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MALIGNANT EXTRA-CRANIAL GERM CELL TUMORS IN CHILDREN AND ADOLESCENTS. RESULTS FOLLOWING THE GUIDELINES OF SFOP/SFCE 95 PROTOCOL

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Abstract Between September 1995 and December 2010, 99 new consecutive assessable patients with extra-cranial MGCT were treated according to SFOP/SFCE TGM95 Protocol. A "watch and wait" strategy for completely resected stage I-II was observed in cases with preoperative high tumor markers levels. Metastatic disease or alpha fetoprotein levels > 15 000 ng/ml cases were treated by VIP chemotherapy (etoposide, ifosfamide and CDDP) 4-6-courses. All other cases were treated by VBP (vinblastine, bleomycin, and CDDP) 3-5 courses. Median age for the whole group was 11.1 (r: 0-17) years. Males: 49, females: 50. Stage I: 19 patients, stage II: 16, stage III: 31 and stage IV: 3. Gonadal disease occurred in 77 cases. Of 21 completely resected stage I-II patients with MGCT who did not receive chemotherapy after surgery, 6 presented disease progression and were successfully treated by chemotherapy and remained disease-free. There were no significant differences in outcome according to age, gender, initial site, staging, and histological variant or high levels of alpha-fetoprotein. Initial non-responsiveness to VIP chemotherapy was the only significant unfavorable prognostic feature. With a median follow-up of 64 (r: 5-204) months, at 10 years EFS and OS estimates for the whole group were 0.82 (SE = 0.05) and 0.90 (SE = 0.03) respectively. Therapy results of MGCT treated with the SFOP/SFCE 95 strategy were excellent. Initial non-response to front line chemotherapy was the only significant adverse prognostic feature. The "watch and wait" strategy for completely resected disease with initial positive markers proved to be safe with optimal outcome.

Key words: malignant germ cell tumors, childhood, adolescence

Resumen ***Tumores germinales malignos extra-cerebrales en niños y adolescentes. Resultados siguiendo las guías del Protocolo SFOP/SFCE 95.*** Entre septiembre de 1995 y diciembre 2010 se registraron 99 nuevos pacientes evaluables consecutivos con tumores germinales malignos (TGM) extra-cerebrales. Los pacientes fueron tratados prospectivamente según los lineamientos del Protocolo SFOP/SFCE TGM95. Se siguió una estrategia de *watch and wait* para la enfermedad estadio I-II completamente resecada. La enfermedad con metástasis y los casos con niveles de alfa fetoproteína > 15 000 ng/ml fueron tratados con etopósido, ifosfamida y CDDP, 4-6 cursos. El resto fue tratado con vinblastina, bleomicina y CDDP, 3-5 ciclos. La mediana de edad fue de 11.1 (r: 0-17) años. Varones: 49, niñas: 50. Estadio I: 19 casos; II: 16; III: 31y IV: 33. De 21 enfermos con estadios tumorales I y II con resección completa inicial que no tuvieron tratamiento adyuvante, seis progresaron, todos fueron exitosamente tratados con quimioterapia y permanecieron libres de enfermedad. No hubo diferencias significativas en los resultados de supervivencia según edad, género, sitio inicial, estadificación, variante histológica o niveles elevados de alfa-fetoproteína. La resistencia primaria a la quimioterapia VIP fue el único factor pronóstico desfavorable significativo. Con una mediana de seguimiento de 64 (r: 5-204) meses, a 10 años las probabilidades de supervivencia libre de eventos y supervivencia global para todo el grupo fueron respectivamente de 0.82 (EE = 0.05) y 0.90 (EE = 0.03). Los resultados con la estrategia SFOP/SFCE 95 fueron excelentes. La ausencia de respuesta a la quimioterapia de primera línea fue el único factor pronóstico adverso significativo. La estrategia de *watch and wait* probó ser segura y eficaz.

Palabras clave: tumores germinales malignos, infancia, adolescencia

Germ cell tumors (GCTs) are rare in children younger than 15 years, accounting for approximately 3% of cancer cases in this age group[1]. The majority of extra cranial GCTs that occur in fetuses and neonates are benign teratomas at midline locations including sacrococcygeal, retroperitoneal, mediastinal, and cervical regions. Extra cranial malignant GCTs are much more common among adolescents aged 15 to 19 years, representing approximately 14% of cancer diagnoses in this age group. GCTs develop from primordial germ cells, which migrate during

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embryogenesis from the yolk sac through the mesentery to the gonads[2]. Childhood extra cranial GCTs can be divided into gonadal and extra gonadal types.

