4527 POSTER

Late relapse and fertility issues after testicular germ cell tumors treatment: a ten-year experience

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Background: Testicular germ cell tumors (GCT) can today be cured in the vast majority of patients, the main concerns of survivors being relapse and long term treatment side effects. Although late relapse is associated with a poor prognosis, reliable predictive factors are yet to be identified. Also, the most psychologically burdening treatment side effect (fertility impairment) often does not appear to have specific risk factors.
Methods: A retrospective study over 10 years' period was designed under uniform inclusion criteria for patients diagnosed with advanced (stage II-III) GCT. All patients were evaluated for history of undescended testis, age, treatment, cell types, lymphovascular/ local invasion, and marker levels. Patient's conserved fertility was defined (based on responses to a questionnaire) in terms of children born without any interventions after treatment for GCT.
Results: 114 patients with histologically confirmed GCT, aged 18−77 (median 31), were treated between 1997 and 2006 with cisplatin-etoposide-based CT. Conventional radiation therapy (RT) was performed in 10 patients (8.8%). All 36 (31.6%) patients with normalized tumor markers and retroperitoneal residual masses underwent nerve-sparing retroperitoneal lymph nodes resection (nsRPLND) – in 16 patients, necrosis only; in 20 patients, persistent carcinoma or teratoma, treated with an additional 3 to 4 cycles of BEP. 16 patients (12.9%) had late relapse (median DFS 31.3 months), 9 as distant metastases (3 liver, 6 lung) and 7 patients as lymph node enlargement, irrespective of initial treatment. Median OS is 84.7 months, 96% of the patients currently alive and disease-free. In our study, late relapse prognostic factors were: absence of teratoma in primary tumor, normal pre-CT LDH level and radiological partial response in lymph nodes after CT. 97 out of 114 patients (85%) responded to our fertility questionnaire. 50 tried to have a child and there were 28 children born without any interventions. There was no statistical difference in fertility by type of treatment: CT alone (17/55; 30.9%), CT plus nsRPLND (8/32; 25%) and CT plus RT (3/10; 30%) ($p > 0.1$).
Conclusions: We did not find treatment-related fertility issues, probably because RPLND was performed selectively. Although rare, late relapse justifies long-time clinical and radiological post-therapeutic surveillance of advanced GCT patients. The predictors identified may help to reach a therapeutic decision in selected cases.

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Upfront medical management of clinical stage (CS) I−IIA testicular cancer patients with embryonal carcinoma predominance and/or lymphovascular invasion

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Background: CS I, IIA testicular cancer with embryonal carcinoma predominance (ECP) and/or lymphovascular invasion (LVI) are considered at high risk of relapse. We retrospectively evaluated the outcome of these patients (pts) who were treated by upfront medical management followed by retroperitoneal lymph node dissection (RPLND) in selected cases.
Materials and Methods: Between 1993 and 2003, 188 pts with CSI-IIA non seminomatous germ-cell testicular cancer were treated in our institution. Of these, 110 had evidence of ECP and/or LVI. Seventy seven pts with CSI were managed by surveillance followed by chemotherapy (CT) and surgical exeresis of residual disease in case of relapse and 33 pts with CSIIA underwent upfront CT and RPLND in case of residual masses. Median follow up (MFU) was 54 months (1–131).

	Patients	RPLND	CT	MFU (mo)	% Alive
This series	110	23 (21%)	65 (59%)	54	109 (99%)
Stephenson et al. [1]	267	267 (100%)	82 (30%)	53	267 (100%)

