of patients in Group A and 65% in Group B were alive. Corresponding numbers of progression-free patients were 53% and 50%.

**Conclusions:** The administration of chemoradiotherapy incorporating weekly docetaxel after induction chemotherapy is a feasible approach in unresectable locally advanced NSCLC, achieving a high ORR with a manageable toxicity profile. Final study results will be presented at the meeting.

# Melanoma and sarcoma

828 POSTER

## cKIT expression in adult primitive neuroectodermal tumor (PNET) and Ewing's sarcoma: a retrospective immunohistochemical study

I.O. Kara[1], S. Erdogan[2], B. Sahin[1], M. Ergin[2], G. Gönlüsen[2], S. Paydas[1]. *[1] Cukurova University Faculty of Medicine, Medical Oncology, Adana, Turkey; [2] Cukurova University Faculty of Medicine, Pathology Department, adana, Turkey*

**Background:** The stem cell factor/c-kit tyrosine kinase receptor pathway has been shown to be important for tumor growth and progression in several cancers, including mast cell diseases, gastrointestinal stromal tumor, acute myeloid leukemia, small cell lung carcinoma, and Ewing sarcoma. We performed immunohistochemical analysis for KIT in 28 of 16 PNET and 12 Ewing's sarcoma.

**Methods:** Formalin-fixed, paraffin-embedded sections were stained with rabbit polyclonal anti-human c-kit (CD117, Dako) using standard avidin-biotin-peroxidase complex technique, antigen retrieval, and an automated stainer.

**Results:** Cytoplasmic c-kit expression was showed immunorecativity of % 50 (6/12) for Ewing's sarcoma group and % 50 (8/16) for primitive neuroectodermal tumor (PNET). Within the each group 2 sections were stained both for cytoplasmic and membranous component.

**Conclusion:** Our results were indicate that target therapy tyrosine kinase receptor inhibitor may be an additional methods to cytotoxic drugs for c-kit positive Ewing's sarcoma and PNET.

828A POSTER

## Vascular endothelial growth factor levels in melanoma. relationship with coagulation and platelet activation markers

F. Guadagni[1], P. Ferroni[2], S. Bucher[3], F. Di Filippo[4], V. Ferraresi[5], C. Catricalà[3], M. Roselli[6], F. Cognetti[5]. *[1] Regina Elena Cancer Institute, Dept. of Diagnosis & Prevention, Rome, Italy; [2] University of Rome La Sapienza, Dept. of Experimental Medicine & Pathology, Rome, Italy; [3] San Gallicano Institute, Dept. of Oncologic Dermatology, Rome, Italy; [4] Regina Elena Cancer Institute, Dept. of Surgery, Rome, Italy; [5] Regina Elena Cancer Institute, Dept. of Medical Oncology, Rome, Italy; [6] University of Rome "Tor Vergata", Dept. of Surgery, Medical Oncology Section, Rome, Italy*

**Background:** Vascular endothelial growth factor (VEGF) is a potent angiogenic factor essential for tumor growth and metastasis. Lately, it was shown that thrombin activation of platelets causes VEGF release, and that VEGF-stimulated endothelial cells promote adhesion and activation of platelets through the generation of thrombin. Thus, the present study was aimed at analyzing whether VEGF levels are increased in patients with various stages of melanoma as a result of platelet and/or coagulation activation.

**Patients and Methods:** Plasma samples were obtained from 95 patients with nodular (30%), superficial spreading (68%) or acral (2%) melanoma [61 males, mean age ± SD: 52 ± 15 years] and 61 healthy donors [14 males, mean age ± SD: 55 ± 14 years). Stage I (n=63) disease was defined as the presence of the primary tumor with no clinically detectable metastatic lesion. Stage II (n=14) disease was defined as the presence of regional lymph node metastasis. Stage III (n=18) disease was defined as widespread disease with metastatic involvement at distant sites. Plasma sP-selectin and VEGF levels were measured by ELISA (both by R&D Systems). Coagulation tests and complete and differential blood cell counts were routinely assayed in each recruited subject.