The histological and genetic properties of these tumors are heterogeneous and vary by primary tumor site and the gender and age of the patient[3, 4]. Morphologically identical GCTs that arise in younger children have different biological characteristics from those that arise in post pubertal and young adults[5]. Malignant GCTs encompass a group of diseases that share a common embryological origin and an extraordinary responsiveness to chemotherapy, particularly to platinum as was initially reported by Einhorn et al[6].

We present the clinical features and outcome of a cohort of consecutive patients with extra cranial germ-cell tumors treated following the guidelines of the French Protocol SFOP/SFCE TGM95 at *Hospital de Pediatría* Garrahan, Buenos Aires, Argentina.

TABLE 1.– *SFOP modified TNM classification*

Clinical staging	
Stage I	Tumor less than 5 cm, N0, M0
Stage II	Tumor more than 5 cm, N0, M0
Stage III	Any size, loco-regional/N1, M0
StageIV	Any size, distant N1, M1
Post-surgical staging	
pStage I	Tumor with no loco-regional extension, completely resected, M0
pStage II	Tumor with loco-regional extension, completely resected, M0
pStage III	Tumor with loco-regional extension, incompletely resected, M0 IIIA: microscopic residue, IIIB: macroscopic residue
pStage IV	Non-resectable metastatic disease

Materials and methods

From September 1995 to December 2010, 107 new consecutive patients with extra-cranial malignant germ cell tumors were registered at our institution and treated prospectively following the guidelines of SFOP/SFCE (*Société Française d´Oncologie Pédiatrique/ Société Française de lutte contre les Cancers et leucémies de l'Enfant et de l'adolescent*) TGM95 Protocol[7].

Eight patients were not considered assessable for evaluation: 1) a 6 month-old boy with localized completely resected testicular yolk sac tumor was very early lost to follow up, 2) a female neonate diagnosed as a liver metastatic placental choriocarcinoma and successfully treated by an alternative therapy as reported by Johnson et al[8] (free of disease-FOD +55 months), 3) one 8 year-old girl with previous central deafness and a mixed malignant GCT of the ovary treated by an alternative chemotherapy to avoid CDDP ototoxicity (FOD +45 months), 4) a 4 month-old girl with a voluminous retroperitoneal mixed malignant GCT treated with an alternative chemotherapy due to initial hepatic failure (FOD +39 months), 5) one 11 year-old girl with Turner disease and a bilateral disgerminoma referred in a very bad condition and treated with an alternative therapy and dying after the first cycle of overwhelming endocarditis with valve destruction, 6) a 14 year-old girl with a mosaic X0/XY genotype referred with advanced bilateral mixed malignant germ cell disease and treated with an alternative regimen because of a very bad clinical condition dying a month after, 7) a boy referred to us with advanced terminal metastatic mixed MGCT, was treated with an adapted chemotherapy schedule and died without finishing the administration of the first cycle, 8) one 9 year-old girl with a metastatic rhabdomiosarcoma originated in a mediastinal teratoma treated with SIOP MMT strategy (FOD +84 months).

Ninety nine assessable patients were prospectively treated following the guidelines of TGM 95 Protocol from the SFOP/SFCE[7]. Diagnosis was established by high levels of typical tumor markers (TM) or histological data provided by tumor resection or biopsy. Staging was studied by Computed Tomography Scanning. A SFOP modified TNM classification was used (Table 1). Radical lymphadenectomy was not recommended. Patients with elevated serum levels of TM: a-fetoprotein (AFP) and b fraction of Human Chorionic Gonadotropin (bHCG) before initial surgery were studied before each chemotherapy cycle until complete normalization, then monthly during the first year and bimonthly during the second year of follow-up.

