss, tinnitus, peripheral neuropathy, and nephrotoxicity.[3] With longer follow-up, cisplatin has been associated with reduced fertility, at least in males, [4] and testicular cancer survivors have a two-fold increase in risk of second malignant solid neoplasms (in addition to the established risk of etoposide-induced leukemias) and early onset of cardiovascular disease.[5,6]

Other platinum-based compounds were developed, with hopes that a less toxic alternative to cisplatin could be found. Carboplatin appeared to be a promising alternative, causing less oto- and nephrotoxicity. Four randomized clinical trials (RCTs) of carboplatin vs. cisplatin were conducted in the late 1980s in adult men with good-risk non-seminomatous testicular germ cell tumors.[7-10] Unfortunately, carboplatin was inferior to cisplatin in every trial. However, carboplatin was being investigated in adult men with testicular cancer, carboplatin was also adopted for treatment of germ cell tumors (GCTs) in children and adolescents by several pediatric clinical trial groups. As summarized by Shaikh et al,[11] in the three pediatric studies using carboplatin at a higher dose and frequency than used in adult trials of carboplatin in men with testicular cancer, 158/179 (88%) of children remained event-free. Since none of the pediatric trials using carboplatin were randomized, the relative effectiveness of carboplatin vs. cisplatin for children and adolescents with GCT remains unclear.

In 2010, investigators from Children's Oncology Group (COG) (United States, Canada and Australia) and Children's Cancer and Leukemia Group (CCLG) (United Kingdom) created the Malignant Germ Cell International Consortium and agreed to pool 25 years of clinical trial data on pediatric and adolescent GCTs. Analysis of MaGIC data identified three factors predicting worse outcome: age 11 years or more, advanced stage of disease and either an ovarian or an extragonadal primary.[12] MaGIC proposed a new risk stratification re-classifying pediatric and adolescent GCT into standard (EFS >80%) and poor (EFS <70%) risk groups based on these clinical features.[12] In this study, we compare outcomes of treatment with carboplatin vs. cisplatin, overall and by site, stage, age as well as in the previously defined by MaGIC risk groups.

Methods

Patients

Details of MaGIC have been reported elsewhere.[12] Briefly, patients with extracranial malignant GCTs treated on clinical trials conducted by either CCLG or COG between 1983 and 2008 were included in the MaGIC dataset, including CCLG GC1 and GC8901 (GC2) from the UK and INT0097, INT0106, P9747, AGCT01P1, and AGCT0132 from COG (Supplemental Table 1).

In the CCLG clinical trials, the regimen 'JEB' consisted of carboplatin 600 mg/m^2 (AUC 7.9), etoposide 360 mg/m^2 and bleomycin 15 mg/m^2 given every 21 days for n+2 cycles (where n is the number of cycles needed to achieve marker normalization; median =5). In COG, the regimen 'PEb (or pediatric-BEP) consisted of cisplatin 100 mg/m^2, etoposide 500 mg/m^2 and bleomycin 15mg/m^2 every 21 days. The number of days over which the total dose of PEb was delivered and the number of cycles (3-6) varied between protocols. One COG trial added another agent (cyclophosphamide - AGCT01P1); another COG trial tested high-dose cisplatin (200 mg/m^2 per cycle - INT0097). Further details of the therapies delivered on each trial are summarized in Supplemental Table 1.

Inclusion in this analysis required a patient had been treated with a platin-based regimen, and the primary tumor contained malignant non-germinomatous GCT histology (i.e. yolk sac tumor, choriocarcinoma, or embryonal carcinoma). There were a total of 1300 patients in the seven studies. The upper age limit varied from age 15y on CCLG trials to 21y on most trials in COG (see Supplemental Table 1). Stage I patients who were initially

treated with surgery and active surveillance, but who were subsequently treated with chemotherapy because of recurrent disease, were excluded from this analysis (n=69), because of very high rate of salvage in this group, on both regimens.[13,14,15] Stage I patients who received chemotherapy immediately following surgery however, as was standard practice for certain sites (extragonadal and ovarian), were included. Patients treated with surgery only (n=363) or non-platin-based chemotherapy (n=4), those with either pure immature teratoma (n=11) or pure seminoma/dysgerminoma (n=68), and those with missing data on stage (n=2) were excluded from the analysis. After exclusions, the dataset included 783 patients.

Statistical analysis

Outcome Measure: Event-free survival (EFS): Patient outcome was calculated as time from the start of chemotherapy until disease progression, diagnosis of a second malignant neoplasm (SMN) death, or date of last follow-up, whichever came first. A patient who experienced disease progression, SMN or death was an event for analysis; otherwise, the patient was censored at last contact.

Statistical Model: A non-mixture cure model was used to model the relationship between treatment and EFS. [13] This model has been shown to provide excellent fit to childhood cancer outcome data. The model provides a coherent methodology to investigate effects of treatment on rate of failure separately from their effect on ultimate cure. A model with a Weibull kernel with no covariates and cured fraction modeled as a logistic function of

the patient characteristics was used. This was the same model used in previous MaGIC analyses[18].