Results: In CSI: 33/77 pts (43%) relapsed: 19 in the retroperitoneum only, 4 in the lung only, 6 in both localizations, 3 had biologic marker elevation only and 1 had relapse in the perineum. Treatment: 18 CT only, 13 both CT and RPLND, 1 CT followed by wedge resection of lung metastases; 1 was lost to follow-up. Median time to relapse was 4.8 months [1−41]. One patient died after RPLND.
In CSIIA: 10/33 pts (30%) required RPLND following CT. Two pts relapsed. One of them had growing teratoma. All pts are still alive with no evidence of disease.
Review of histological specimen at relapse for all pts showed 13 necrosis (54%), 9 teratoma (38%) and 2 residual embryonal carcinoma (8%).
The table summarizes treatment requirements and survival in our series compared to an upfront RPLND management and secondary CT in selected cases.
Conclusion: Upfront medical management is the preferred treatment option for CSI-IIA testicular cancer pts with ECP and/or LVI. Up to 79% of pts avoid RPLND.

References

[1] Stephenson A, Bosl G, Bajorin D, et al.: Retroperitoneal lymph node dissection in patients with low stage testicular cancer with embryonal carcinoma predominance and/or lymphovascular invasion. J Urol 174: 557–560, 2005.

4529 POSTER

Immature teratoma in resected post-chemotherapy residual tumors: patient's outcome and prognostic factors

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Background: Unlike other viable malignant germ cell tumors, immature teratoma is characterized by a low proliferative potential and poor sensitivity to chemotherapy (CT). There are no data about prognosis and management of NSGCT pts with resected immature teratoma in post-CT residual masses. We performed this retrospective survey to study the natural history of pts with immature teratoma in resected post-CT residual masses.
Patients and Methods: From December 1987 to May 2006, 315 pts with advanced NSGCT, whose tumor markers were normalized after induction etoposide- and cisplatin-based CT (EP, BEP, C-BOP-3BEP or T-BEP regimens), underwent resection of residual tumor masses in our center. The morphology of resected residual masses was classified according to the worst histological findings presented: carcinoma (n = 58), immature teratoma (n = 15), mature teratoma (n = 97), or necrosis (n =145).
Results: All 15 pts with immature teratoma had testicular primary tumor and initially belonged to good (n = 7), intermediate (n = 3) and poor (n = 5) IGCCCG prognostic groups. 10 post-CT retroperitoneal lymph node dissections, 5 pulmonary resections and 2 supraclavicular LN dissections were performed. 8 pts received 2 cycles of adjuvant CT (commonly VAB-6) after resection. 2 pts died due to massive intraoperative bleeding, which was a complication of retroperitoneal lymph node dissection and there were two other deaths due to disease progression (both pts received adjuvant CT). With median follow-up of 65 (range, 14–150) months, 5-year OS is 69%, which is comparable with OS of pts with resected viable tumor (62%), and lower than resected residual tumor, which contained mature teratoma (82%) only. 'No evidence of disease (NED)' status after surgery was the only prognostic factor: among 11 pts, who became NED, 10 (91%) pts are still alive, compared with 1 (25%) out of 4 pts with persistent residual tumor.
Conclusions: In general prognosis of pts with immature teratoma in resected residual tumor after induction chemotherapy is poor. Aggressive surgery, which attempts to resect all residual masses, can substantially improve the prognosis of pts.

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Individual treatment with stem cell rescue in patients with germ-cell tumours

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Background: Treatment with high dose chemotherapy and autologous stem cell rescue in pacients with poor risk germ cell tumors is still controversial. Results of multicentric randomized EBMT study IT 94 presented at ASCO 2002 show benefit in 1-year EFS in high dose arm

(52% versus 48%), 3-year EFS was the same in both arms (53%) in salvage treatment. Individual treatment with stem cell rescue as upfront treatment offers a survival benefit.

Methods: Autologous stem cell rescue was provided in our center, from September 1997 to February 2007 to 54 patients. High dose chemotherapy was indicated to 32 patients in salvage setting after 2nd line of treatment (VeIP) and to 22 patients as upfront treatment after 1st line treatment (BEP). Median age was 29 years and tumor markers were elevated: HCG in 10 pts, AFP in 13pts.