**Results:** Median plasma VEGF levels were higher in melanoma patients (19.0 pg/ml) compared to control subjects (2.2 pg/ml; $p<0.001$). In particular, median VEGF levels were higher in stage III compared to stages II and I melanoma (27.9 pg/ml *vs.*, 22.9 pg/ml, *vs.*, 14.1, Anova test: $F=3.2$, $p<0.05$). Similarly, metastatic patients had higher levels of sP-selectin ($F=4.7$, $p< 0.02$) and a prolonged International Normalized Ratio (INR)($F=17.0$, $p< 0.0001$) than stage I and II melanoma. Correlation analysis showed that VEGF levels strongly correlated with sP-selectin ($r=0.57$, $p<0.0001$) in melanoma patients. Thus, to further analyze the relationship between VEGF and clinical and laboratory variables of melanoma, a multiple regression analysis including age, sex, stage, diagnosis, VEGF and sP-selectin levels, blood cell counts and coagulation tests was performed. Final model by stepwise analysis showed that only sP-selectin (beta=0.27, $p<0.05$) and INR (beta=0.29, $p<0.05$) were independently related to VEGF.

**Conclusions:** These results suggest that elevated plasma VEGF levels are strictly related to the presence of haemostatic activation in patients with advanced stage of melanoma.

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829 POSTER

## Adults with Ewing's sarcoma/PNET: is it possible to improve survival (Phase II trial: induction chemotherapy adriablastin-cisplatin)

Z. Tomasevic, M. Mihailovic, S. Jelic, D. Ristic, N. Milanovic, A. Karaferic. *Institute for Oncology and Radiology of Serbia, Medical Oncology, Belgrade, Serbia*

**Background**: Ewing's sarcoma/PNET is a disease rarely seen in adults. The literature data regarding outcome of adults with this disease, are insufficient.

**Purpose**: to assess outcome and survival of adults Ewing's sarcoma/PNET treated with neoadjuvant and adjuvant adriamycin-cisplatin chemotherapy (CT) combination.

**Patients and methods**: Since November 1998, fourteen adults with non-metastatic Ewing's sarcoma (12 pts.) and PNET (2 pts.) have been treated at our institute. Twelve pts. were male and 2 were female. The median age was 24.5 years (range 20-44). Nine pts. had tumor located in the central axis skeleton (3 in the pelvic bones, 3 in the spine and 3 in the chest wall). In 5 pts., sites of primary tumor were distal parts of the leg. Nine pts. had locally advanced disease (tumor volume greater than 150 ml) and 5 pts. had small volume localized disease (less than 150 ml).

Treatment consisted of 4-6 cycles neoadjuvant CT with doxorubicin 25 mg/sqm D1-3 and cisplatin 30 mg/sqm D2-5, followed by local treatment and adjuvant CT with EVAIA regimens. In three pts. CT was used with adjuvant intention.

Local treatment was: surgery (6 pts.), surgery followed by radiotherapy (3 pts.), radiotherapy followed by surgery (2 pts.) or radiotherapy alone (1 pt.). One patient was not treated locally.

**Results**: At completion of induction CT, the response, as assessed by NMR imaging, was: 10 PR and 1 SD. Radiological response of the soft tissue mass, separately, was: 6 CR, 4 PR and 1 SD. Histological response to induction CT was evaluated in 7 of 9 pts. who underwent surgery immediately after induction CT. Five of seven pts. were good responders with viable tumor cells of 10% or less.

The median of follow-up was 20 months. For all pts., the median probability of overall survival and median probability of time to progression were, at the moment, 38 months (range 7-42) and 24 months (range 6-42), respectively.

The chemotherapy was well tolerated. No cases of adriamycin cardiotoxicity were seen. Seven pts. experienced transitory grade 4 granulocytopenia at least in one cycle, without febrile episodes.

**Conclusion**: These preliminary results showed very promising activity of adriamycin-cisplatin regimen, and further testing is needed.

830 POSTER

## A clinicopathologic review of uncommon vascular hemangiopericytomas with follow up and analysis of outcome: a 12 year study

K. Gupta[1], O.P. Singh[1], N. Kapoor[2], H.U. Ghori[1]. *[1] Gandhi Medical College, Department of Radiation Oncology, Bhopal, India; [2] Gandhi Medical Colege, Department of Pathology, Bhopal, India*

**Background:** Having a pericytic origin, hemangiopericytoma(HPC) is an uncommon vascular tumor of adults and shared histology with synovial sarcoma, mesenchymal chondrosarcoma and solitary fibrous tumor stems the long lasted diagnostic dilemma. Along with endeavour to solve this problem, this study also defines clinical nature and prognosis of affected patients.