The Kaplan-Meier estimate of proportion event-free as a function of time since the start of follow-up was calculated for selected groups of patients. The log rank test was used to compare equality of risk across selected patient groups.[16] The parametric and non-parametric estimators of EFS as a function of time were compared as suggested by Sposto et al.[17] The hazard ratio (HR) of patients treated with JEB relative to PEb was estimated by Cox regression. For comparisons where maximum likelihood estimate of HR did not converge, the method of Firth[18] was applied to obtain a finite estimate of HR and its 95% confidence interval. A two-sided p-value of 0.05 or less s identified as significant.

Covariates:

MaGIC-defined risk groups: The significant prognostic factors (age≥11y, advanced stage and either ovarian or extragonadal site) identified in the previous MaGIC risk stratification were used to construct two risk groups: standard risk (SR) (EFS>80%) and poor risk (PR) (EFS<70%).[12] The standard risk group is divided by age into two further categories. Patients age 10y or less are in the SR1 group, which includes COG stage II-IV and all sites (ovarian, extragonadal, and testicular). Patients age 11y and older with COG stage II-III ovarian, stage II extragonadal and IGCCC good risk testicular are in the SR2 group. The poor risk group is comprised of patients age 11y and older with COG stage IV

ovarian, COG stage III-IV extragonadal, and IGCCC intermediate and poor risk testicular. The outcomes of patients treated on JEB vs. PEb were compared in these three summary MaGIC risk groups.

Other covariates: Age was dichotomized as 0 – 10y or greater than or equal to 11y. The serum AFP in ng/ml was defined as the measurement closest to, but not later than, the first surgical intervention prior to the start of chemotherapy.[17] In prior analyses, multiple methods of defining the optimal cutpoints for AFP were examined, but none were more informative than the traditional cutpoint of > vs. ≤ 10,000 ng/ml. Stage was defined used COG criteria.[12] Histology was defined either as pure yolk sac tumor, choriocarcinoma, embryonal carcinoma, or mixed malignant GCT (containing one of these components with teratoma, or at least two of these components without teratoma). Site was defined as testicular, ovarian, or extragonadal GCT. In sensitivity analyses, we included only patients on COG trials using standard dose cisplatin and excluded any patient who had also received either cyclophosphamide or high dose cisplatin.

Results

A comparison of patient characteristics treated on PEb vs. JEB is presented in Table 1. On average, patients on a carboplatin-containing regimen received one more cycle of chemotherapy than those of a cisplatin-containing regimen (5 vs. 4 cycles). Of note, other patient characteristics are not balanced between the two regimens because these data represent clinical trial data from two different clinical trial organizations and are not a randomized trial. Patients treated with carboplatin were more likely to be younger (61%

were ages 0-4y vs. 49% in the cisplatin group), have extragonadal disease (57% vs. 40%), pure yolk sac tumor (64% vs. 47%), pre-operative AFP≥10,000 ng/ml (60% vs. 38 %) and stage IV disease (34% vs.24 %).

In Table 2, the 4-year estimates of EFS and 95% confidence intervals (95% CI) are presented overall and by the univariate risk factors[19]. When the entire analytic population is considered, there is no significant difference in outcome between PEb (4y EFS 86%) vs. JEB (4y EFS 86%; HR 1.04; p=0.87). Risk of an event also was not significantly different in stratified univariate analyses defined by age, primary tumor site, histology, pre-operative AFP level, or stage.

In Figure 1, EFS is presented as a forest plot of hazard ratios in combinations of age, site and stage, as previously defined by MaGIC. (A table of EFS in these combined risk groups is included as Supplemental Table 2). The outcome comparing PEb vs. JEB did not exclude zero in any combination of age, stage or site. In some strata, the number of patients treated, particularly on the JEB regimen, was relatively small and consequently the confidence intervals are quite wide. Patients were also classified by the new MaGIC risk groups: SR1, SR2, and PR. Outcomes between JEB and PEb were again not significantly different in either SR1 [(HR) 1.50; p=0.20), SR2 (HR 1.34; p=0.55) or PR (HR 0.80; p=0.72)] (Supplemental Table 2).

In Figure 2, overall EFS survival curves are presented overall, for age, stage, site and by MaGIC risk group (SR1, SR2 and PR). EFS is not significantly different in any of these groups.

We performed multivariate modeling of outcome using the cure model[17]. After including in the model the variables for age, site and stage, effect of treatment (PEb vs JEB) was not significant (estimated log odds -0.09; p=0.73) (Table 3). In sensitivity analysis, we included only patients treated with standard PEb (excluding patients treated with PEb + cyclophosphamide on AGCT01P1 and patients treated with high dose cisplatin on INT0097) and none of the conclusions were significantly altered (Supplemental Table 3).

Discussion

No significant difference in outcome was observed among pediatric and adolescent extracranial GCT patients treated with a cisplatin-based regimen (PEb) vs. a carboplatin-based regimen (JEB), when comparing groups by age, site and stage. Additionally, the treatment regimen received (cisplatin vs. carboplatin) was not significant in the results of the multivariate model (Table 3) controlling for other known risk factors. We acknowledge that individual risk stratum is relatively small in terms of total patient numbers, nonetheless, in the absence of randomized data in this age group, we suggest there is equipoise regarding relative effectiveness of cisplatin vs. carboplatin for pediatric and adolescent GCT.

