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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.

851 POSTER

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

questionnaire to the Italian RT Departments belonging to the AIRO Group. Both studies evaluated the number of pts treated, the specific prognostic factors, the RT concepts and schedules according to age, stage, PSA value, RT timing and hormonal therapy. Treatment positioning, immobilisation, simulation, quality assurance procedures were required in the first questionnaire.

Results: 454 pts treated with RT after radical prostatectomy in 2000 were enrolled by the first questionnaire (24 RT institutions, with an accrual of approximately 20 patients per Center). Age range was 45–81 years (33.8% pts >70). RT was delivered in an adjuvant setting (within 6 months after RP) in 297 pts (65.4%) (mean time: 3.4 months) and in an salvage setting for biochemical or micro-macroscopic recurrence in 157 (34.6%). 355 pts (78.2%) were locally advanced. Hormonal manipulation was prescribed directly by the urologists in 244 pts (53.8%). Positive margins, capsular invasion, Gleason Pattern score > 7 were present in 50% pts. Prognostic algorithms (Partin table or Roach formula) in the decision on volume of irradiation were routinely used in 11 Centers (46%). Acute and late toxicity were registered using the RTOG (90%) and/or the SOMA LENT (16.5%) scale. Localization films or digital portal imaging were routinely used. Only 8 Centers (33.3%) occasionally performed in vivo dosimetry. These data were confirmed in the second multicenter prospective study that enrolled 236 pts in the first 6 months of 2002 with these characteristics: age range: 42–78; 154 pts (65.3%) treated with adjuvant intent, 82 pts (34.7%) with salvage RT; 190 pts (74.2%) in locally advanced stage (pT3a-pT4); 112 pts (47.5%) treated with hormonal manipulation (Table 1).

Conclusion: The 2002 prospective survey confirms the 2000 retrospective analysis despite the well known limitations of a study based on mailed questionnaires. These data can help the AIRO Group in evaluating the national state of the art of adjuvant RT after radical prostatectomy and address future multicentric clinical studies within the AIRO Group.

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Conformal irradiation for prostate cancer: biochemical relapse-free survival with standard fractionation versus hyperfractionation

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Purpose: To evaluate biochemical relapse-free survival (bRFS) comparing standard (STD) versus hyperfractionated (HFX) radical conformal irradiation (CRT) in prostate cancer.

Materials and Methods: The medical records of 370 consecutive prostate cancer patients (pts) treated with CRT in the period January 1993-January 2003 were examined. 209 pts received STD (2.0 Gy/day) CRT, while 161 received HFX (1.2 Gy, BID, interfraction interval e 6 hours). 179 pts (87%) in the STD group and 151 pts (94%) in the HFX group were evaluable. STD pts characteristics were: median age 71 yrs (range: 54-85); clinical stage: Tx 1.1%, T1 10.1%, T2 54.7%, T3 30.2%, T4 3.9%; median GPS: 6 (range 2-10); mean initial PSA: 23.2 ng/ml (range: 0.2-280 ng/ml); median ICRU 50 prescription dose to the prostate: 74 Gy (70-76 Gy); pelvis irradiation: 42.5%, median ICRU 50 prescription dose: 48 Gy (range: 40-50 Gy); androgen deprivation therapy (AD): 78.2%; median follow up: 25.2 mos (range: 2-118 mos). HFX pts characteristics were: median age: 69 yrs (range: 50-80); clinical stage: Tx 0.7%, T1 7.3%, T2 53%, T3 35.8%, T4 3.3%; median GPS: 6 (range 2-10); mean initial PSA: 20.2 ng/ml (range: 1.9-520 ng/ml); median ICRU 50 prescription dose to the prostate: 79.2 Gy (70-82.8 Gy); pelvis irradiation: 43.7%, median ICRU 50 prescription dose: 50.4 Gy (range: 40.8-50.4 Gy); AD: 70.9%; median follow up: 36.7 mos (range: 3-107 mos). Pts were treated using a 4-5 field technique, blocking rectal anterior wall at 70 Gy (STD) or 74.4 Gy (HFX). bRFS was defined following ASTRO definition. 5-yr actuarial probability of bRFS was calculated using Kaplan-Meier method.

Results: No significant difference was observed with respect to pre-treatment and treatment variables. 5-yr bRFS rates for STD vs HFX pts were 70.0% (±6.9%) and 82.6% (±3.9%), respectively. 5-yr bRFS rates for STD vs HFX pts receiving no AD were 63.8% (±12%) vs 85.9% (±6.2%), respectively. For pts undergoing neo-adjuvant AD, the 5-yr bRFS rates with STD vs HFX CRT were similar (78.1% ± 14.7% vs 84.0% ± 7.7%) as those noted in the adjuvant AD pts (78.8% ± 5.5% vs 80.2% ± 5.2%).