Stem cell mobilization was performed after the 3rd cycle of VeIP or BEP in combination with G-CSF. The amount of CD34+ cell/kg b.w. was $2.0-13.4\times10^6$. High-dose conditioning regimen CARBOPEC (carboplatin 1,600−2,200 mg/m^2, etoposide 1,800 mg/m^2, cyclophosphamide 6,400 mg/m^2) was used. The treatment was well tolerated without transplant-related mortality.

Result: WHO criteria non-hematological toxicity was predominantly grade 2 to 3. Engraftment was rapid, recovery of hematopoiesis in neutrofils over 1.0×10^9/l and platelets over 50×10^9/l was reached an average on days +10 and +13 respectively. Additional post-transplant treatment for persistence, progression or relapse had 20 patients (9 pts had 2nd line treatment VEIP, 12 pts had 3rd line treatment with paclitaxel + gemcitabine and 5 pts had retroperitoneal lymphadenectomy).

The follow-up period ranging from 3 to 107 months, at present 40 (74%) patients are alive, 14 (26%) pts died. Median TTP of all pts is 10 months, median OS of all pts is 39 months. Median DFS of surviving pts is 38 months.

Conclusion: high-dose chemotherapy with autologous stem cell rescue in patients with poor risk germ cell tumors is feasible and beneficial method of the individual treatment. High-dose chemotherapy as upfront treatment for poor prognosis germ cell tumors and as salvage treatment in good risk pts seems to be good possibility of the individual treatment.

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Prognostic significance of primary tumor morphology on progression-free survival (PFS) in patients (pts) with metastatic nonseminomatous germ cell tumors (NSGCT)

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Purpose: IGCCCG classification is currently used to determine prognosis of pts with metastatic germ cell tumors. One of the limitations of IGCCCG classification is the absence of data about histological subtypes of primary tumor. We studied the prognostic significance of histological subtypes in pts with metastatic NSGCT.

Patients and Methods: We analyzed data of 693 chemotherapy-naive pts with advanced NSGCT treated in our department from 1987 to 2005 with etoposide- and cisplatin-based regimens (EP, BEP, C-BOP-3BEP and T-BEP). Median follow-up time was 32 months (range 3–215); 181 (26%) pts relapsed. 35 of 250 (19.3%) pts, 51 of 257 (28.3%) pts and 95 of 186 (52.4%) pts from good, intermediate and poor prognostic groups relapsed, respectively. Multivariate Cox regression analysis was performed to determine independent factors, which influenced on progression-free survival (PFS) inside IGCCCG prognostic groups.

Results: Multivariate analysis revealed the following negative prognostic factors as independent: in the IGCCCG good prognostic group – mature and immature teratoma complex in primary tumor (hazard ratio [HR] 3.384; 95% CI 1.534−7.463), absence of embryonal cancer component (HR 2.136; 95% CI 1.251−3.649), number of metastatic sites (HR 2.806; 95% CI 1.487−5.296). In patients with the intermediate prognosis: presence of immature teratoma (HR 1.738; 95% CI 1.132−2.669). In IGCCCG poor prognostic group: presence of non-pulmonary visceral metastases (HR 1.45; 95% CI, 1.056−1.992).

Conclusion: In good and intermediate prognostic groups, morphology of NSGCT has an independent prognostic value. It should be taken in to account while defining the prognosis and choice of treatment.

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Bone abnormalities in male germ-cell cancer survivors

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Background: Survival of men with testicular cancer is long due to successful therapeutic intervention, which usually includes orchidectomy. Therefore, we studied the prevalence of osteoporosis in a single center cohort of long term survivors of germ cell cancer.