Our conclusions differ from those observed in the four published randomized comparisons of cisplatin vs. carboplatin in adult men with non-seminomatous testicular germ cell tumors, which are summarized in Supplemental Table 4.[7-10] There are several explanations for the observed differences. Our results are not derived from a randomized trial but rather comprise an analysis of clinical trials conducted contemporaneously and thus are admittedly less conclusive. However, there are several aspects of the design of adult trials predisposing the results to be unfavorable to carboplatin. Most importantly, all of the adult trials used a dose of carboplatin significantly lower than the dose used in pediatric regimens (AUC 3-5 vs. AUC 7.9 or 350-500 mg/m^2 vs.600 mg/m^2). The dose employed in the adult trials may therefore have been insufficient. Secondly, 2 [7,10] of the 4 trials administered carboplatin every 28 days whereas the cisplatin regimen was administered every 21 days. Inadequate dose-density of carboplatin arms may have

predisposed the carboplatin arm to do worse. A third trial [8] used a lower dose of etoposide on the carboplatin arm of the trial than on the cisplatin arm of the trial (360mg/m^2 vs 500mg/m^2). This lower dose of etoposide has been shown to produce inferior results by Grimison et al. [20] Although these adjustments (increased cycle length and decreased etoposide dose) were made to compensate for the expected increased myelotoxicity of carboplatin, both would be expected to bias the results against carboplatin.

Another explanation for the apparent enhanced performance of carboplatin in pediatric GCTs is that underlying biology of pediatric disease is different from adult GCTs. In younger children, histology is likely to be predominately yolk sac tumor whereas in adolescents and adults, histology is generally "mixed". GCTs in younger patients show variable loss of imprinting (LOI) whereas GCTs of adolescents and adults, have more complete LOI, implying the origin of the tumor occurred at a later stage in embryologic development..[21] Using comparative genomic hybridization, GCTs arising in younger patients consistently show a loss of 1p and 6q, whereas post-pubertal children exhibit pathognomonic amplification of 12p seen in adults.[22] Gene expression profiling segregates pediatric vs. adult GCTs.[22] The biology of pediatric GCTs may render these tumors more inherently sensitive to chemotherapy.[23]

The study has its limitations. Although the data presented here are not derived from a randomized comparison, the data have been harmonized to provide the maximal comparability possible outside of an RCT. The precision is greater among younger patients (age 10y and less) due to larger sample size (n=507). The sample size in patients

aged 11y or older is smaller, however analysis of 276 adolescents age 11y and older (233 treated with cisplatin, and 43 treated with carboplatin), there is no evidence that carboplatin is inferior (p=0.96). However, upper age limit on the UK carboplatin trials was age 15y, and therefore we cannot comment on the relative effectiveness in older adolescents. Another caveat to our results is that we do not know the actual numbers on cycles delivered on each regimen because this information was not collected as part of several of the clinical trials, only the number of cycles "prescribed" by the regimen. In general, however, patients who received carboplatin were prescribed on average one more cycle of chemotherapy than those who received cisplatin (5 vs. 4 cycles). Therefore, it is possible that an additional cycle of carboplatin is needed to achieve similar outcomes to those of cisplatin.

Based on available data, a randomized controlled trial of carboplatin vs. cisplatin, using pediatric carboplatin dosing and schedule, was deemed warranted and is underway (COG AGCT1531). To have sufficient sample size, particularly among children age 10y or less in whom incidence of GCT is lower, enrollment from international sites is necessary. AGCT1531 will enroll patients from Canada, United States, Australia, New Zealand, United Kingdom, TATA Memorial Hospital in Mumbai, and Japanese Children's Cancer Group to meet accrual goals. This trial will clarify relative effectiveness of carboplatin vs. cisplatin in standard risk patients age 0-25y and will carefully document any associated toxicities. The intention is to facilitate patient-centered conversations in the future that can enumerate trade-offs in terms of efficacy vs. toxicity of cisplatin vs. carboplatin.

Conflict of Interest statement:
Dr. A. Lindsay Frazier is on the clinical advisory board for Decibel Therapeutics. This has no relation to the manuscript.