Conclusion: The 5-yr bRFS rate observed with HFX CRT appears higher than STD CRT. Despite the limited median follow up available, these data can have intriguing implications in the current radiobiological discussion on the proper fractionation to be adopted in prostate cancer.

854 POSTER

Postoperative dilemma of rising PSA levels in patients with prostatectomy: Evaluation of 11C-Choline-PET/CT examination for radiation therapy

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Background: To optimise therapy regimes in patients with rising PSA levels after radical prostatectomy is difficult. There is no diagnostic tool for early and reliable detection of a locoregional relapse in an ealry stage. We studied 11-C Choline-PET/CT in 45 patients with hormonal suspicion of relapsing prostate cancer.

Material and Method: Between 07/2002 and 02/2003 45 patients (pts.) (mean age: 65.2 y) with rising PSA levels after radical prostatectomy were investigated. All patients underwent dedicated 11C-Choline-PET/CT from neck to prox. femur (GE Discovery LS). Image fused PET/CT was used to determine local relapse, lymph node (lnn.) involvement or distant metastasis. CT detected lnn.were measured, localised and compared to PET. In case of focal increased 11C-choline uptake the size of lnn. was correlated to the SUV. In PET SUV was measured in case of local recurrence (LR), single ln.or distant metastasis (lnn.,bone) and correlated to the PSA levels.

Results: 32/45 patients were positive at PET/CT (PSA mean: 21.6 ng/dl). Local recurrence was found in 3 (PSA 2.4 ng/ml), local recurrence and intrapelvic lymph nodes in 5 patients (PSA 22.9 ng/ml), intrapelvic single nodular relapse in 11 patients (PSA 1.7 ng/ml) and distant lymphonodular metastasis, i.e. paraaortal lymph nodes and intrapelvic regional lymph nodes in 13 patients (PSA 63.9 ng/ml). 7 of these patients had also skeletal metastases. SUV was 2.3 in local recurrence (2.1 in single lymph node relapse and 3.4 in nodular conglomerates). Diameter of 22 intraabdominal lymph nodes positive at PET/CT (12.75 mm, range 4.25mm ? 25.5mm) and 45 intraabdominal nodes negative at PET/CT (11mm, range 4.00mm ? 29.75mm) was not significantly different.

Conclusion: The 11-C Choline PET/CTdetects local regional relapse and distant lymphonodular as well as skeletal metastases with high accuracy above the PSA cut off of 0.5 ng/ml. 11-C Choline uptake but not CT measured size is a reliable indicator of lymphonodal involvement in prostate cancer.

855 POSTER

Detection of local recurrence by means of 11C-Choline-PET/CT after radical prostatectomy for conformal radiation therapy

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Background: After radical prostatectomy approximately 25% of men develop biochemical recurrence during long-term follow up. In case of isolated clinical local recurrence (LR) patients appeared to have a more favorable prognosis, but the diagnostic detection of these patients is difficult. The purpose of the study was to assess the utility of 11C-Choline-PET/CT in the detection of local recurrence after radical prostatectomy.

Methods: Between 06/2002 and 02/2003 10 patients (age:xm 66.5 y) with rising PSA levels after radical prostatectomy (RPE) and pelvic lymphadenectomy were investigated. All patients underwent dedicated 11C-Choline-PET/CT examination from neck to inguinal region (GE Discovery LS: GE Lightspeed Plus/Advance Nxi PET-Scanner). Data acquisition started 10 min after injecting 1077 Mgq 11C-Choline and a non-ionic contrast agent in bolus tracking technique. Four row multidetector helical CT, iterative CT-corrected 2-D-reconstructed PET images and fused PET/CT were employed to determine local recurrence or distant metastasis. Patient data about postoperative tumor classification (TNM,Grading,Gleason,R-classification), postop. PSA-level and PSA-level before PET/CT, kind of postoperative systemic therapy and diagnostic investigations before PET/CT were collected.

Results: All pts. before PET/CT-examination were in cN0 M0-Status. In 9/10 Patients (90%) the rising PSA-level is caused by a LR. In 3/10 pts.(30%) only a LR was detected, in 7/10 pts (70%) LR and lymph node involvement was seen. 7/10 pts.(70%) were proved by histology (n=5) or diagnostics (CT/TRUS/MR;n=2). In 3 pts.only 11C-Choline-PET/CT demonstrated the LR.

Conclusions: 11C-Choline-PET/CT differentiates between relapse and scare, so that these patients are selected for curative therapy such as surgical intervention or radiation therapy. The detection of local recurrence after radical prostatectomy by 11C-Choline-PET/CT is also possible in soft tumor masses under 2 cm.