1246 POSTER

Treatment of non metastatic peripheral Primitive Neuroectodermal Tumour (PNET)/Extra osseous Ewing's sarcoma (EOES): experience in the SIOP MMT 89 study

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Objectives: To report the outcome of treatment for non metastatic PNET/EOES treated in the SIOP MMT 89 study.

Patients & treatment: PNET/EOES = 42/199 (22%) of all patients with non Rhabdomyosarcoma MMT registered and histologically reviewed in MMT 89.

32 (76%) were non metastatic. M:F ratio 1.9:1. Median age 9 yrs (3 months - 16.8 yrs). Median follow up 7 years. Localised, complete primary excision (Stage I pT1, pT2) received chemotherapy (CT) with VA x 2; Localised, incomplete initial excision (Stage I, II pT3a (microscopic residual), pT3bc (macroscopic residual) received IVA x 6; Stage III (node positive) received intensified "6 drug" CT. Radiotherapy (RT) was given only for residual disease after initial CT ± second surgery. Sites of disease were limbs (13), trunk/walls (12), head & neck (7).

Results: Five year overall (OS) and event free (EFS) survival were 59% (42-76) and 44% (27-61). Initial causes of failure were: no CR (5 = 16%), local relapse (5 = 16%) or metastatic relapse (9 = 28%). Seventeen patients were alive in 1st or 2nd+ CR of whom 9 had been treated with CT alone (1) or CT + conservative surgery (8), 7 had received RT and 1 radical surgery (amputation). Size of primary had a significant effect on 5 year EFS (86% if T < 5cm (n = 7) vs. 30% if T > 5 cm (n = 23) p = 0.05).

Conclusions: Outcome for non metastatic patients with PNET/EOES is less favourable than for RMS (5 year OS 71%). The most common cause of failure was metastatic relapse (first event in 28% vs. 6% in RMS). Tumour size seems more important to prognosis than in RMS.

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Synovial sarcoma in children and adolescents: experience of the International Society of Paediatric Oncology (SIOP)

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Objective: To review outcome for non metastatic patients with a diagnosis of Synovial Sarcoma (SS) confirmed by central pathology review, treated in SIOP MMT 84 & 89 studies (1989-1995).

Patients & Methods: Forty patients with median age 12 yr (3m - 16 yr). M:F 1.9:1. Primary site was Limbs (30 = 75%) (lower limb 22/30); Trunk/Walls (7); Head & Neck (3). TNM Clinical Stage I (23), II (17), III (0). Post surgical stage pT1, pT2 (9); pT3a (12), pT3b(18). All patients received chemotherapy - Stage pT1, pT2 (complete primary resection) received IVA (Ifosfamide, Vincristine, Actinomycin D)x 3 in MMT 84 and VA x 2 in MMT 89; patients with incomplete primary surgical resection (pT3ab) received IVA x 6-10 in MMT 84 & 89 (to a maximum cumulative Ifosfamide dose = 60 g/m2). Local therapy (second surgery +/- RT) was given to patients not achieving complete remission with primary surgery +/- chemotherapy.

Results: 5 year overall and event free survival was 87% (73-94) and 69% (58-81) at a median follow up of 98 (3-149) months. Multivariate analysis revealed Clinical Stage (p=0.01) as the only significant prognostic factor. Twenty five patients (62%) are alive in 1st CR. Progressive disease occurred in two patients, both died. Thirteen patients relapsed (local 9, local and metastatic 1, metastatic 3). Overall 11/33 long term survivors (defined as follow up > 3 yr from last event) received RT and 2 required amputation.

Conclusion: Non metastatic SS has an excellent prognosis. Most patients can be cured with chemotherapy and conservative local therapy. Relapse was predominantly local and chemotherapy appears to offer a role in improving local control and reducing the risk of distant metastases.

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Hemithorax irradiation in Ewing tumors of the chest wall

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Purpose: In the CESS 86 and the EICESS 92 trials, hemithorax irradiation was performed in patients with Ewing tumors of the chest wall involving the pleura or contaminating the pleural cavity. The results of these patients were evaluated and compared to patients with chest wall tumors who did not receive hemithorax irradiation.

Methods: Between 1985 and 1996, 138 patients presented with a non metastatic Ewing tumor of the chest wall. They were treated in a multimodal treatment regimen including polychemotherapy, surgery and/or radiotherapy depending on the tumor characteristics. Hemithorax irradiation was performed with 15 Gy for patients < 14 years and with 20 Gy for patients > 14 years. 42 patients received hemithorax irradiation (group 1), 86 patients did not (group 2). In 10 patient, no sufficient data was available.