References

1. Einhorn LH, Donohue JP: Improved chemotherapy in disseminated testicular cancer. J Urol 117:65-9, 1977
2. Einhorn LH: Testicular cancer as a model for a curable neoplasm: The Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res 41:3275-80, 1981
3. Travis LB, Beard C, Allan JM, et al: Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst 102:1114-30, 2010
4. Chow EJ, Stratton KL, Leisenring WM, et al: Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol 17:567-76, 2016
5. Travis LB, Fossa SD, Schonfeld SJ, et al: Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 97:1354-65, 2005
6. Haugnes HS, Wethal T, Aass N, et al: Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol 28:4649-57, 2010
7. Bajorin DF, Sarosdy MF, Pfister DG, et al: Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol 11:598-606, 1993
8. Bokemeyer C, Kohrmann O, Tischler J, et al: A randomized trial of cisplatin, etoposide and bleomycin (PEB) versus carboplatin, etoposide and bleomycin (CEB) for patients with 'good-risk' metastatic non-seminomatous germ cell tumors. Ann Oncol 7:1015-21, 1996
9. Horwich A, Sleijfer DT, Fossa SD, et al: Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. J Clin Oncol 15:1844-52, 1997
10. Tjulandin SA, Garin AM, Mescheryakov AA, et al: Cisplatin-etoposide and carboplatin-etoposide induction chemotherapy for good-risk patients with germ cell tumors. Ann Oncol 4:663-7, 1993
11. Shaikh F, Nathan PC, Hale J, et al: Is there a role for carboplatin in the treatment of malignant germ cell tumors? A systematic review of adult and pediatric trials. Pediatr Blood Cancer 60:587-92, 2013
12. Frazier AL, Hale JP, Rodriguez-Galindo C, et al: Revised risk classification for pediatric extracranial germ cell tumors based on 25 years of clinical trial data from the United kingdom and United States. J Clin Oncol 33:195-201, 2015
13. Cushing B, Giller R, Cullen JW, et al: Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ

cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 22:2691-700, 2004

14. Rogers PC, Olson TA, Cullen JW, et al: Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: A Pediatric Intergroup Study--Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 22:3563-9, 2004

15. Mann JR, Gray ES, Thornton C, et al: Mature and immature extracranial teratomas in children: the UK Children's Cancer Study Group Experience. J Clin Oncol 26:3590-7, 2008

16. Kalbfleisch JD, and Prentice, R. L. : The Statistical Analysis of Failure Time Data (ed Second). Hoboken, NJ John Wiley & Sons, Inc. , 2002

17. Sposto R: Cure model analysis in cancer: an application to data from the Children's Cancer Group. Stat Med 21:293-312, 2002

18. Firth D: Bias Reduction of Maximum Likelihood Estimates. Biometrika 80:27-38, 1993

19. Kaplan EL, Meier P: Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association 53:457-481, 1958

20. Grimison PS, Stockler MR, Thomson DB, et al: Comparison of two standard chemotherapy regimens for good-prognosis germ cell tumors: updated analysis of a randomized trial. J Natl Cancer Inst 102:1253-62, 2010

21. Schneider DT, Schuster AE, Fritsch MK, et al: Multipoint imprinting analysis indicates a common precursor cell for gonadal and nongonadal pediatric germ cell tumors. Cancer Res 61:7268-76, 2001

22. Palmer RD, Barbosa-Morais NL, Gooding EL, et al: Pediatric malignant germ cell tumors show characteristic transcriptome profiles. Cancer research 68:4239-47, 2008

23. Collinson K, Murray MJ, Orsi NM, et al: Age-related biological features of germ cell tumors. Genes Chromosomes Cancer 53:215-27, 2014

24. Mann JR, Pearson D, Barrett A, et al: Results of the United Kingdom Children's Cancer Study Group's malignant germ cell tumor studies. Cancer 63:1657-1667, 1989

25. Mann JR, Raafat F, Robinson K, et al: The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 18:3809-18, 2000

26. Cushing B, Giller R, Cullen JW, et al: Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 22:2691-700, 2004

27. Marina N, London WB, Frazier AL, et al: Prognostic factors in children with extragonadal malignant germ cell tumors: a pediatric intergroup study. J Clin Oncol 24:2544-8, 2006

28. Malogolowkin MH, Krailo M, Marina N, et al: Pilot study of cisplatin, etoposide, bleomycin, and escalating dose cyclophosphamide therapy for children

with high risk germ cell tumors: a report of the children's oncology group (COG). Pediatr Blood Cancer 60:1602-5, 2013

29. Billmire DF, Cullen JW, Rescorla FJ, et al: Surveillance After Initial Surgery for Pediatric and Adolescent Girls With Stage I Ovarian Germ Cell Tumors: Report From the Children's Oncology Group. J Clin Oncol, 2014

