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High Dose Doxorubicin–Ifosfamide (HDDI) Combination Therapy for Soft Tissue Sarcomas (STS)

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Background: Doxorubicin (D) and ifosfamide (I) are the most effective drugs used in STS. The value of dose intensive regimens both in localized and advanced disease is unclear. The aim of this study was to evaluate safety and efficacy (RECIST) of HDDI in terms of objective Response Rates (RR), Time to Progression (TTP) and Overall Survival (OS). Independent factors for OS were also analyzed.
Methods: Retrospective analysis of medical records from our STS database of 1287 patients (pts) from January 2000 to May 2008. We selected pts treated in the neoadjuvant, adjuvant and advanced settings. Chemotherapy regimen used was: D 75 mg/m^2 in 72 hs continuous infusion (c.i.); I 10 g/m^2 (5 doses of 2 g/m^2); MESNA and G-CSF every 21 days. Kaplan Meyer method was used for survival; log rank test and cox proportional regression for univariate and multivariate analysis.
Results: 73 pts were treated, 29 females, 44 males. Median (Md) age: 41 years (15−67). Most frequent histologic subtypes: leiomyosarcoma 19%, malignant fibrous histiocytoma 16%, liposarcoma 15%. 59 pts were advanced (81%); 9 neoadyuvant; 5 adyuvant. Md metastatic sites: 1 (1−4). PS 0−1: 97%. Md of cycles: 4 (1−12). Md follow up: 59 months (2−96). Overall RR 51%, Complete Response (CR) 15%, Partial Response (PR) 36%, Clinical Benefit 81% (CB). Md TTP 7 months (IC95% 6−11), Md OS 21 months (IC95% 16−31). R0 surgery after HDDI (27 pts) was the only significant factor for OS in multivariate analysis. Febril Neutropenia: 40 pts (65%). 2 related deaths (1 for sepsis/1 secondary leukemia).
Conclusion: The combination of HDDI is an effective therapy in terms of response rates. The management of toxicity must involve a multidisciplinary team. This regimen should be considered as an option for first line therapy in patients with STS.

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The Prognostic Value of Genetic Variations of VEGF-a and VEGFR2 Genes in GIST Patients Treated With Sunitinib

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The present study investigated the influence of the single nucleotide polymorphisms (SNPs) in vascular endothelial growth factor A (VEGF-A)gene: −2578C/A, −460 T/C, +936C/T and +405 G/C and VEGF Receptor 2 (KDR)gene: 1416T/A and rs 1531298 on prognosis and sunitinib-related toxicity in patients with gastrointestinal stromal tumour.
Methods: Blood samples were collected from 37 patients with locally advanced or metastatic GIST, treated with sunitinib due to imatinib resistance. The SNPs of the genomic DNA were analysed by PCR and their relationship with disease progression and incidence of adverse events grade >2 according to Common Toxicity Criteria were studied.
Results: In VEGFA gene, the C-allele in the −460 T/C and the T-allele in the +936 C/T polymorphism were associated with significantly higher risk of hypothyroidism (OR: 10,1; P = 0.041 and OR: 10.5; P = 0.015, respectively). No impact of SNPs on arterial hypertension, hand-foot-syndrome and diarrhea was observed. The genotype +405CC was related to lower probability of disease progression (OR: 0.17; P = 0.049). The analysed polymorphisms in VEGFR2 gene were not correlated with any of the outcomes studied.
Conclusions: The results indicate that the three polymorphisms of VEGFA gene have a functional influence on disease progression and sunitinib-related toxicity in GIST patients, plausibly through changed VEGF-A protein level. The possible clinical implications of these findings need further investigation.

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Combination Chemotherapy With Gemcitabine and Docetaxel in the Treatment of Metastatic Soft Tissue Sarcomas − a Single Institution Experience