**Methods:** A total of 51 patients with documented diagnosis of primary, recurrent or metastatic HPC were selected from a prospectively main-

tained record of the period between July 1990 and December 2002.Aiming confirmation, a thorough histopathologic re-review was undertaken of the well preserved pathologic material available of 45 cases.With specialised techniques like immunohistochemistry and electron microscopy using unanimously agreed, defined and strict criteria for pathologic diagnosis, out of 51 cases, only 26 were classed as conventional HPC. These patients were further analysed with respect to clinical variables (site,age at diagnosis, gender),operation variables(gross or microscopic margins) ,tumor variables like size (<5; 5-10 and >10 cms),recurrence and metastasis.Kaplan-Meier survival statistics were used for disease free and disease specific survival.

**Results:** Of 51 patients at initial presentation, pulmonary(34.6%)and extremity (36.4%)sites were the most common, followed by trunk (30.7%) of total cases. 19(73%)patients were in the <50 year age group and 7(27%)had age >50 years. Primary tumors comprised of 18(69%)cases. 5(19%)had locally recurrent tumors and 3(11.5%)had metastatic disease.Median follow up (n=26)was 39 months(range:5-72 months).Overall survival rates at two and five years were 87%and 78% respectively. At last follow up disease specific survival was 76%.88% mean survival at 48 months was noted in patients undergoing complete resection(n=13).

**Conclusions:** Currently, the recommended approach is complete resection of the tumors. Unlike a majority of studies this analysis emphasizes a more favourable survival outcome.Hence, outright major surgical intervention is cautioned against and a more conservative approach is advocated,especially for pathologically well confirmed conventional hemangiopericytomas

831 POSTER

## Post-operative radiotherapy for soft tissue sarcoma of the anterior compartment of the thigh: should the sartorius muscle be included?

G.C. Barnett[1], A. Hoole[2], N. Twyman[2], S. Jefferies[1], N. Burnet[3].
*[1]Addenbrooke's Hospital, Oncology Centre, Cambridge, United Kingdom; [2]Addenbrooke's Hospital, Department of Medical Physics, Cambridge, United Kingdom; [3]Addenbrooke's Hospital, University of Cambridge Department of Oncology, Cambridge, United Kingdom*

**Background:** The clinical target volume (CTV) of post-operative radiotherapy for soft tissue sarcoma of the limbs conventionally includes the whole of the transverse cross section of the affected anatomical compartment. In the anterior thigh, sartorius appears to lie within its own fascial compartment, and could be safely excluded. We investigated the potential impact of omitting sartorius from the anterior muscle compartment on patients with soft tissue sarcoma of the thigh.

**Materials and Methods:** Using CT data, the anterior compartments of six patients were outlined twice, initially including and then excluding the sartorius muscle. The length of the CTV was set to be the same as the original plan. Full conformal radiotherapy plans were prepared. The volume of the anterior compartment, both with and without sartorius, and the corresponding planning target volume (PTV) were calculated. For both volumes, the unirradiated normal tissue corridor was outlined on each CT slice, in order to calculate its circumference at each level and its total volume. The corridor was defined as the volume of normal tissue outside the projections of the treatment beams or conformal blocks, which should therefore receive less than 50% of the prescribed dose. The corridor circumference at each level was expressed as a percentage of the total leg circumference and the mean of these values was calculated.

**Results:** For the six patients, the mean reduction in volume of the anterior compartment when sartorius was excluded was 10% (95% confidence interval 8 to 12%), whilst the mean decrease in PTV was 11% (95% CI 7 to 14%). There was a substantial increase in the volume of the unirradiated normal tissue corridor with a mean value of 77% (95% CI 41 to 114%) when sartorius was excluded. In addition, the increase in the means of the normal tissue corridor expressed as a percentage of the whole leg circumference was considerable.

**Conclusions:** It is essential to know the anatomy of the sartorius muscle to be able to exclude it from the anterior compartment. The increase in the size of the normal tissue corridor when sartorius is excluded should deliver clinical advantage by decreasing the normal tissue adverse effects.