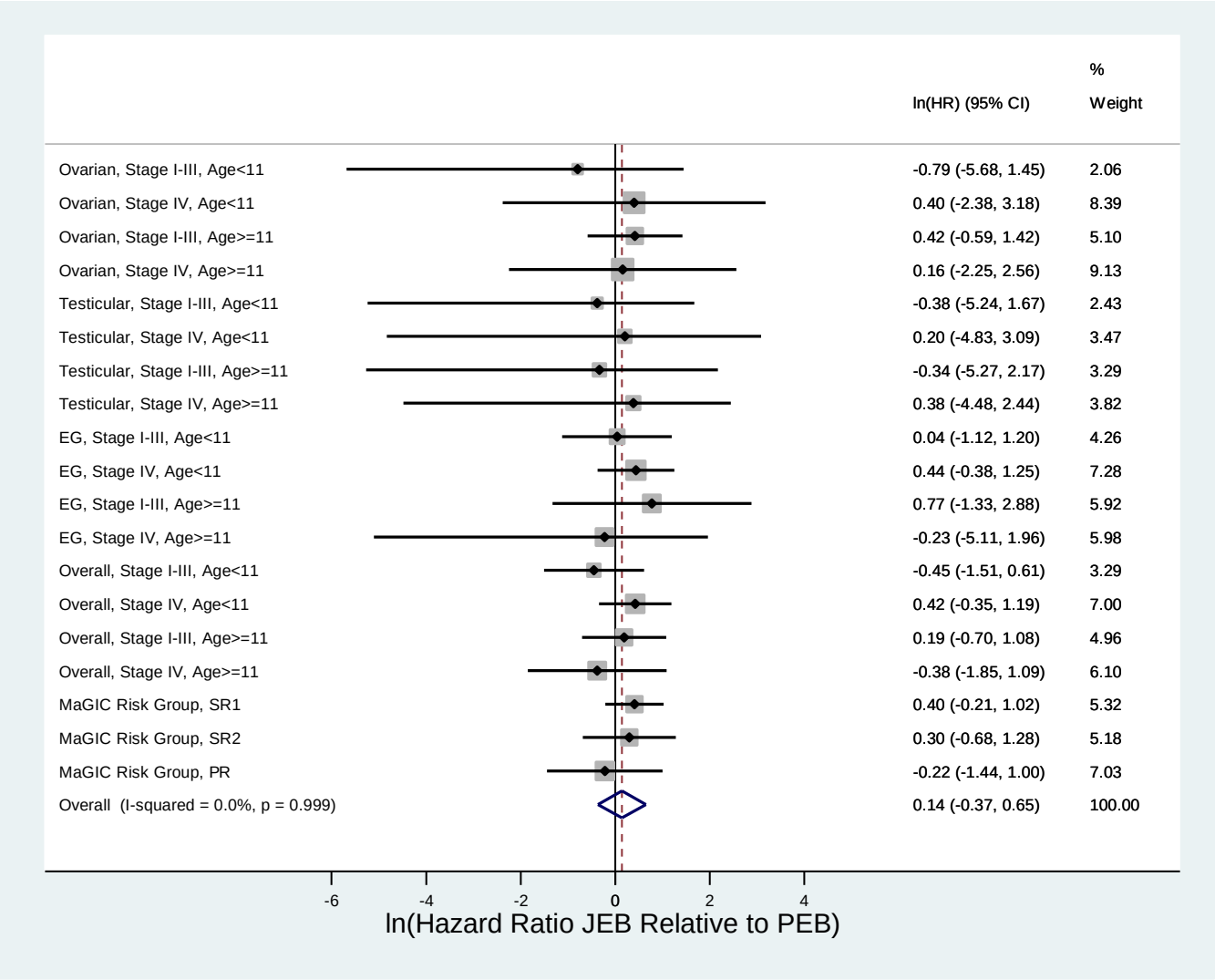

Figure 1: Forrest plot showing estimates of hazard ratio (HR) of patients treated with Jeb vs PEb, according to prognostic risk groups.