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Background: Soft tissue sarcomas (STS) constitute a heterogeneous family of solid tumours of the mesenchymal cell origin and accounting for approximately 1% of all cancer diagnoses. Metastatic STS (mSTS) remains an incurable disease, except resectable lung metastases or localized metastatic disease.
Multidisciplinary treatment is the standard of care of primary lesions and limited metastatic disease. Chemotherapy (ChT) is the main option treatment for unresectable mSTS.
Gemcitabine (Gmb) and Docetaxel (Dtx) combination is an active treatment in mSTS especially in leiomyosarcoma (LMS) subtype.
Material and Methods: We review 13 cases of mSTS, who received Gmb 675 mg/m^2 intravenously (IV) over 60−90 minutes on days 1 and 8 plus Dtx 60−75 mg/m^2 IV on day 8 +/− Filgastrim or Pegfilgastrim support every 3 weeks between January 2005 and February 2011 in our hospital. Tumour response in 2 patients (pts) is pending evaluated. Pts did not receive in any case more than 8 cycles.
Median age was 58 years (37−80). 4 pts were men and 9 women. 8 pts (61%) presented advanced LMS. 1 patient (pt) presented an Angiosarcoma. 1 pt a Pleomorphic malignant fibrous histiocytoma. 1 pt a Myxoid liposarcoma. 1 pt a Small round cells monofasic synovial sarcoma. 1 pt a low grade Malignant fibrous hystiocitoma. The median of previous ChT lines was 0 (0−4). Gmb/Dtx combination was the first line in 7 pts.
Results: From 11 pts evaluable for response, 2 pts (18%) obtained partial response (PR) and 2 pts (18%) stable disease (SD). 7 pts (64%) presented progression disease (PD). The global response rate (RR) was 18%, the clinical benefit (CB) (RR+ SD) was 36%, and the median progression free survival (PFS) was 121 days (60–184). 1 pt remains with PR since the end of treatment 18 months ago. 2 pts with lung metastases obtained SD with Gmb/Dtx treatment and they were operated of lung metastases in two times.
Toxicities grade 3−4: aenemia: 1 pts (8%); febrile neutropenia: 2 pts (15%); neutropenia: 2 pts (15%); thrombocytopenia: 3 pts (23%); diarrhea: 3 pts (23%); Alopecia: 9 pts (69%). No patient stopped ChT by toxicity. There were no toxic deaths.
Conclusion: In our experience, Gmb/Dtx combination is an active ChT regimen in mSTS. The toxicity profile is good and the toxicities are manageable. Gmb/Dtx is a good alternative of treatment in mSTS in first line, especially in LMS, or after progression to Doxorubicin and/or Ifosfamide ChT regimens in other subtypes of STS.

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Viscum Album Fermentatum Pini Versus Oral Etoposide as Adjuvant Treatment in Osteosarcoma Patients After Second Relapse

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Background: Osteosarcoma is a highly malignant bone tumour affecting mainly adolescents. With the recommended neoadjuvant chemotherapy it can be cured in approximately 60% of cases. Few experimental target drugs are currently available through phases I and II trials for relapsed and inoperable patients. We know from historical controls that the risk to relapse increases after the second relapse. Relapse-free survival then decreases to <20% after 12 months. Although no final proof of evidence for oral Etoposide is available, it is often used in clinical practice due to reported good results in advanced childhood cancer with response rates of 15%. Oral Etoposide is well tolerated, easy to administer and affordable. Interferon or MTP-PE (muramyl tripeptide phosphatidyl ethanolamine; Mepact®) have also been used as adjuvant treatment with encouraging results in advanced osteosarcoma (improved disease-free survival [DFS] of 7%) but these treatments are significantly more expensive and less well tolerated.
Material and Methods: Viscum album fermentatum Pini (Viscum) is a highly popular herbal medicinal product across central Europe with immunomodulatory activity. Encouraged by the preliminary findings of a pilot study that showed a prolonged DFS of more than 12 months in four out of five with Viscum album treated osteosarcoma patients after their second relapse, we started a two-arm randomized study comparing Viscum album fermentatum Pini s.c. to oral Etoposide in patients free from disease after

their second metastatic relapse. Primary end point is the DFS at 12 months compared to a historical group of patients.
Results: To date, we have enrolled 17 patients: 8 patients were enrolled in the Viscum arm and 9 patients in the Etoposide arm, 8 female and 9 male, median age 35 years (11−65), median follow up 19 months (1−42). Median DFS is currently 17.5 months (5−42) for the Viscum album arm and 4 months (1−12) for the Etoposide arm. Viscum patients had a lower toxicity compared to patients treated with Etoposide. An interim analysis will be done once we have 20 treated study patients (10 for each arm).
Conclusions: Viscum album showed promising results as adjuvant treatment in prolonging DFS after a second relapse. It seems to have the same advantages compared to other immunostimulants (IFN, MTP-PE) at lower costs. A larger multi-center trial would be desirable to determine efficacy of Viscum therapy in osteosarcoma patients compared to other immunostimulants currently approved in osteosarcoma treatment like Mifamurtide.

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Pharmacokinetics and Pharmacodynamics of Liposomal Mifamurtide in Patients With Osteosarcoma