According to this protocol, the first strategy used to treat extra-cranial malignant GCTs was the surgical removal of the tumor whenever feasible. Pure mature and immature teratomas cured by surgery alone were not considered for analysis in this report. Completely resected GCTs with low alpha fetoprotein (AFP < 15 000 ng/ml) levels were not further treated and strictly monitored. The remaining tumors were treated with chemotherapy: VBP courses (vinblastine 3 mg/m^2 days 1-2, bleomycin 15 mg/m^2 days 1-2, and cisplatin 100 mg/m^2 on day 3) for patients allocated to the low-risk group (non-metastatic tumors and AFP < 15 000 ng/ml) or VIP courses (etoposide 75 mg/m^2 days 1-5, ifosfamide 3 g/m^2 days 1-2, and cisplatin 20 mg/m^2 days 1-5) for patients allocated to the high-risk group (either metastatic tumors and/or AFP > 15 000 ng/ml). After normalization of tumor markers, patients received two additional chemotherapy courses with a maximum of 5 for low risk cases and 6 for the high risk group. A surgery (including the organ primarily involved) was performed in patients with residual disease after chemotherapy or in patients who did not undergo initial resection. Massive extra-gonadal tumors of mediastinal or sacrococcygeal localization were initially treated by chemotherapy. Gonadal primary always prompted the complete surgical organ ablation. The coccyx was always resected in sacrococcygeal primaries. The surgery was considered complete if the tumor was resected *in toto* without evidence of rupture. In case of complete resection after chemotherapy, no additional treatment was administered even if the pathological analysis revealed viable malignant components. In case of non-remission (i.e., non normalization of TM, incomplete resection of viable tumor), progression during chemotherapy or recurrent malignant GCT, different salvage chemotherapy schedules were recommended according to previous therapy, followed by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) when a complete remission was achieved. Complete disease remission was established when a sustained normalization of TM or no evidence of histological malignant disease could be found by second look of residual tumor masses. Non response to high-risk chemotherapy (i.e. VIP schedule) was considered a protocol failure and initial refractory disease. Radiotherapy was not recommended as first line therapy and was only administered in the context of palliative care[7, 9].

The Common Terminology Criteria for Adverse Events v4.0 (CTCAE) from the NCI, USA was used to classify toxic findings[10].

Data were updated to December 31, 2013. This phase III therapy trial was approved by national authorities and an informed consent was obtained from each patient and/or his or her legal guardian.

Overall survival (OS) and event-free survival (EFS) distributions were estimated by the method of Kaplan and Meier[11]. The log-rank test was used to assess the statistical significance of survival comparisons. OS time was defined as time from diagnosis to death or date of last follow-up in surviving patients. EFS was defined as time from complete initial remission to first relapse, second malignancy, death or date of last follow-up in patients with uneventful survival. Patients with initial refractory disease were censored at time "0" for EFS estimate. Standard error (SE) was calculated following the method described by Peto[12]. For statistical analysis, GraphPad Prism version 4.00, for Windows, GraphPad Software, San Diego California USA, 2003.

Results

Assessable patients (n = 99), 49 boys and 50 girls (M/F = 0.98) had a median age of 11.1 (r: 0-17) years. Age distribution is shown in Figure 1 and Table 2. The number of analyzed patients allowed not giving redundant percentage figures.

Eighty five patients were diagnosed by biopsy or complete surgical resection and tumor markers (TM). Fourteen were initially diagnosed by TM alone. Site, stage, gender, histology and risk group therapy distribution are shown in Table 2.

Gonadal tumors (n = 77) could be divided in 4 groups: germinomas (n = 15), malignant non-seminomatous GCT of the ovary (n = 25), pure yolk-sac tumors in prepubertal testicles (n = 18) and post-pubertal malignant mixed GCT of the testis (n = 19). Extra gonadal tumors (n = 22) were also divided into 4 groups: malignant GCT of the mediastinum (n = 6), pure high-grade immature teratomas (n = 3), yolk sac tumors in sacrococcygeal region (n = 8) and pure yolk-sac tumors of other unusual primary localizations (cranial basis, face, stomach, and pelvis) in young patients (n = 5).

Histology distribution was as follows: mixed malignant GCT: 51, pure yolk-sac tumors: 27, pure germinomas: 15, pure high-grade immature teratomas: 3, pure choriocarcinoma: 2 and pure embryonal carcinoma: 1. There was a very good correlation between TM and histological findings, though sometimes some secreting component could be missed in a small initial biopsy. Gonadal disease occurred in 77 cases, and 22 were extra-gonadal. All non seminomatous malignant GCT in post pubertal male gonads (n: 19) and in the majority of ovaries (n: 25) and mediastinum localization (n: 6) were mixed with various different components including yolk sac tumor, germinoma, choriocarcinoma, embryonal carcinoma, and mature and immature teratoma. All pre-pubertal testicular disease corresponded to pure yolk sac tumors (n: 18). Pure germinomas, all of gonadal origin, were found in 13 girls and 2 males. All sacrococcygeal cases displayed yolk sac tumor as only malignant component, associated with mature teratoma (n: 7). All other cases of extra-gonadal localization corresponded to pure yolk sac tumors in small children (n: 5) with different localizations: pelvic, gastric, skull base, and facial area (Fig. 1, Table 2).

Nineteen cases were stage I, 16 stage II, 31 stage III and 33 stage IV. Metastases occurred mainly in the lungs (n: 28). Other localizations were liver (n: 4), bone (n: 3), distant ganglionar disease (n: 2) and brain (n: 1).