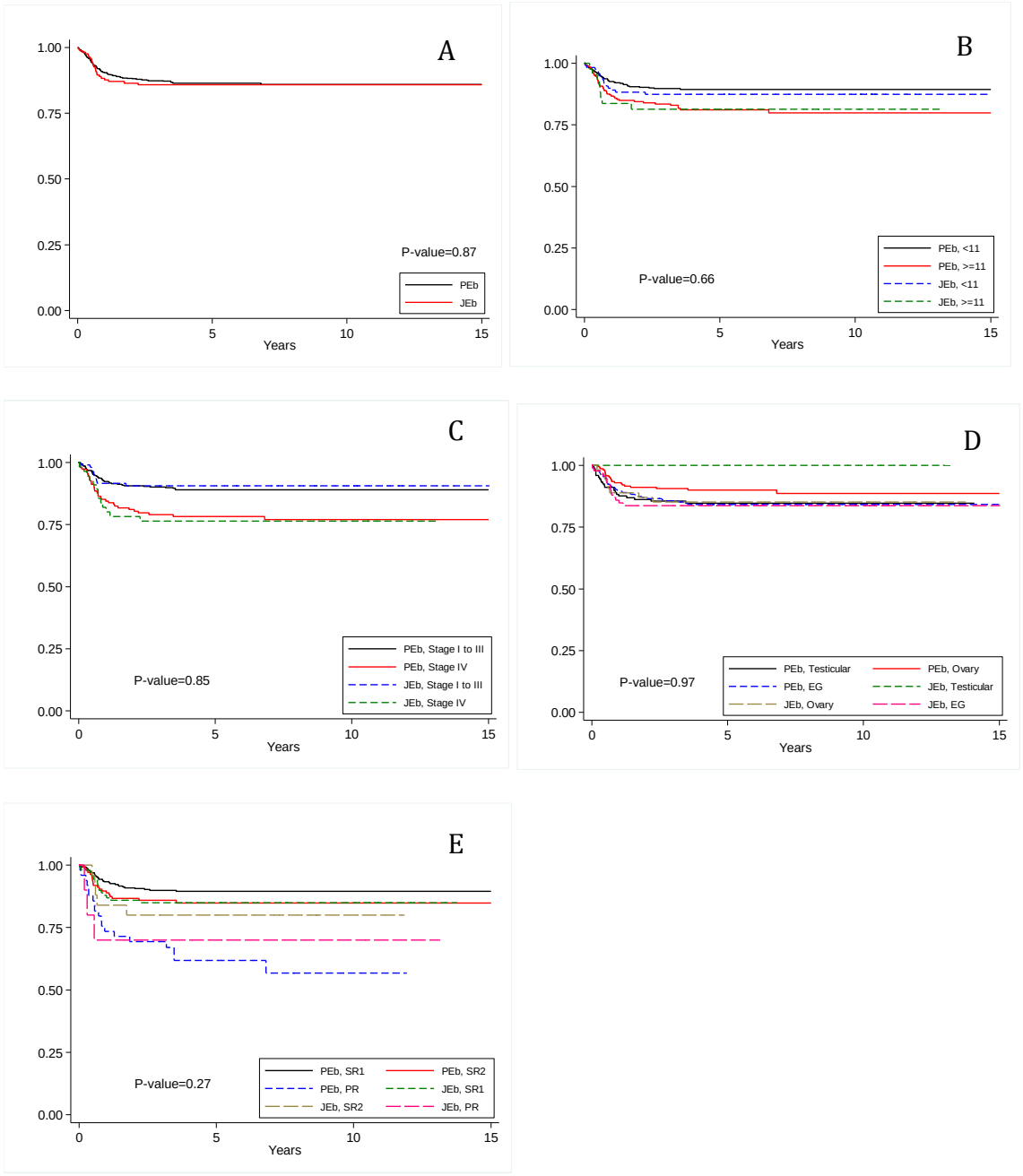

Figure 2. Kaplan-Meier estimates of EFS of patients treated with PEb vs. JEb. Overall (2a), by age (2b), by stage (2c), by site (2d), by MaGIC risk group (2e)

Table 1: Patient characteristics treated with Cisplatin-based regimens (PEb) vs. Carboplatin-based regimens (JEB) in MaGIC.

	Assigned Treatment		
	PEb (n; %)	**JEB (n, %)**	**Total (%)**
Total	620 (79.2%)	163 (20.8%)	783
Median Cycles (Range)	4 (3-7)	5 (1-9)	
Age (years)			
0 – 10	387 (62.4%)	120 (73.6%)	507 (64.7%)
11+	233 (37.6%)	43 (26.4%)	276 (35.3%)
Site			
Testes	147 (23.7%)	16 (9.8%)	163 (20.8%)
Ovarian	224 (36.1%)	54 (33.1%)	278 (35.5%)
Extragonadal	249 (40.2%)	93 (57.1%)	342 (43.7%)
Sacrococcygeal	124 (20.0%)	45 (27.6%)	169 (21.6%)
Mediastinal	56 (9.0%)	13 (8.0%)	69 (8.8%)
Other EG	69 (11.1%)	35 (21.5%)	104 (13.3%)
Histology			
Embryonal Carcinoma	5 (0.8%)	3 (1.8%)	8 (1.0%)
Yolk Sac	292 (47.1%)	104 (63.8%)	396 (50.6%)
Choriocarcinoma	9 (1.4%)	1 (0.6%)	10 (1.3%)
Mixed GCT	280 (45.2%)	55 (33.8%)	335 (42.8%)
Other/Missing	34 (5.5%)	0	34 (4.3%)
AFP			
0 – 9,999	358 (57.7%)	61 (37.4%)	419 (53.5%)
>= 10,000	233 (37.6%)	98 (60.1%)	331 (42.3%)
Missing	29 (4.7%)	4 (2.5%)	33 (4.2%)
Stage			
I	125 (20.1%)	28 (17.2%)	153 (19.5%)
II	129 (20.8%)	35 (21.5%)	164 (21.0%)
III	218 (35.2%)	44 (27.0%)	262 (33.5%)
IV	148 (23.9%)	56 (34.3%)	204 (26.0%)
Treatment Regimen[a]			
HD-PEb*	156 (25.2%)	0	156 (19.9%)
PEb	450 (72.6%)	0	450 (57.5%)
C-PEb**	14 (2.2%)	0	14 (1.8%)
JEb	0	163 (100%)	163 (20.8%)

*HD-PEb: PEb with high dose cisplatin (200 mg/m^2)

** C-PEb: PEb plus cyclophosphamide

Table 2: Comparison of 4-year KM EFS (95% Confidence Intervals) in Patients Treated with cisplatin (PEb) vs. carboplatin (JEB).

