

**Discussion:** It is believed that post chemotherapy new expression or no down-regulation of the erbB-4 molecule represents tumor aggressiveness and increased capability of growth and spread.

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### Isolated limb infusion for the treatment of advanced extremity soft tissue sarcomas

J.H.W. de Wilt<sup>1</sup>, R. Scolyer<sup>2</sup>, L. Watson<sup>1</sup>, J.F. Thompson<sup>1</sup>. <sup>1</sup> Sydney Melanoma Unit, Royal Prince Alfred Hospital, Department of surgery, Sydney, Australia; <sup>2</sup> Sydney Melanoma Unit, Royal Prince Alfred Hospital, Department of pathology, Sydney, Australia

Extremity soft tissue sarcomas (STS) are often large at presentation and as a result resection without compromise to limb function can be difficult or impossible. Regional high dose chemotherapy can be used to avoid amputations in patients with advanced or recurrent STS. Isolated limb infusion (ILI) is such a technique, performed using percutaneous catheters, which makes it a simpler and less invasive procedure than conventional isolated limb perfusion (ILP). Response rates in patients with advanced melanoma after ILI with melphalan and actinomycin-D have been comparable with results obtained after ILP. To evaluate the role of ILI in advanced soft tissue sarcoma all patients treated with this technique at the Sydney Cancer Centre were studied to assess short and long-term results.

Between 1994-2000 a total of 19 patients underwent 20 ILI procedures (4 upper limbs, 15 lower limbs). Three patients presented with multiple tumours whereas all other patients had a single tumour. In all but one patient melphalan was used in combination with actinomycin-D (n=15), mitomycin-C (n=3) or both (n=1). The remaining patient was infused with a combination of mitomycin-C, adriamycin and cisplatin. In 9 patients the ILI was performed with the aim of decreasing tumour size and enabling a radical tumour resection. In the other 10 patients the ILI was performed for local control to avoid amputation and was not followed by surgical resection. All ILIs were performed under hypoxic and mild hyperthermic conditions (mean maximum temperature 37.8°C).

Wiederink Grade II limb toxicity occurred in 7 patients, Grade III toxicity in 10 patients, and Grade IV toxicity in 3 patients. Fasciotomy was necessary in two of the latter group of patients. Overall clinical response after ILI was 79% (complete response 26%, partial response 53%, no change 11%, progressive disease 11%). None of the patients treated with an additional surgical resection of the tumour developed a local recurrence (mean follow-up 20 months (9-42)). Of the patients treated with ILI only, local control was maintained for a mean of 11 months (1-37). Four of these patients eventually came to amputation, and in one patient local control for a further period was achieved with local radiotherapy.

In conclusion, ILI for advanced STS using melphalan and actinomycin-D as the infused drugs is a feasible and useful technique, with low morbidity and a high overall clinical response rate.

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### Histamine enhanced antitumor effect of docetaxel and dacarbazine in human clear cell sarcoma xenografts in nude mice

R. Lofvenberg<sup>1</sup>, S. Cnalic<sup>1</sup>, L. Lundgren-Eriksson<sup>2</sup>, R. Henriksson<sup>2</sup>. <sup>1</sup> Umeå University Hospital, Orthopaedics, Umeå, Sweden; <sup>2</sup> Umeå University Hospital, Oncology, Umeå, Sweden

**Background:** Clear cell sarcoma has melanocytic features and is intimately associated with tendons and aponeuroses. It is rare. In the Scandinavian sarcoma registry 18 cases (0.8%) of clear cell sarcoma were registered between 1986 and 1996. Extensive surgery so far the primary treatment.

The aim of the present study was to investigate if histamine enhances the antitumor effect of dacarbazine (DTIC) and docetaxel.

**Method:** Human clear cell sarcoma tumor tissue was obtained during operation of a 58-year old woman. The tumor (UMCCS-1) was maintained by serial s.c. transplantations in nude mice. DTIC (200mg/kg, i.p.) given 3 times with an interval of 2 days, docetaxel (20 mg/kg, i.p.) single dose and histamine (4 mg/kg, s.c.) daily, 5days per week was administered in tumorbearing nude mice. DTIC and docetaxel was given separately or in combination with histamine. Tumor volume in the groups (n=7) was measured repeatedly and compared with a control group (given saline i.p.). The antitumor effect is considered significant when TC-ratio is 0.4 or less.

**Results:** The tumors were followed until day 21. The lowest TC-ratio was noted at day 21 in the DTIC group - 0.54. The corresponding TC-ratio value for the combination histamine-DTIC was 0.37. In the docetaxel-group the lowest TC-ratio- 0.39 was observed at day 13. TC-ratio in the combination

docetaxel-histamine was 0.33. The TC-ratio was reduced at all measuring occasions when histamine was given in adjuvant with DTIC and docetaxel.