832 POSTER

## Ifosfamide, carboplatin, etoposide induces a 50% overall response rate and 1 year overall survival rate in patients with recurrent/refractory soft tissue and bone sarcoma: Embryonal rhabdomyosarcoma histology and complete response to ICE are independent factors signicantly associated with improved survival

M.S. Cairo[1], V. Davenport[1], P. Van Winkle[2], K. Cheung[1], A. Angiolillo[3].
*[1]Children's Hospital of New York, Columbia University, Pediatric Oncology, New York, USA; [2]Childrens Hospital of Los Angeles, Pediatric Oncology, Los Angeles, USA; [3]Children's National Medical Center, Pediatric Oncology, Washington, DC, USA*

**Background:** Survival after relapse in patients with soft tissue sarcoma (STS), especially rhabdomyosarcoma (RMS), Ewing's sarcoma (ES) and osteosarcoma (OTS) has historically been poor (Pappo et al JCO, 1999; Ward et al JCO, 1994). Ifosfamide (I), carboplatin (C) and etoposide (E) (ICE) each have single agent activity against STS and bone sarcoma (Pinkerton et al Can Clin Pharm, 1985; Ettinger et al Cancer, 1999 and Kung et al Invest New Drugs, 1998).

**Material and Methods:** We evaluated the overall response rate (ORR) and overall survival (OS) in patients with recurrent/refractory sarcoma treated with ICE chemotherapy in 3 successive CCG trials (CCG 0894, CCG 0924, CCG 0931). I (1800 mg/m$^2$/d, days 0-4), C (400 mg/m$^2$/d, days 0-1) and E (100 mg/m$^2$/d, days 0-4) were administered to 104 patients. Each ICE cycle was repeated every 21 days following recovery of ANC $*$ 1000/mm$^3$ and platelet $*$ 100k/mm$^3$. Post ICE TX was investigator choice and included either additional chemotherapy, radiotherapy and/or Auto/SCT.

**Results:** There were 97 evaluable patients for tumor response: median age 14.1 yrs (2.8-22.5), 56% male and 46% female. Histological categories included OTS (n=34), RMS (n=27), ES (n=21), other sarcomas (n=15). Response rates in all patients included 27% CR, 24% PR (ORR=51%), 33% SD and 16% PD. The ORR by histological groupings were RMS: 66%, ES: 48%, OTS 36%, other sarcomas 60%. Grade III/IV hematological toxicity occurred in all patients. There was a 7% incidence of grade IV non-hematological toxicity. The 1 and 2 yr OS rates were 50% and 29%, respectively. Patients obtaining a CR after ICE had an 81% and 54% 1 and 2 yr OS rate, respectively (P<0.001). Patients with RMS with embryonal histology had a 1 and 2 yr OS rate of 86% and 46% vs in other histologies of rhabdomyosarcoma 40% and 20%, respectively (p<0.014).

**Conclusion:** In summary, ICE chemotherapy has an excellent induction ORR in patients with refractory/recurrent sarcoma. Patients with recurrent/refractory sarcoma who attain a CR, RMS histology or RMS embryonal histology have a significantly improved survival following ICE reinduction therapy.

833 POSTER

## Pterin-dependent tyrosine hydroxylase mRNA is not expressed in human melanoma cells

B. Kågedal, M. Johansson, A. Kullman, L. Lenner, C. Träger. *Department of Biomedicine and Surgery, Division of Clinical Chemistry, Linköping, Sweden*

**Background:** Tyrosinase (EC 1.14.18) is a key enzyme in pigment formation. It acts by hydroxylation of L-tyrosine to L-dopa and then by oxidation of L-dopa to dopaquinone, which is then further processed to pigment. With mammalian tyrosinase the hydroxylation step is characterized by a lag period, which is eliminated by the addition of L-dopa. In addition to tyrosinase the enzyme tyrosine hydroxylase (EC 1.14.16.2) has occasionally been described to occur in melanocytes side by side with tyrosinase and suggested to produce L-dopa as the co-substrate for tyrosinase. It is therefore important to quantify the amount of the transcript of this enzyme in pigment cells and melanoma cells to understand whether this enzyme could possibly take part of pigment formation.

**Material and methods:** Twelve different melanoma cell lines and 8 neuroblastoma cell lines were investigated. The melanoma cells were characterized as pigmented or non-pigmented according to the results from pigment degradation studies. Total RNA was extracted from 10$^6$ cells by the QIAamp RNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany) and eluted in 40 μl of RNAse-free water. First strand cDNA was synthesized from 10 μl RNA. A real-time reverse transcription-polymerase chain reaction method was used to quantify tyrosine hydroxylase mRNA. The calibrator used was obtained by amplification of a segment of cDNA from tyrosine hydroxylase mRNA, which included the target and allowed estimation of the number of transcripts per cell.