Therapy risk groups, response, events and survival estimates for each subset of patients are showed in Table 2.

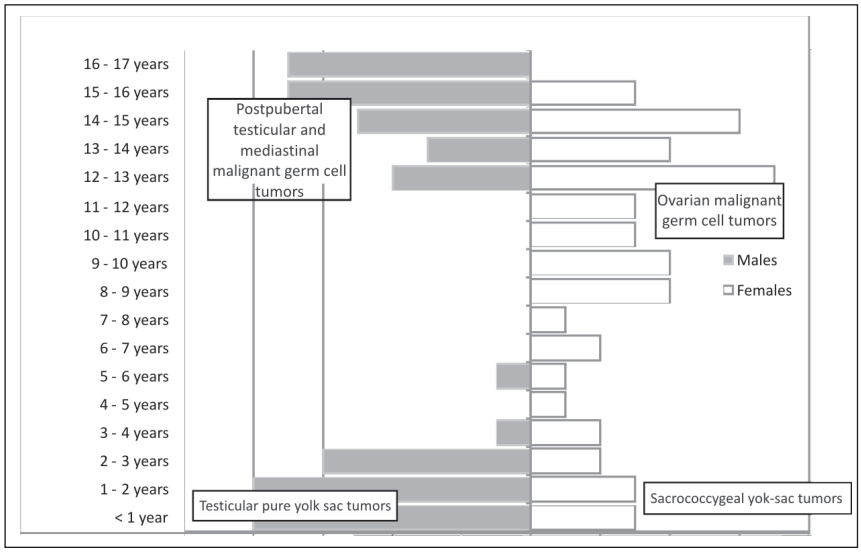

Fig 1.– Distribution of 99 malignant germ cell tumors by age.

TABLE 2.– *Patients grouping by primary site and histological group according to gender, age, staging, therapy and outcome*

Primary site	Histological Group	n	Gender (range)		Median age years	Staging				Therapy				Response		Events			10–year Survival Estimates	
			M	F		I	II	III	IV	W&W	LR	HR	SX	CR	NR	REL	2nd M	DE	DFS (SE)	OS (SE)
Gonadal		*77*	*39*	*38*	*12.4 (0.3-17)*	*19*	*14*	*23*	*21*	*15*	*36*	*26*	*76*	*72*	*5*	*4*	*2*	*5*	*0.78 (0.07)*	*0.92 (0.03)*
Ovary	Non Sem GCT	25	–	25	10.6 (1.9-15.8)	–	5	12	8	–	14	11	24	22	3	1	–	4	0.81 (0.09)	0.81 (0.09)
	Germinomas	13	–	13	12.5 (8-15.2)	–	7	5	1	–	12	1	13	13	–	1	–	–	0.70 (0.21)	1
Testicle	Germinomas	2	2	–	15.6 (15.1-16.2)	–	–	2	–	–	2	–	2	2	–	–	1	–		
	Postpub GCT	19	19	–	15.4 (12.6-17)	6	2	2	9	4	5	10	19	18	1	2	1	1	0.66 (0.17)	0.95 (0.05)
	Prepub GCT	18	18	–	1.4 (0.3-5)	13	–	2	3	11	3	4	18	17	1	–	–	–	0.88 (0.12)	1
Extragonadal		*22*	*10*	*12*	*2.7 (0-14.8)*	*–*	*2*	*8*	*12*	*–*	*2*	*20*	*16*	*20*	*2*	*1*	*–*	*3*	*0.86 (0,08)*	*0.86 (0.08)*
Sacro–coccys	Yolk–sac T.	8	1	7	1.5 (0.5-3.7)	–	1	2	5	–	–	8	8	8	–	–	–	–	1	1
Mediastine	Non Sem GCT	6	6	–	13.6 (3-14.8)	–	–	1	5	–	–	6	5	4	2	–	–	2	0.67 (0.19)	0.67 (0.19)
Various	Yolk-sac T.	5	2	3	1.7 (0.9-3.6)	–	1	2	2	–	–	5	3	5	–	1	–	1	0.75 (0.2)	0.75 (0.22)
	High grade pure Immature teratomas	3	1	2	9.3 (0-11.8)	–	–	3	–	–	2	1	–	3	–	–	–	–	1	1
Totals		99	49	50	11.1 (0-17)	19	16	31	33	15	38	46	92	92	7	5	2	8	0.82 (0.05)	0.90 (0.03)

Non Sem GCT: Non seminomatous germ cell tumor; Postpub GCT: Post–pubertal germ cell tumor; Prebub GCT: Pre–pubertal germ cell tumor; W & W: Watch and wait strategy; LR: Low–risk; HR: High risk; SX: Surgery, CR: Complete response; NR: Non–remission; REL: Relapse, 2nd M: Second malignancy; DE: Death, DFS: Disease–free survival; SE: Standard error; OS: Overall survival.
Median follow up: 64 (r: 5–204) months (5.3 years).

