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Multidisciplinary treatment of central nervous system (CNS) metastases in patients with metastatic testicular germ cell tumor (GCT)

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Background: CNS metastases (mets) occur frequently in patients (pts) with metastatic disease at first diagnosis. The sequence and modus of local treatment approaches to systemic chemotherapy in those pts is still unknown.

Material and methods: Data of 95 pts [med. age: 32 years (12-47)] presenting with CNS mets at initial diagnosis have been collected between 1994 to 2002 by systematic request. Median follow-up from diagnosis of CNS mets for all pts were 20 mos (range, 1-131) and 37 mos (3-131) for surviving pts.

Results: In total, 2 pts (2%) had seminoma and 92 pts (97%) a nonseminomatous primary GCT (n.e.=1). Disseminated CNS involvement was found in 64% of patients. Additional metastatic sites included lungs (95%), mediastinal LN (22%), bone (3%) and other (35%). Treatment for CNS mets consisted of 4 cycles of platinum based chemotherapy (CT) ±extracerebral secondary resection (SR) (n=29), CT + local treatment (LT) (radiation or/and neurosurgery) ±SR (n=63) or LT alone (n=1) (n.e.=2). Estimated 2-yr PFS and OS rates were 51.4% (CI95%, 39.8-62.9) and 57.1% (46.2-68.1), respectively. No significant differences seen regarding extent of CNS involvement, dose intensity of chemotherapy as well as sequence or dose of radiation. Multivariate testing identified the following independent adverse factors for PFS and OS: CT (without LT/SR), histology of chorionic carcinoma, presence of visceral disease (PFS only).

Conclusion: Curatively intended CT will result in survival rates comparable to pts presenting with 'poor prognosis' criteria according to IGCCCG. The addition of radiotherapy applied as whole cranium irradiation simultaneously or as consolidation therapy appears to be a standard approach particularly in symptomatic pts or in pts with disseminated extent of CNS disease. The indication of secondary resection of a solitary post-therapeutic residual mass is unclear; however, secondary surgery is mandatory if residual tumor masses outside the brain are found after completion of chemotherapy.

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Refractory germ-cell tumors (GCTs): salvage high-dose chemotherapy (HDCT) combining 2 mobilization regimen followed by 3 HDCT with blood stem cell transplantation (the taxif regimen – Getug group).

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Cis-platinum resistant or refractory GCTs possess a very bad prognosis with a 5-year survival rate ranging from 5 to 20%. Tandem HD-CT using the ICE regimen (Ifosfamide, Carboplatin, Etoposide) is able to circumvent cis-platinum-resistance, but expectancy of cure remains low. New strategies are warranted with new drugs and sequential HD-CT. Rationale: Epirubicine (E) and Paclitaxel (P) possess anti-tumor activity in GCTs, and allow us to collect PBSC. Cyclophosphamide (CPM) and Thiotepa (TTP) can be combined at high-dose with a good activity and tolerance. The ICE regimen is a worldwide used HD-CT regimen. Protocol: Pts were planned to receive 2 mobilization regimens (day 1 & 14) combining E (100 mg/m2) and P (250 mg/m2) supported by filgrastim, followed by 3 consecutive HD-CTs [one course combining a 2-day continuous infusion of CPM, 3 g/m2 + TTP, 400 mg/m2, followed by two ICE regimens (IFM, 10 g/m2, CBDCA, AUC 20, VP16, 1500 mg/m2), both given with PBSCT at days 35 and 70]. PBSC were collected after the first and the second courses of EP with the aim to collect 9 x 106 CD34+/kg. We report herein on the preliminary results of this multicentric study.

Results: From 02/98 to 11/01, 45 pts (median age: 28 y; range: 17-47) with refractory testicular or extra-gonadal GCTs were enrolled. Pts were treated as 2nd-line therapy (n = 7) or as 3rd line (n= 38) therapy after BEP & VeIP regimens. Fifteen pts (33%) were alive with a median time of F/U of 31.8 months (range: 5-57); 4 of them (8%) obtained a CR, 9 a PR with negative serum markers, 3 a PR with positive serum markers (Overall Response Rate: 35.5%). One-year Overall Survival time was 40%. It was 50% for the patients who have received the 5 cycles of CT. Median survival time was 11.5 months for the whole population and 12.5 months for the patients who have received the 5 cycles of CT. Median PFS was 6 months with a plateau beginning at 12 months. Five pts (11%) died of toxicities (2 of cerebral haemorrhage in a context of cerebral metastases, 1 of respiratory distress, 1 of acute renal insufficiency and 1 of infectious shock). Twenty-five pts (55.5%) died of disease progression during or after HD-CT. These results deserve further studies on multiple HD-CT in poor prognosis refractory GCTs. A second protocol (TAXIF II) is planned for 09/2003 for poor prognosis patients with non-refractory disease.

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Cost-effectiveness of treatment with zoledronic acid (Zometa®) in prostate cancer patients

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Background: Bone metastasis is a catastrophic complication for most patients with prostate cancer. This includes major clinical manifestations such as pain, impaired mobility, hypercalcemia, and bone marrow infiltration. Each of these skeletal related events (SREs) may impair a patient's quality of life and is associated with substantial medical costs. Zometa® has been shown to reduce both the number of SREs and the proportion of patients with SREs. To measure in potential economic value of Zometa® in prostate cancer, a cost effectiveness analysis assessing the additional costs per event avoided or the additional costs per patient who avoids an SRE has been carried.

Methods: In a 15-month phase III randomized, double blind trial, Zometa® 4 mg was compared to placebo for the prevention of SREs in 422 prostate cancer patients with bone metastases. SREs were defined as pathological fractures, spinal cord compression, surgery to bone, radiation to bone, and change of anti-neoplastic therapy. Since there is currently no active treatment to prevent SREs related to prostate cancer, an active comparator is not used in the economic evaluation. The resource use estimation was based upon a panel of experts. Costs are in Canadian dollars.

Results: Efficacy of Zometa®: Treatment with Zometa® resulted in a relative reduction of 25% in the proportion of patients with an SRE (33% vs. 44%; p = 0.021). The number of each type of SRE was consistently lower in the Zometa® group, with a relative reduction of 32% in the total number of SREs (91 vs. 134; p= 0.01). Cost of treating SREs: Compared to placebo, Zometa® reduced the total costs of treating SREs ($107,000 vs. 184,000). The average cost per patient was $497 for Zometa® vs. $883 for the placebo. Cost effectiveness ratio: Treatment with Zometa® resulted in a cost effectiveness ratio of $59,000 per patient avoiding an SRE or $32,000 per SRE avoided.

Conclusion: Zometa® is the first bisphosphonate to confirm efficacy in the treatment of bone metastases due to prostate cancer. The economic analysis shows that the use of Zometa® to achieve this benefit costs an additional $32,000 per event avoided or an additional $59,000 for each additional man in whom an event is avoided. These ratios fall within the threshold point considered as acceptable economic value.

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Post-operative irradiation of prostate carcinoma: results of the Italian survey performed by the AIRO National Working Group on Prostate Radiotherapy.

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Background: The post-operative subgroup of the AIRO National Working Group on Prostate Radiotherapy (RT) conducted a multi-center survey to analyse the Italian standard of care in post-operative radiotherapy (RT) after radical prostatectomy (RP).

Materials and Methods: A January-December 2000 rectrospective study and a January-June 2002 prospective study aimed at assessing patient (pt) accrual in post-operative setting were performed by sending a structured