Results: Comparing both groups, initial pleural effusion, pleural infiltration and intraoperative contamination of the pleural space were significantly more frequent in group 1. Event free survival after 7 years was 63% for patients in group 1 and 46% for patients in group 2 (n.s.). 7 year local relapse rates including combined relapses were 12% in group 1 and 10% in group 2. The corresponding systemic relapse rates were 22% vs. 39%.

Conclusion: In the unfavorable subgroup of patients who received hemithorax irradiation, there is a non significant improvement in EFS due to reduced systemic relapses. Local control is equivalent.

1249 POSTER

Prognostic factors in patients with localised tumor of the Ewing family (ET). Update of the EW88 study of the French Society of Pediatric Oncology (SFOP)

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Purpose: 1) To improve survival in patients with ET using semi-continuous chemotherapy (CT) and performing resection of the primary, as often as possible, 2) To identify prognostic factors.

Patients and methods: 141 patients with localised tumour entered the trial between 01.88 and 12.91. Induction CT consisted of 5 courses of Cyclophosphamide, 150 mg/m2 x 7 days, followed by Doxorubicin, 35 mg/m2 IV on day 8. Surgery was recommended. The delivery and the doses of radiation therapy (RT) was based on the quality of resection and the histological response to CT. Maintenance CT consisted of vincristine + actinomycin and cyclophosphamide + doxorubicin.

Results: After a median FU of 8.5 years, the OS at 5 years was 66% and DFS was 58%. In patients treated by surgery, the only prognostic factor was histological response to CT: DFS was 75% for good responders (< 5% of residual cells), 48% for intermediate responders and only 20% for poor responders (> 30% of cells) p < 0.0001.The tumour volume by itself had no influence on DFS in these patients. In contrast, it had a strong impact on DFS in patients treated by RT alone. Age had no impact on outcome.

Conclusion: Trials for localised ET should be based on the histological response to chemotherapy or on the tumour volume according to the modality of local therapy.

Work partly supported by Association pour la Recherche sur le Cancer

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Management of ewing's family of tumors of the chest wall (EFTCW) in childhood: a twenty-year single-institutional experience with 41 consecutive patients

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Introduction: In the study period 1975-1995 we treated 41 consecutive children with EFTCW at onset. Despite an improvement of the diagnostic

techniques and a modification of the treatment program, the treatment strategy was not altered. All patients received chemotherapy (CT) and a local treatment consisting in surgery and/or radiotherapy (RT). Surgery was performed in patients with nonmetastatic disease (M0), and was planned after primary CT; RT was delivered in patients with unresectable tumors, or with microscopical residual disease, or with metastatic disease (M1).

Methods: There were 25 females and 16 males, with a median age of 13 yrs (range 1-18). Nine patients (22%) had distant metastases (M1); in 14/32 with M0 there was at least one of the following: loco-regional lymph node involvement (n=5), pleural effusion (n=10), infiltration for contiguity of the mediastinic structures (n=4). CT consisted in the period 1975-1988 in 9 monthly cycles with VCR+EDX+ADR+DACT, with the addition of IFO from 1985. From 1989 the teatment plan consisted in VCR+VP16+CDDP +epi-ADR alternated to IFO for 8 monthly cycles, followed by hemi-body irradiation as consolidation treatment (10Gy for each session, 4 week apart). Local treatment was planned after 4 cycles.

Results: The response rate to CT (RC+RP) was 86%. Among M0 patients, 24/32 received surgery and 23/32 received local RT; 3/23 who received local RT had second primary tumors (2 breast cancer, 1 thyroid cancer). The median f-up for M0 is 131 months and the 5-year EFS and S probabilities are 0.43 and 0.54, respectively. All patients with M1 died (spread progression in 6, intratoracic progression in 3), with a median survival of 14 months (range 3-26). Unfavorable prognostic factors in the present series were: M1, pathologic LDH level, minor/non response to CT, failure in complete "local" control with surgery and/or RT; the local extension at diagnosis did not have prognostic impact. The regimen 1989-95 obtained a higher response rate and permitted an higher % of radical surgery than the previous one.

Conclusion: Children with nonmetastatic EFTCW can benefit from a multidisciplinary treatment strategy; intensive primary chemotherapy could lead to a radical resection of the tumor thus limiting the use of RT. On the contrary new therapeutic approaches are necessary for patients with metastatic disease.

1251 POSTER

Genomic imbalances in paediatric ependymomas; a United Kingdom Children's Cancer Study Group (UKCCSG) approved study

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Ependymomas are the third most common primary brain tumour of childhood accounting for 10-15% of all CNS tumours in this age group. Analysis of the traditional clinico-pathological variables of histology, age and site has yielded conflicting results and currently there are no clear prognostic factors for childhood ependymomas. Part of the reason for this relates to our poor understanding of the biology of these tumours.