A "watch and wait" strategy was used in patients with initial complete resection of localized non seminomatous malignant GCTs: 1 pure yolk sack tumor of the ovary, 13 pure yolk sack tumors in prepubertal boys and 6 post pubertal adolescents with mixed malignant GCT who achieved a sustained normalization of TM after surgery. One case of testicular seminoma was also followed by imaging with this approach. Six patients showed evidences of progressive disease with a median time latency of 13.2 (r: 3.4-26.2) months by TM elevation or the appearance of a retroperitoneal adenomegaly in the seminoma case. Chemotherapy was delivered according to staging (5 low-risk. and 1 high-risk) and all 6 remained disease free after therapy. Eleven (88%) pure yolk sack tumors in prepubertal boys and 4 (66%) post pubertal adolescents with mixed malignant GCT achieved a sustained normalization of TM after surgery and did not required any further therapy (Table 2).

Three high-grade pure immature teratomas displayed unusual features of rapid local invasiveness, non-resectability and outstanding complete response to chemotherapy. A 2 months-old infant male with a fast growing tumor mass in the skull basis was operated three times, the tumor mass reproduced itself in just 5-7 days after each resection. The disease finally responded completely to 3 courses of low-risk VBP chemotherapy. A 12 year-old girl with massive peritoneal tumor dissemination did not respond to low-risk chemotherapy (VBP) and did completely with the high-risk schedule (VIP). Another 9 year-old girl with a mediastinal rapid growing primary also responded to 3 cycles of the low-risk regimen. They all three remained in continuous complete remission +50, +88 and +179 months, respectively.

Only 2 cases stage III (one ovarian mixed malignant GCT and one pelvic pure high-grade immature teratoma) initially treated with low-risk chemotherapy did not respond completely after 3 cycles of VBP and achieved complete and continuous remission with the high-risk schedule. (FOD: +35, and +179 months).

Noteworthy, surgery did not play any significant curative role in 7 cases: 3 immature teratomas, 1 malignant mixed GCT of the ovary (the gonad was destroyed by the tumor), 2 extra-gonadal yolk sac tumors and one mediastinal choriocarcinoma. In all these cases disease disappeared completely with chemotherapy alone.

Initial surgery included: simple biopsy in 7 patients, complete partial resection in 9 patients, and complete resection in 1 patient. Gonadectomy was initially performed in 67 patients. Surgical removal of persistent residues was done in 15 patients, 4 of them with residual mature teratoma. A second look surgery with no evidence of disease was carried out in 3 cases. Resective surgery for

peritoneal teratoma growing syndrome was necessary in 2 male patients and one girl who required 3 consecutive resections of peritoneal teratoma implants. Contra lateral gonadectomy was done in 5 cases: 1 ovarian germinoma with a wrong suspicion of bilateral tumor disease, 2 ovarian non seminomatous GCT where residual teratoma included the other gonad and 2 new tumors in contra lateral testes whose therapy included gonadectomy.

Chemotherapy risk group distribution, number of cycles and acute hematological toxicity is shown in Table 3.

With a median follow-up time of 64 (r: 5-204) months, at 10 years EFS and OS estimates for the whole group were 0.82 (SE = 0.05) and 0.90 (SE = 0.03) respectively (Fig. 2).

Seven patients did not achieve a complete response with high-risk chemotherapy and were assumed as initial refractory disease. Second line chemotherapy was used and local surgery was carried out incompletely in three cases. Three patients were treated with high-dose chemotherapy followed by ASCT, but only one of these cases could be rescued and survived (FOD + 35 months). Overall survival for this subset of patients was dismal [0.14 (SE: 0.13)]. The condition of initial refractory disease to VIP regimen was a conspicuous significant adverse risk factor in overall survival when comparing with good responders by log rank test (p = < 0.0001, Fig. 3). The difference was still significant (p = 0.003, Fig. 4) comparing OS with patients with other events [i.e. relapse or appearance of malignant disease in the other gonad, n = 7, overall survival: 0.71 (SE: 0.17)].