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Background: Liposomal mifamurtide (muramyl tripeptide-phosphatidyl ethanolamine; L-MTP-PE, MEPACT®) is an immunomodulator indicated for osteosarcoma (OS) treatment in combination with post-operative multi-agent chemotherapy. Here we report the results of a pharmacokinetic (PK) and pharmacodynamic (PD) substudy in a primarily pediatric and adolescent high-grade OS population in an ongoing compassionate use study (MTP-OS-403; EudraCT 2009–017204−89).
Materials and Methods: Patients with relapsed or metastatic OS received L-MTP-PE at 2 mg/m^2 via intravenous infusion over 30 or 60 mins twice-weekly for 12 weeks then weekly for 24 weeks. Blood samples were collected for up to 72 hours following the first infusion. Serum MTP-PE concentrations were measured by LC-MS/MS; TNF-α and IL-6 levels were by sandwich immunoassay. PK/PD data were analyzed by noncompartmental analysis using WinNonlin.
Results: Data from 28 patients were included in the PK (17/11 had 30-/60-min infusions) and 27 in the PD (13/14 had 30-/60-min infusions) analyses. The median (range) age was 15 (6−39)/15 (6−42) years and body surface area (BSA) was 1.58 (0.77–2.31)/1.55 (0.77–2.24) m^2; 61%/56% were male. Following an initial rapid decline in MTP-PE serum concentrations during the first 30 mins after infusion cessation, MTP-PE serum concentrations declined in a log-linear manner over 2−6 hours post-dose with a mean (%CV) terminal half-life of 2.04 hours (22%). BSA-normalized geometric mean (%CV) clearance was 1,250 mL/min/m^2 (43%) and steady-state volume of distribution was 262 L/m^2 (45%). Serum IL-6 levels peaked at 4 hours (regardless of infusion duration) and TNF-α peaked at 2 hours in the 30-min and 4 hours in the 60-min group, returning to baseline ~24 hours post dose. No readily apparent relationships were observed between age and BSA-normalized MTP-PE clearance or effects on serum IL-6 and TNF-α.
Conclusions: The PK properties of L-MTP-PE observed in this study in a largely pediatric and adolescent OS population are similar to those previously reported in healthy adults (Venkatakrishnan et al. ENA 2010, abstract 661). Importantly, there were no readily apparent effects of age on BSA-normalized MTP-PE clearance and the immunomodulatory PD effects. These results support the use of L-MTP-PE at the current recommended dose of 2 mg/m^2 across the age range relevant to its indication in the treatment of OS. Evaluation of safety and efficacy is ongoing.

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MGMT Promoter Methylation in Soft Tissue Sarcoma

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Background: Gene silencing of MGMT (O6-methylguanine-DNA methyltransferase) by promoter methylation increases the efficacy of combined therapy of alkylating chemotherapeutic and radiation. The purpose of this study was to assess the frequency of MGMT promoter methylation in soft tissue sarcoma to identify patients eligible for alkylating agent chemotherapy with concurrent radiotherapy.
Material and Methods: Paraffin tumour blocks of 61 patients with different STS subtypes were evaluated. The methylation status of the MGMT promoter was assessed by methylation-specific polymerase-chain-reaction analysis. Furthermore immunehistochemistry was applied to verify expression of MGMT.
Results: MGMT promoter methylation was detected in 12/61 patients (19%, 4/17 liposarcoma, 3/11 MFH, 1/8 leiomyosarcoma, 0/8 myxofibrosarcoma, 1/8 MPNST and 3/9 synovial sarcoma). There was no correlation of MGMT promoter methylation with age, gender, tumour grade, size or site.
Conclusion: Generally, MGMT-promoter methylation is not a frequent event in soft tissue sarcoma. A general recommendation to use alkylating agents combined with irradiation in soft tissue sarcoma cannot be justified. However, there might be subtypes like synovial sarcoma better prone for radiosensitizing with alkylating agents based on MGMT promoter methylation results. Further research in this area is clearly warranted.

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Assessing Tumour Diameter Versus Tumour Volume as a Prognostic Value at Diagnosis in Rhabdomyosarcoma

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Objective: The purpose of this study is to determine whether measuring tumour volume is more prognostic than tumour maximum diameter at the time of diagnosis and local control for pediatric rhabdomyosarcoma patients.
Patients and Methods: Medical records of one hundred and nine patients who were diagnosed with rhabdomyosarcoma from July 2007 till July 2010 were reviewed retrospectively. Eighty-seven cases were found to be non metastatic. And, for the sixty-two patients with measurable disease, patient demographics, including age, sex, pathologic report as well as surgical grouping were obtained. Tumour diameter was assessed radiologically at diagnosis, at time of local control and at end of treatment. The initial CT, MRI, or both, were obtained for all patients (n = 62) and were reviewed by the study radiologist. Also, we estimated the association between patients' characteristics and the risk of failure or death using cox proportional hazards regression models.
Results: The tumour diameter ranged from 1.8 to 18 cm with a mean of 6.7 cm and a tumour volume ranging from 1.62 to 1099.7 cm^3 with a mean volume of 139.7 cm^3. No significant correlation was found between tumour diameter or tumour volume with sex, age or histological subtype. Both initial tumour diameter and tumour volume did not have a significant effect on overall survival but both had a significant effect on failure free survival.
Conclusion: Both tumour diameter and tumour volume changes significantly affects failure free survival and both act as a good prognostic factor to detect treatment response.

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Whole-body-PET/MRI a New Way of Imaging in Soft Tissue Sarcomas

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Background: Simultaneous positron emission tomography (PET) and magnetic resonance imaging (MRI) is a new imaging technique combining metabolic and cross-sectional diagnostic imaging. Up to now the only available clinical data are drawn from feasibility studies in small series of head and neck cancers and intracranial tumours. So far there exist no data of PET/MRI for evaluating soft tissue sarcomas (sts). MRI is the recommended imaging method in most types of sarcomas. PET is of emerging importance for the management of patients with sts. The combination of MRI with metabolic PET imaging could provide an interesting approach for imaging in sts.
Methods: We report the first two patients examined with an Ingenuity PET/MRI system (Philips Healthcare). It combines a 3 Tesla MRI scanner and a PET scanner with time-of-flight technology. MRI and PET data are acquired sequentially in analogy to PET/CT. All patients were examined before start and after two cycles of chemotherapy. The first patient