	Assigned Treatment			
	PEb (4-year KM EFS; 95% CI)	**JEb (4-year KM EFS; 95% CI)**	**p-Value**	**HR* (95% CI)**
Overall	0.86 (0.83-0.89) N=620	0.86 (0.79-0.90) N=163	0.87	1.04 (0.65-1.65)
Age (years)				
<11	0.89 (0.86-0.92) N=387	0.87 (0.80-0.92) N=120	0.54	1.20 (0.66-2.18)
>= 11 years	0.81 (0.75-0.86) N=233	0.81 (0.66-0.90) N=43	0.96	0.98 (0.46-2.09)
Site				
Testes	0.85 (0.78-0.90) N=147	1 N=16	0.10	0.185** (0.001-1.332)
Ovarian	0.90 (0.85-0.93) N=224	0.85 (0.73-0.92) N=54	0.38	1.43 (0.64-3.22)
Extragonadal	0.84 (0.79-0.88) N=249	0.84 (0.74-0.90) N=93	0.85	1.06 (0.58-1.93)
Sacrococcygeal	0.88 (0.81-0.92) N=124	0.86 (0.72-0.94) N=45	0.80	1.13 (0.44-2.91) 1.06 (0.30-3.76)
Mediastinal	0.77 (0.63-0.86) N=56	0.77 (0.44-0.92) N=13	0.93	1.08 (0.40-2.93)
Other EG	0.83 (0.72-0.90) N=69	0.83 (0.66-0.92) N=35	0.87	
Histology				
Yolk Sac	0.88 (0.84-0.91) N=292	0.87 (0.79-0.92) N=104	0.85	1.06 (0.56-2.01)
Mixed GCT	0.85 (0.81-0.89) N=280	0.84 (0.71-0.91) N=55	0.80	1.10 (0.53-2.27)
AFP				
0 – 9,999	0.89 (0.85-0.92) N=358	0.93 (0.83-0.97) N=61	0.25	0.55 (0.20-1.54)
>= 10,000	0.84 (0.78-0.88) N=233	0.80 (0.71-0.87) N=98	0.37	1.29 (0.74-2.24)
Stage				
I	0.90 (0.83-0.94) N=125	1 N=28	0.09	0.17** (0.001-1.268)
II	0.92 (0.85-0.96) N=129	0.94 (0.79-0.99) N=35	0.66	0.71 (0.16-3.26)
III	0.87 (0.81-0.91) N=218	0.82 (0.67-0.90) N=44	0.34	1.46 (0.66-3.21)
IV	0.78 (0.71-0.84) N=148	0.76 (0.63-0.86) N=56	0.86	1.06 (0.56-2.01)

*PEb is the reference group

** Estimated using the method of Firth

Supplemental Table 1: Pediatric Germ Cell Tumor Clinical Trials included in MaGIC

	National Group	Eligibility of the Trial	Treatment Regimen	Cycle (days)	Number of cycles	Number of patients
GC1[24]	UK	All patients with MGCT	Etoposide 120mg/m2 D1-3, Bleomycin 15 IU/m2 D2, Cisplatin 100mg/m2 D1	21	n* + 2 (n=courses to marker normalization)	21
GC2[25]	UK	All patients with MGCT	JEB	21	n* + 2	163
INT-106/ POG9048/CCG-8891[14]	US	Stage II testicular; Stage I-II ovarian	PEB	21	4 (+2 if PR)	118
INT-0097/ POG9049/CCG-8882[26]	US	Stage III and IV gonadal and extragonadal tumors	PEB vs. HDPEB	21	4 (+2 if PR)	261
P9749[27]	US	Stage III and IV extragonadal tumors	Amifostine 825mg/m2 D1-5 + HDPEB	21	4 (+2 if PR)	26
AGCT01P1[28]	US	Stage III and IV extragonadal tumors	C-BEP	21	4 (+2 if PR)	14
AGCT0132[29]	US	Stage I-III ovarian Stage I-IV testicular Stage I-II extragonadal	Compressed PEB	21	3 (+3 if PR)	180

Supplemental Table 2: Comparison of 4-year KM EFS (95% Confidence Intervals) of Pediatric GCT Patients Treated with cisplatin (PEb) vs. carboplatin (JEB).