Five patients who achieved a complete disease remission with initial chemotherapy relapsed with a median time of 5 (r: 4-31) months. Two died of disease and three achieved a second continuous complete remission with a second line schedule (two of them plus high-dose chemotherapy followed by autologous stem cell transplantation) + 67, + 63, + 52 months. There was not a conclusive role of surgery in these rescued cases. Only one had a residual fibrotic mass resected by a second look surgery after ASCT.

Two patients underwent a metachronous bilateralization as a second malignant disease: one adolescent initially treated with low-risk chemotherapy because of a stage III seminoma, developed massive intratubular germ cell neoplasia (24 months after initial remission) in the contra lateral testicle and the gonad had to be resected (FOD + 124 months). Another young man originally treated because of a stage II mixed malignant GCT of one testicle at 15 years of age developed a stage I seminoma in the contra lateral gonad six years later and had it resected in an adult center (FOD + 175 months).

Second line chemotherapy was mainly JEB (carboplatin, bleomycin, etoposide, n: 7, one patient rescued) or POG (paclitaxel, oxaliplatin, gemcitabine, n: 7)[13]. This last regime was very well tolerated and allowed the rescue of two patients: one with refractory and one with relapsed disease.

Beyond initial refractory disease, there was not any other significant adverse risk factor that could be identified by univariate log rank test. Age > 10 years, AFP > 15 000 ng/ml, extra-gonadal disease, and stage IV were not significantly associated to worse outcome. No significant differences were found comparing survival results by site of tumor origin, though some unfavorable trend could be observed in mediastinal and ovary non seminomatous GCT primaries.

Ototoxicity was observed in only one girl treated with low-risk chemotherapy (audiogram: 70 db fall at 4000Htz). Nephrotoxicity was found in a few cases in terms of transient magnesium losing tubulopathy. Only one girl showed a transient fall of DLCO in functional respiratory studies after finishing the low-risk chemotherapy schedule.

TABLE 3.– *Chemotherapy: risk distribution, number of courses and acute hematological toxicity*

	Chemotherapy Schedule	
	Low risk (VBP)	High risk (VIP)
Patients (n)	47	38
Number of cycles: n, median cycle #/patient (range)	125, 3 (3-5)	258, 6 (4-6)
Nadir < 1 000 ANC/µl n (%)	49 (39)	188 (73)
Nadir < 500 ANC/µl n (%)	11 (9)	95 (37)
Febrile neutropenia Grade III n (%)	4 (3)	54 (21)
Febrile neutropenia Grade IV n (%)	–	1 (< 1)
Thrombocytopenia 100 000-150 000/µl n (%)	10 (8)	26 (10)
Thrombocytopenia 50 000-100 000/µl n (%)	1 (1)	7 (18)
Thrombocytopenia < 50 000/ µl n (%)	–	88 (34)

VBP: Vinblastine, bleomycin, and cisplatin; VIP: VP16(etoposide), ifosfamide, and cisplatin; ANC: Absolute neutrophil count

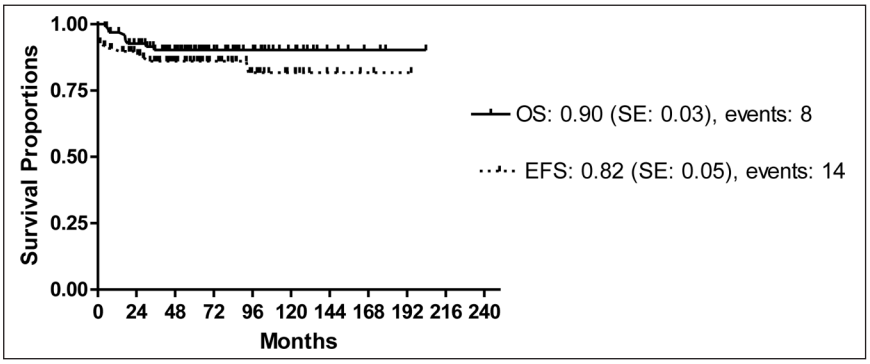

Fig. 2.– Overall Survival and Event-Free Survival estimates at 10 years, n: 99, median follow up: 64 months.