**Conclusions:** Histamine seems to enhance the antitumor effect of dacarbazine and docetaxel in this clear cell sarcoma tumor model.

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### Primary soft tissue sarcomas of the extremities: Treatment outcome with postoperative radiotherapy

K. Kanfir, C. Le Péchoux, L. Alzieu, A. Le Cesne, S. Bonvalot, P. Terrier. Institut Gustave Roussy, Villejuif, France

**Purpose:** The outcome of adult patients with primary localized soft tissue sarcoma of the extremities with conservative surgery and adjuvant irradiation (RT) was evaluated.

**Methods and Materials:** From 1975 to 1996, 107 patients (pts) with a median age of 44 years (range, 16 to 86 years) were treated at the Institut Gustave Roussy (IGR) with conservative surgery and adjuvant radiotherapy. The median tumor size was 7 cm (range, 1 to 20 cm) with 27, 36 and 36% stage I, II and III respectively. Histologic examination revealed negative histologic margin in 16%, close or positive margin in 75.5%, grossly positive in 2% and undocumented in 6.5%. The most common histological subtype was: malignant fibrous histiocytoma (27%), synovial sarcoma (27%), liposarcoma (6.5%), and leiomyosarcoma (6.5%). The histologic grade was 1 for 14 patients (13%), 2 for 40 pts (37%), 3 for 50 pts (46%) and unknown for 3 pts (3%). All patients underwent a function-sparing surgery. Forty six patients (43%) were reoperated, residual tumor were found in 82% of pts (38/46). All adjuvant radiation therapy was performed at the IGR. The median external beam dose was 50 Gy (36-65). Chemotherapy was used selectively in 18 patients.

**Results:** With a median follow-up was 132 months (36-288), the 5- and 10-year local control rates were 81% [CI, 72-88%] and 74% [CI, 63-83%] respectively. The 5-year disease-free and overall survival rates were respectively 53% [CI, 43-62] and 69% [CI, 59-78]. Histologic grade was a significant predictor for local recurrence (p=0.04). There was no significant association between local recurrence and margin status, histology, re-resection, residual disease, size, RT dose, or depth. Significant independent adverse prognostic factors for DFS were RT dose less than 50 Gy (p=0.008) and grade 3 tumors (p=0.02). Despite the moderate dose, a substantial rate of long-term side effects was observed. Most of these complications were mild or moderate. No patient had to be amputated because of treatment-related toxicity.

**Conclusion:** Based on our experience and a review of the literature, we concluded that, in the postoperative setting a radiation dose below 50 Gy did not seem optimal. The optimal dose and long-term sequelae should be evaluated in a prospective randomized trial.

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### Localized osteosarcoma of adult patients: Comparison with pediatric population in the same institution over a 16-year period

A. Le Cesne, M.C. Le Deley, L. Brugières, C. Kalifa, G. Misenard, P. Terrier, T. Tursz. Institut Gustave Roussy (IGR), Villejuif, France

**Objective:** To evaluate outcome of patients (pts) with localized osteosarcoma (LO) treated in two Departments (Adult-AD- and Pediatric-PD) of IGR.

**Methods:** All pts treated for a LO with induction chemotherapy (CT) either in AD (n=71) or in PD (n=149) between 1982 and 1998 are included in the analysis. Pts treated in PD received a MTX-based regimen while 3 different protocols were used in AD: modified-T10 (1983-1992), DOX-CDDP (AP) (1983-1993) and DOX-CDDP-IFO (API-AI) since 1992 (ASCO-2001).

**Results:** Median age and median tumor size were 20.8 yr [15.4-63] and 10 cm [3-25] in AD and 12.4 yr [range = 4.4-20] and 12 cm [1-29] in PD respectively. High-dose MTX was more toxic in adults than in younger pts. Good responders to CT ( $\geq 95\%$  necrosis) were 36% and 48% in AD and PD respectively (p=0.08). In AD, this rate varied according to the protocol from 25% (AP), 30% (T10) to 48% (API-AI). The 5-year overall survival (OS) of the entire population was 73% [66-79%] and the event-free survival (EFS) was 60% [53-67%]. OS and EFS were significantly better in PD than in AD: 5-yr OS = 79% [72-85%] in PD versus 59% [46-70%] in AD (p=0.001) and 5-yr EFS = 65% [57-73%] in PD versus 48% [36-61%] in AD (p=0.003). This difference was similar when we restricted analysis to the teenagers (35 in AD and 33 pts in PD). The pts treated in AD with API-AI regimen had a similar EFS to those treated in PD.

**Conclusion:** Over this period of 16 years, pts treated in PD had a better outcome than pts treated in AD. However this difference seems to disappear

if we consider only pts treated with the API-AI protocol in AD. The results observed with this non containing MTX regimen have to be validated by a large multicenter study and consecutively tested in teenagers.