		Assigned Treatment			
Tumor Site	**Stage and Age**	**PEb (4-year KM EFS; 95% CI)**	**JEb (4-year KM EFS; 95% CI)**	**p-Value**	**HR* (95% CI)**
Ovarian	Stage I-III, Age < 11	0.95 (0.86-0.98) N=78	1 N=18	0.32	0.45 (0.003-4.25)**
Ovarian	Stage IV, Age < 11	0.80 (0.20-0.97) N=5	0.67 (0.05-0.95) N=3	0.78	1.49 (0.09-23.94)
Ovarian	Stage I-III, Age >= 11	0.87 (0.80-0.92) N=138	0.81 (0.61-0.92) N=27	0.41	1.52 (0.56-4.14)
Ovarian	Stage IV, Age >= 11	1 N=3	0.67 (0.19-0.90) N=6	0.90	1.17 (0.11-12.98)
Testicular	Stage I-III, Age < 11	0.87 (0.77-0.93) N=78	1 N=5	0.40	0.68 (0.005-5.31)**---
Testicular	Stage IV, Age < 11	0.93 (0.59-0.99) N=14	1 N=4	0.59	1.22 (0.008-21.88)**---
Testicular	Stage I-III, Age >= 11	0.91 (0.68-0.97) N=23	1 N=6	0.45	0.71 (0.005-8.78)**---
Testicular	Stage IV, Age >= 11	0.72 (0.53-0.84) N=32	1 N=1	0.57	1.46 (0.01-11.51)**---
EG	Stage I-III, Age < 11	0.92 (0.85-0.96) N=129	0.92 (0.80-0.97) N=49	0.95	1.04 (0.32-3.30)
EG	Stage IV, Age < 11	0.83 (0.73-0.90) N=83	0.75 (0.59-0.86) N=41	0.29	1.55 (0.69-3.48)
EG	Stage I-III, Age >= 11	0.72 (0.49-0.86) N=26	0.50 (0.01-0.91) N=2	0.46	2.17 (0.26-17.75)
EG	Stage IV, Age >= 11	0.30 (0.06-0.60) N=11	1 N=1	0.45	0.80 (0.006-7.06)**---
Overall	Stage I-III, Age < 11	0.91 (0.87-0.94) N=285	0.94 (0.86-0.98) N=72	0.40	0.64 (0.22-1.83)
Overall	Stage IV, Age < 11	0.84 (0.76-0.90) N=102	0.77 (0.62-0.86) N=48	0.28	1.52 (0.71-3.28)
Overall	Stage I-III, Age >= 11	0.85 (0.79-0.90) N=187	0.83 (0.66-0.92) N=35	0.68	1.21 (0.50-2.94)
Overall	Stage IV, Age >= 11	0.65 (0.49-0.77) N=46	0.75 (0.31-0.93) N=8	0.61	0.68 (0.16-2.97)
MaGIC Risk Group	Standard Risk 1	0.90 (0.85-0.93) N=303	0.85 (0.76-0.91) N=100	0.20	1.50 (0.81-2.77)
	Standard Risk 2	0.85 (0.77-0.90) N=143	0.80 (0.58-0.91) N=25	0.55	1.34 (0.50-3.58)
	Poor Risk	0.62 (0.46-0.74) N=49	0.70 (0.33-0.89) N=10	0.72	0.80 (0.24-2.71)

*PEb is the reference group

** Estimated using the method of Firth

Supplemental Table 3: "CURE" model of prognostic factors for pediatric germ cell tumors, including treatment with either cisplatin (PEb) or carboplatin (JEb)

Factor	**Characteristic**	**Estimated Log Odds (p value)**
Chemotherapy	PEb	-
	JEb	-0.09 (0.73)
Tumor Site	Testicular	-
	Ovarian	0.61 (0.25)
	Extra gonadal	0.15 (0.70)
Tumor Site by Age Interaction	Testicular and 11+ Years	-
	Ovarian and 11+ Years	-0.90 (0.18)
	Extragonadal and 11+ Years	-1.48 (0.02)
Extent of Disease	Stage I-III	-
	Stage IV	-1.00 (0.001)
Age at Enrollment	10 years of age or less	-
	11 years of age or older	-0.16 (0.73)

Supplementary Table 4. Characteristics of RCT of Carboplatin vs. Cisplatin in Men with "Good Risk" NS-GCT

Study [Reference]	Risk Criteria	Histology	Testes Site (%)	No. of Patients	Chemotherapy Regimen**	Event-free survival
Bajorin et al. [7]	MSKCC	NS+S	96	131 EC 134 EP	C 500 mg/m[a] and E 500 mg/m^2 **q28d** x 4 P 100 mg/m^2 and E 500 mg/m^2 q21d x 4	74% at 3y 87% at 3y*
Tjulandin et al. 10]	Indiana	NS +S	95	23 EC 39 EP[c]	C 350 mg/m^2 and E 500 mg/m^2 **q28d** x 4 P 100 mg/m^2 and E 500 mg/m^2 q21d x 4	61%[b] 79%
Bokemeyer et al. [8]	Indiana	NS	100	25 CEB 29 PEB	C to achieve AUC 5 mg/mL/min, E **360** mg/m^2, and B 90 mg q21d x **4**[c] P 100 mg/m^2, E 500 mg/m^2 and B 90 mg q21d x 3	63% at 2y 74% at 2y*
Horwich et al. [9]	MRC / EORTC	NS	100	298 CEB 300 PEB	C to achieve AUC 5 mg/mL/min, E 360 mg/m^2 and B 30 mg q21d x 4 P 100 mg/m^2, E 360 mg/m^2 and B 30 mg q21d x 4	77% at 1y 91% at 1y

**Differences among the two treatment arms other than the choice of platinum agent are shown in bold.

- ≠ 20% of the initial patients in this trial were treated with a dose of carboplatin <500 mg/m^2
- ≠ Time-interval was not reported.
- ≠ Only the first 22 patients in the cis-platin arm were randomized. The last 17 patients were "assigned" cisplatin because carboplatin was no longer available.

AUC, area under the curve; B, bleomycin; C, carboplatin; CR, complete response; d, days; E, etoposide; EORTC, European Organization for Research and Treatment of Cancer; I, ifosfamide; IGCCCG, International Germ Cell Cancer Collaborative Group; MSKCC, Memorial Sloan-Kettering Cancer Center; MRC, Medical Research Council; N/A, not available; NS, non-seminoma; P, cisplatin; S, seminoma; V, vinblastine.