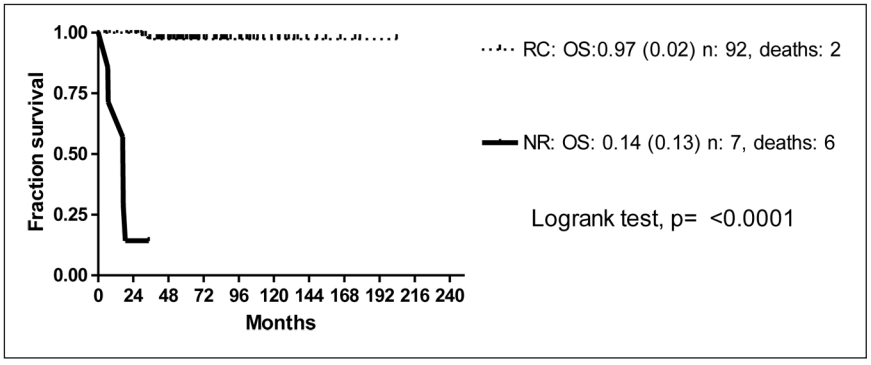

Fig. 3.– Overall Survival comparison between initial refractory disease (n: 7) and the population achieving initial complete remission (n: 92)

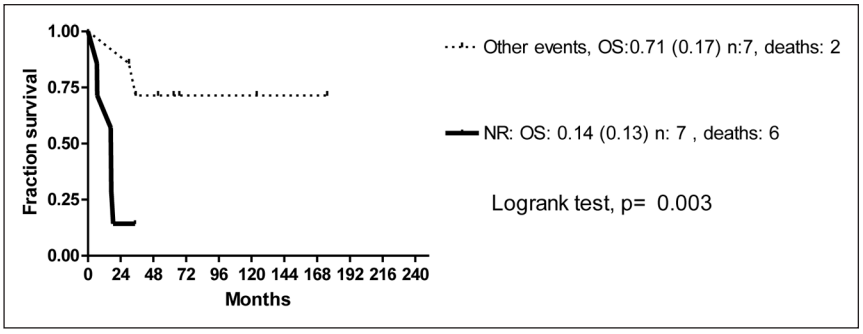

Fig. 4.– Overall Survival comparison between initial refractory disease (n: 7) and other events: relapse or second malignant diseases (n:7)

By the time of the present report, 2 males and 4 females were known to have their fertility preserved. All of them had been treated with the low-risk regime.

Discussion

MGCTs have an outstanding good response to chemotherapy regimens with CDDP or other platinum compounds. Results were excellent in our setting. It is important to consider that MGCT constitute a spectrum of diseases with special characteristics. This leads to a better comprehension of tumor behavior and a good interpretation of chemotherapy response and final outcome (Table 2). Age at diagnoses was high (median 11.1 years) in our setting and so was the rate of advanced disease (high-risk therapy initially required in 47/99 patients) which gives additional value to our results.

A report from SFOP/SFCE TGM 95 Protocol showed excellent good results, with an EFS and OS at 5 years of 0.90 and 0.93 respectively[9]. Similar good results were also obtained by the UKCCSG experience[13] or the German Intergroup[14] or the COG series[15-17]. Many papers reported partial results on ovary, testis, mediastinum or sacrococ-

cys GCT localizations or by risk groups[18-20]. Reports using a common strategy to treat all MGCT in pediatric patients are lacking in the last decade. Besides it is sometimes difficult to compare survival benefits in reports that include teratomas that were cured by surgery alone.

A good response to initial chemotherapy predicts an uneventful outcome. In our setting, the only significant risk factor by univariate log rank overall survival comparison was initial non response to front line chemotherapy ($p = < 0.0001$, Fig. 3). Noteworthy, when comparing survival of patients with initial refractory disease and patients with disease relapse and secondary malignant disease, the overall survival difference was still significant ($p = 0.003$, Fig. 4). All other univariate comparisons in overall survival by age, gender, high alpha fetoprotein levels, site, presence of metastases and histology, did not show any significant differences. These findings may be related to our small numbers and the effects of therapy intensity stratification according to risk. The original French SFOP/SFCE Protocol also reported that alpha fetoprotein levels > 15 000 ng/ml had been no longer significantly associated to unfavorable outcome with the same risk-stratified strategy. On the other hand, the French Protocol did show significant adverse differences in EFS for age more than 10 years and presence of metastases[9].

Ovarian MGCT presented with advanced disease (stage III: 48%, stage IV: 32%). This precluded the application of a "watch and wait" strategy and the high-risk therapy was subsequently needed in 44% of cases.

Sacrococcygeal yolk-sac tumors occurred mainly in females (87%) as expected. Advanced disease was also the rule (stage III: 25%, stage IV: 62%) and high risk therapy was administered in all cases with local surgery before and/or after chemotherapy including the coccyx. Two cases initially operated in other centers had some kind of minor neurological sequel. All patients treated in our institution underwent a small surgery after chemotherapy with coccyx removal and did not have any complications. Delayed surgery in sacrococcygeal GCTs is the best conduct in these cases as it was clearly stated by Göbel et al in 2001[21].