## Adult leukemia/Lymphoma

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### Gender plays an important role in prognostic power of tumor distribution pattern in b-chronic lymphocytic leukemia (B-CLL).

B. Jaksic<sup>1</sup>, O. Jaksic<sup>2</sup>, F. Morabito<sup>3</sup>, M. Brugiatielli<sup>3</sup>. <sup>1</sup> University Hospital "Mercur", Medicine, Zagreb, Croatia; <sup>2</sup> University Hospital "Dubrava", Medicine, Zagreb, Croatia; <sup>3</sup> Azienda Ospedaliera "Bianchi-Melacrino-Morelli", Hematology, Reggio Calabria, Italy

**Purpose:** B-cell chronic lymphocytic leukaemia (B-CLL) has highly variable clinical presentation, course and prognosis. In order to evaluate the impact of tumor cell distribution pattern on clinical course, the prognostic analysis was performed on 341 B-CLL patients.

**Design and Methods:** we introduced the model for tumor distribution (TD) assesment based on Total Tumor Mass (TTM) scoring system, where TD value represents percentage of total tumor mass infiltrating peripheral blood and bone marrow ( $TD = TTM1/TTM$ ). TD can be categorized into 3 subgroups: "pure leukemia" if  $TD = 100\%$ , "predominantly leukemia" if  $TD = 50\%-99\%$  and "predominantly lymphoma"  $TD < 50\%$ .

**Results:** We found following distribution pattern among 341 B-CLL patients: 22.6% were "pure leukemia", 56.0% "predominantly leukemia" and, 21.4%, "predominantly lymphoma" cases, with a median overall survival of 95, 61 and 36 months respectively ( $p < 0.0001$ ). TD parameter significantly correlates with TTM size, Rai and Binet stages, spleen size, beta-2 microglobulin, but failed to correlate with age, lymphocyte count, soluble CD23, and bcl-2/bax ratio. Highly significant association of DT with prognosis was found in overall population of B-CLL patients ( $p < 0.0001$ ). However, to our surprise, both in univariate prognostic analyses and in multivariate Cox analysis this effect is much stronger in female patients, while virtually failing in male patients. In female patients DT is the strongest independent predictor of prognosis ( $p = 0.000$ ) followed by age ( $p = 0.058$ ), and Binet stage ( $p = 0.026$ ).

**Conclusions:** Tumor mass distribution pattern, a quantitative and simple clinical parameter is independent and strong prognostic parameter in B-CLL. Unexpected finding of substantial difference in prognostic power of DT between genders points out to an interesting, yet unexplained biological impact of gender in pathogenesis of B-CLL.

## Adult Hodgkin's lymphoma

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### Cardiopulmonary response to exercise in patients cured with chemo-radiotherapy for Hodgkin's disease

F. Villani<sup>1</sup>, V. Bonfante<sup>2</sup>, A. Fede Catania<sup>1</sup>, C. Materazzo<sup>3</sup>. <sup>1</sup> Istituto Nazionale Tumori, Pneumology, Milan, Italy; <sup>2</sup> Istituto Nazionale Tumori, Medical Oncology, Milan, Italy; <sup>3</sup> Istituto Nazionale Tumori, Cardiology, Milan, Italy

**Purpose:** Combined CT and RT, including the mediastinum, can produce subclinical and cardiac toxic effects. From 1998 we evaluated cardiopulmonary response to exercise in pts with HD treated with this combined modality and in complete remission after >5 year follow-up.

**Methods:** The study was performed in 94 pts, M/F 40/54, mean age 36 yr (range 21-65). Initial stage was I in 7 pts, II in 73 pts, III in 3 pts and IV in 11 pts. CT regimens included ABVD in 56 pts, MOPP/ABVD in 10 pts, VEBEP (Vepesid, Epirubicin, Bleomycin, Cyclophosphamide, Prednisone) in 28 pts. The median cumulative dose administered was 77 mg/sqm for Bleomycin, 160 mg/sqm for Doxorubicin and 313 mg/sqm for Etoposide. The median RT dose delivered to the mediastinum was 34.4 Gy, range 27-44. Before exercise test pts were divided into 3 groups according to lung function parameters: group 1 (52 pts) with normal values; group 2 (33 pts) with total lung capacity (TLC) normal, but transfer lung factor for CO (DLCO) < 80% of predicted; group 3 (9 pts) with both spirometry and DLCO < 80% of predicted. The median drugs and RT doses received by these 3 groups of pts were similar. Pts were submitted to respiratory and arterial blood

gasses analysis, determination of cardiac output (acetylene rebreathing method) before and during a symptom limited exercise on cycloergometer using an incremental protocol. Expiratory gasses were analyzed by a mass spectrometer.