Methods: In a cross-sectional study design, we studied 225 male patients with a mean age of 39.9 years (range 18.2−66.9), who were treated between 1977 and 2006 for germ cell cancer. 223 (99.1%) patients underwent an unilateral orchidectomy and in 2 (0.9%) patients no orchidectomy but retroperitoneal or mediastinal tumor biopsy was performed to confirm the diagnosis. 159 (70.7%) patients received cisplatin-based combination chemotherapy for metastases or primary extra-gonadal tumor at a mean age of 30.9 years (range 14.2−61.1). Between 2003 and 2007, bone mineral density (BMD) was measured at the lumbar spine and femoral neck by DXA and Z-scores calculated. Vertebral deformities were evaluated by a semi-quantitative measurement on lateral x-rays of the spine. Non-vertebral fractures were evaluated by questionnaire and confirmed by x-ray. All patients had normal total testosterone, estradiol, parathyroid hormone, 25(OH)-vitamin D and 1,25$(OH)_2$-vitamin D concentrations, evaluated by fasting blood samples.

Results: BMD was low in 73 (32.4%) patients; 59 (26.2%) patients had Z-scores between −1 and −2 SD, while fourteen (6.2%) had Z-scores below −2 SD. Vertebral deformities were present in 73 of 190 (38.4%) evaluated patients, twenty-five of whom also had low BMD. There was no relationship between vertebral deformities and either age, chemotherapy or testosterone/estradiol levels. No correlation was found between vertebral deformities and low BMD. Nine of 182 (4.9%) patients who responded to the questionnaire had non-vertebral fractures at a mean age of 39.1 years (range 21−51); 1−17 years after the initial diagnosis of testicular cancer.

Conclusions: More than one third of the eugonadal male survivors of germ cell cancer have vertebral abnormalities which are not related to age, chemotherapy or genital hormone concentrations. The underlying mechanism remains unknown. This high prevalence of bone abnormalities indicates that screening should be advocated in all germ cell cancer survivors.

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Combination of gemcitabine and doxorubicin in sarcomatoid and/or rapidly progressive metastatic renal cell carcinoma (MRCC)

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Background: Clinical presentation of MRCC could be rapidly aggressive especially when tumor exhibit sarcomatoid or Furhman's grade 4 profile. In 2004, Nanus et al. reported efficacy of the association of Gemcitabine (G) and Doxorubicin (D) in sarcomatoid or rapidly progressive MRCC (Cancer). In this retrospective study, we evaluated G+D in this setting.

Methods: All patients (pts) had MRCC, with sarcomatoid feature or a significant progression in previous 4 months. G: 1500 mg/m^2 and D: 50 mg/m^2 were given every 2 weeks with G-CSF support. Pts were evaluated bimonthly for toxicity using NCI/CTCAE scale and every 4 cycles for efficacy using RECIST criteria.

Results: From June 2003 to August 2005, 29 pts were treated. Five (17%), 19 (65%) and 4 (14%) pts had an ECOG performance status of 0, 1 and 2, respectively. Twenty-one pts (86%) had at least 2 metastatic sites. Sarcomatoid feature was predominant in 6 pts (20%) while 6 pts had papillary tumor. Clear-cell histology was pure in 17 pts (59%) and mixed in 5 pts, while Furhman's grade 4 was predominant. All pts had progressive MRCC in the last 4 months. Twenty-five pts had received a previous systemic therapy. A median of 4 courses of G+D was given. Only 4 pts (14%) had a dose reduction or a time delay for subsequent course. No grade 4 toxicity or drug-related death was reported. One pt had grade 3 vomiting and reversible grade 3 renal insufficiency. No febrile neutropenia was seen. One pt had a partial response (7 months), one pt had a mixed response and 14 pts had a stable disease for at least 4 months for 9 pts. No response was seen in sarcomatoid tumors. The median disease-free survival was 3.7 months, including 8 pts (28%) with a time to progression $\geqslant$6 months and median overall survival was 7.1 months including 6 pts (21%) leaving more than 12 months.

Conclusion: In this study, the combination of D+G in sarcomatoid and/or rapidly growing MRCC showed a lower response rate than previously reported (Nanus. Cancer 2004). Nevertheless, some patients