Mediastinal MGCT occurred in males (100%) with a median age of 13.6 years. Eighty-three percent were metastatic at onset. One third did not respond to initial surgery and died of progressive disease. Our small numbers precluded useful comparative results that anyhow were not worse than other series[19].

The particular group of very fast growing high-grade pure immature extra-gonadal teratomas that could not be controlled by surgery and responded exquisitely to chemotherapy in our setting (n = 3), should deserve further attention in larger series and needs to be analyzed separately from other gonadal counterparts. Slower growing immature teratomas classified as Grade 3 by Norris criteria of the ovary and immature teratomas that appear after malignant transformation in mixed GCT of the testis do not seem to fit into the same clinical course and therapy outcome of these three cases. Teratoma histological genesis responds to multiple mechanisms and has particular genetic and clinical characteristics in each case[22].

High-dose chemotherapy followed by ASCT was used in refractory/relapsed disease that showed objective complete response to a second line chemotherapy (n: 5). Three cases were alive and disease-free with a long follow-up after ASCT. So for selected chemotherapy responders in relapsed or initial refractory disease, the use of HD chemotherapy followed by ASCT may play a role as was described in adult cases[23, 24]. Taking into account recent COG studies it was clearly stated that intensifying CDDP[14, 15] or adding ciclophosphamide at high doses[16] to standard regimens in high-risk disease did not showed significant benefits in terms of overall survival and exposed most of patients to unnecessary additional toxicity.

Rapid good responders received less chemotherapy in our setting. This was particularly true for the low risk group where most of the patients received only 3 courses. Contrariwise, high risk patients required a median of 6 cycles of more intense chemotherapy to achieve the same good outcome results.

The application of SFOP/SFCE TGM95 Protocol in our setting improved our historical results and led to a standard of care of MGCT in Argentina since 1995. The approach was easy to apply and could be feasible in other developing countries.

The identification of refractory cases may be the clue to try new drugs or strategies in this unfavorable subset of patients.

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Conflict of interests: None to declare

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LA TAPA

Guillermo Bekes. **"La Mañana"**. Año: 2014
Técnica: Óleo sobre tela. Medidas: 70 x 100 cm.

Guillermo Bekes nació en Santa Fe, Argentina, en 1962. Desde 1982 ha participado en numerosas muestras colectivas, Ferias y ha recibido diversos Premios.

En algo más de 30 años, ha realizado 39 exposiciones individuales en Argentina, Uruguay, Brasil y España.

Entre 1993 y 2003 vive en el campo argentino en donde pinta una extensa serie de paisajes. En 2004 se traslada a Buenos Aires, centrando su trabajo en la figura y el paisaje urbano. Para tres exposiciones efectuadas en Madrid y Galicia (2006, 2009 y 2012) recorre y representa diferentes regiones de España. Actualmente reside en Madrid. Su obra forma parte de colecciones públicas y privadas de Argentina, Uruguay, Brasil, Chile, EE.UU., España, Francia, Reino Unido, Mónaco, Israel, Rumania y Austria.

Ha realizado numerosas exposiciones individuales, las más recientes, en 2015 y 2016, en Galería Zúccaro, Madrid y en septiembre 2016 expone en Buenos Aires, en Ag Espacio de Arte. Entre 1995 y 2014 expuso sus obras en diversos centros. En 1995 en el Centro de Cultura "Inah E. Martensen", Río Grande, Brasil y en el Museo de Bellas Artes de Paraná, Argentina; en 1997 en Park Hyatt y en ese mismo año y en 1998 en Praxis Arte Internacional, Buenos Aires; en 1998 en Galería El Socorro, Buenos Aires; en 2000 en Galería Pérez Quesada, Arte Contemporáneo de Buenos Aires; en 2001 en Galería Ursomarzo y Galería Ag, Espacio de Arte de Buenos Aires; en 2003 y 2004 en Galería El Socorro; en 2006 en Galería Sargent, Madrid y Galería El Socorro, B. Aires; en 2007 y 2008 en Espacio Ag, Buenos Aires; también en 2008 realiza una retrospectiva en el Museo de Bellas Artes de Santa Fe; en 2009 en el Hotel Balneario Mondariz, Pontevedra, Galicia; en 2010 y 2012 expone en Galería El Socorro; en 2010 y 2011 en Galería Ag Espacio de Arte, Buenos Aires; en 2012 nuevamente en Galería El Socorro y en 2014 en Gal. Artemio de Tandil y en Casa de Galicia, Madrid.