**Results:** Pts of groups 2 and 3 in comparison with those of group 1 showed a lower oxygen consumption ( $VO_2$  max: group 1 vs group 2 and vs group 3: 59.3%, vs 58% vs 52.5 of predicted) and a significant lower cardiac output per oxygen uptake.

Significant correlations were observed between basal TLC, stroke index and  $VO_2$  max.

**Conclusions:** These data show a reduction of the physiological response to exercise in pts with pulmonary impairment after CT-RT, in particular when the reduction of DLCO is associated with modification of spirometric parameters.

This lower capacity to exercise seems to be due to a combination of lung impairment for gasses diffusion and to a reduction of myocardial function with decrease of stroke volumes.

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### Early Hodgkin's disease: treatment without radiotherapy

P. Provencio<sup>1</sup>, P. España<sup>1</sup>, I. Millan<sup>1</sup>, A. Sanchez<sup>1</sup>, B. Cantos<sup>1</sup>, M. Yebra<sup>2</sup>, J. Vargas<sup>2</sup>, F. Roman<sup>2</sup>, C. Miralles<sup>1</sup>, B. Bonilla<sup>1</sup>. <sup>1</sup> Clinica Puerta De Hierro, Medical Oncology, Madrid, Spain; <sup>2</sup> Clinica Puerta De Hierro, Internal Medicine, Madrid, Spain

The treatment of choice for patients with early stage Hodgkin's disease (HD) has been extended field or subtotal nodal irradiation. Remission rates of over 95% have been obtained, however, about 5% of stage I and II patients will suffer from progressive disease while on therapy and an additional 15% - 20% will relapse. Chemotherapy (CT) alone has not been adequately tested in early-stage HD.

**Patients, methods and results:** All HD stage I and II patients treated with CT alone between 1980 and 1997 were reviewed. Thirty-five patients were treated between 04/80 and 12/97. All patients achieved complete remission. The median follow-up was 119 months (range 21-240 months), no patients were lost at follow-up. Overall survival was 97% (IC 95%, 92-100) at 5 years and 88% (IC 95%, 75-100) at 10 years. Failure free survival was 93% (IC 95%, 83-100) at 5 years and 66% (IC 95%, 47-86) at 10 years. Three (8.5%) patients died: 2 due to a second tumour (non-Hodgkin's lymphoma and myeloid acute leukaemia) and the other due to sepsis post-Ch. Univariate and multivariate analysis only associated histology subtype relative risk 4.0 nodular sclerosis (95% IC, 1.0 - 5.5;  $p = 0.02$ ) with higher relapse. Other prognostic factors did not reveal significant differences with respect to failure free or overall survival.

**Conclusions:** We believe that death from HD in early-stage patients is unusual and mortality from causes other than HD occurs many years later. Outside clinical trials due to the lack of clear prognostic factors, with the exception of specific situations, patients should be informed of all the possible alternatives as well as the consequences of the treatments employed. In our experience it appears that using CT alone in the initial stages does not jeopardise overall patient survival, with similar results being achieved.

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### Feasibility of the Integration of Stanford V ct regimen with highly active antiretroviral therapy (HAART) and G-CSF in patients (pts) with HD and HIV infection (HD-HIV)

M. Spina<sup>1</sup>, J. Gabarre<sup>2</sup>, E. Vaccher<sup>1</sup>, A. Re<sup>3</sup>, A. Palmas<sup>4</sup>, A. Antinori<sup>5</sup>, M. Clerico<sup>6</sup>, U. Tirelli<sup>1</sup>. <sup>1</sup> National Cancer Institute, Medical Oncology A, Aviano, Italy; <sup>2</sup> Pitié-Salpêtrière, Hematology, Paris, France; <sup>3</sup> Civil Hospital, Oncology, Brescia, Italy; <sup>4</sup> Civil Hospital, Oncology, Nuoro, Italy; <sup>5</sup> Spallanzani Hospital, Oncology, Rome, Italy

The outcome of pts with HD-HIV is still poor, mainly because the duration of complete remission (CR) is quite short. In order to try to improve the prognosis of HD-HIV, a feasibility study with the intensive 12-week CT regimen with adjuvant radiotherapy, Stanford V and concomitant HAART was started in previously untreated HD-HIV pts with bulky limited stage or stage III-IV. Pts were treated with CT(mg/mq) including doxorubicin 25 and vinblastine 6 on wks 1, 3, 5, 7, 9, 11; nitrogen mustard 6 wks 1, 5, 9; etoposide 60 x 2 wks 3, 7, 11; vincristine 1.4 (max 2) and bleomycin 5 wks 2, 4, 6, 8, 10, 12 and prednisone 40 qod. Since April 1997, out of 49 pts entered, 46 are now evaluable for toxicity and response. The median age was 36 yrs (range 28-63). All pts but 5 were males, 20 were IDUs, 14 homosexuals and 12 heterosexuals. The median CD4+ cell count at entry