We have initiated a large, retrospective comparative genomic hybridisation (CGH) study of 70 formalin fixed paraffin embedded (FFPE) ependymomas. The use of FFPE-CGH was validated in our laboratory using 15 fresh/FFPE ependymoma pairs. Complete correlation of paired fresh/FFPE tumour CGH profiles was observed.

To date, we have analysed 33 primary and 9 recurrent FFPE ependymal tumours collected from 38 children. Genomic imbalances were observed in 20/33 (61%) primary ependymomas and 8/9 (89%) recurrent tumours. The mean number of imbalances for both primary and recurrent tumours was 2.7. Whole chromosome imbalances were more common in the primary tumours, whereas partial gains and losses predominated in the recurrent tumours. The most common imbalances observed in primary ependymomas were gain of 1q (27%), gain of 9p (24%), loss of 17p (12%) and loss of 6q (9%). The recurrent ependymomas most frequently exhibited gain of 1q (67%) and loss of 6q (22%).

CGH analysis of the remaining 28 FFPE ependymoma samples is in progress and results from the complete series will be correlated with clinical details.

1252 POSTER

Cytotoxicity of L-Threitol-1,4-Dimethanesulfonate (Treosulfan) against human neuroectodermal tumor cells in vitro

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Background: New approaches to achieve higher cure rates or palliation with the least possible side effects are warranted for patients suffering from advanced stage neuroblastoma. Treosulfan, a bifunctional alcylating agent known for its use in the treatment of ovarian cancer, shows a low degree of non-hematological toxicities at doses up to 12,5 g/m2. Pharmakokinetic studies have yielded Treosulfan plasma levels of 306 µg/ml at doses of 10 g/m2. This study is the first to assess the activity of treosulfan against neuroectodermal tumor cells.

Methods: The cytotoxicity of treosulfan against the neuroblastoma cell line LAN1 and the PNET cell line CHP100 was tested using the Sulfohrodamine-B-(SRB)-assay. Stock cultures were grown at 37°C, 10% CO2, using MEM-Iscove medium with glutamine and 7,5% fetal calf serum. Treosulfan was transformed from prodrug to active metabolites by adding sodium hydroxide to the freshly prepared drug solution. Cells were plated to 96 well culture plates. Treosulfan was added after 24 hours at concentrations ranging from 1 to 3300 µmol/l. Incubation time was two hours. After 120 hours overall cells were fixed with trichloroacetic acid,washed and stained with SRB-dye. Protein-bound dye was extracted and optical density determined using a 96-well microtiter plate reader. Cytotoxicity was assessed as loss of optical density compared to untreated controls.

Results: Treosulfan was active against LAN1 and CHP100 cells at doses of 10 µmol/l and above. We determined the ED 50 for both cell lines at 52 µmol/l. At 1000 µmol/l, equalling 300 µg/ml, 30% of LAN1 cells and only 5% of CHP100 cells survived.

Conclusions: Treosulfan is active against human neuroectodermal tumor cells in vitro at concentrations equivalent to plasma levels achieved in vivo. Its possible value for the treatment of neuroblastoma is being studied further.

1253 POSTER

Does myeloablative BuMel therapy improve survival of poor-risk localized tumor of the Ewing family (ET)? Experience of the French Society of Pediatric Oncology (SFOP)

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Purpose: Attempts to improve outcome of patients (pts) with poor prognosis ET have focused on chemotherapy (CT) dose intensification strategies. From the EW88 study, ES/PNET tumours with poor histological response (> 30% residual cells) were identified with very poor survival when treated with conventional maintenance CT. 3 year survival of the fifteen poor responder pts was 20% (0 -40%). The purpose of the EW92P and EW93 studies was to improve the prognosis of such pts by the use of high dose BuMel CT + Blood stem cell support following surgery.

Patients and Methods: 52 pts with poor histological response were included in this strategy (11 in the pilot EW92, and 41 in the EW93 study). After surgery, they received 2 courses of VP16 + ifosfamide before high dose CT consisting of busulfan 600 mg/m2 and melphalan 140-180 mg/m2) (BuMel).

Results: Nine pts did not undergo high dose CT, because of early progression, 43 received high-dose BuMel. 25 survived without relapse from 2 to 86 months (median 36 months) after transplant. For the whole group of 52 pts, 3-year event-free survival of was 51% (36-66). Six pts developed veino-occlusive disease, one of them died from thrombotic microangiopathy.

Conclusion: As compared to the experience of conventional CT, myeloablative therapy with BuMel was a promising approach for patients with poor-risk ES/PNET. The present Euro-Ewing Intergroup study is currently assessing the value of high dose BuMel in a randomised trial.

Work partly supported by Association pour la Recherche sur le Cancer.