7509 POSTER

Peculiarities of metabolic activity of leiomyosarcoma uteri by the level of NADPH-dependent enzymes content

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Background: One of the major morphological parameters of tumor cell is enzymatic activity with determina-tion of various direction of metabolic profile. Microcirculation channel, determined with the help of alkaline phosphatase, enables to define rate and character of the tumor blood supply. Objectives of the giving work is determination of the activity degree of enzymes of Krebs cycle, an-aerobic glycolysis and characteristic of microcirculation channel in leiomyosarcoma of high-grade differentiated level.
Methods and Materials: 16 leiomyosarcoma of high-grade differentiated level (stage 1, FIGO 1998). Histochemical reaction was made on frozen section on NADH2-diaphorase (IUBMB 1.6.99.1), succinate dehydrogenase SDG (IUBMB 1.3.99.1) and lactate dehydrogenase LDG (IUBMB 1.1.1.27) with quantitative assessment of tetrazolium falling. Peculiar properties of the microcirculation channel was defined by Gomory method on alkaline phosphatase AP (IUBMB 3.1.3.1). The data received were compared with cell leiomyoma of mitotic activity. (27 cases).
Results: Total metabolic activity of sarcoma atypical smooth muscle cells by content of NADH2-diaphorase was higher against cellular leiomyoma: 81.9 ± 9.5 and 32.8 ± 3.8 respectively. The process of aerobic respiration by content of SDG in leiomyosarcoma were significantly higher than in cellular leimyomas: 49.9 ± 2.6 against 11.9 ± 4.5. Intensity of anaerobic glycolysis processes in leiomyomas was also higher than in cellular myoma: 24.7 ± 10.3 against 15.1 ± 3.4.
Cellular leiomyoma were characterized by intensive staining of vessels on alkaline phosphatase and presence of number of genuine capillary vascular lemniscus. There was also noted presence of incompleteness of structure of some lemniscus and number of growing neogenic capillaries. Intensity of reaction on AP in leiomyosarcoma has been rising with increase in the number of growing capillaries. Capillary pattern get the form of laces. Percentage ratio of vessels to the total size of tumor in cellular leiomyoma amounted to $10.13 \pm 1.54\%$, and in sarcoma upped to $17.2 \pm 2.7\%$ ($p < 0.05$).
Conclusion: Enhancement of processes of the total metabolic activity of tumor cells and aerobic oxidation within the framework of Krebs cycle was found in direct strong correlation from the degree of tumor blood supply ($r = 0.78$; $p = 0.0001$).

7510 POSTER

Molecular aspects of Kaposi's sarcoma in Cameroon

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Background: Kaposi's sarcoma has been discovered in 1872 and endemic form was described in people without AIDS living in EAST and CENTRAL Africa. Human Herpes Virus 8 is now considered as the Etiologic agent of disease. But many cofactors do exist including immune deficiency. Tumors cells also secrete progestrone and the disease sem to decrease during pregramcy. Molecular studies on Kaposi's sarcoma are scarce.
We then carried out this preliminary descriptive study the aim of which was to present the molecular aspects of few cases of Kaposi's sarcoma in Cameroun (Central Africa).
Material and Method: We perform molecular analysis using immunohistochemistry and polymerase chain reaction on paraffin embeded biopsies of Kaposi's sarcoma cases.
12 primary antibiodies were tested. For the PCR, we used the following primers:
– HHV8 26A: 5′-CCG AAA GGA TTC CAC CAT TGT-3′
– HHV8 26 B: 5′-GCC GAT ATT TTG GAG TAG ATG TG-3′
– HHV8 75A: 5′-GCG ATA GAG GTT AGG GTA GGT GT-3′
– HHV8 75B: 5′-TCT GCT CCA TCT CTA CCA CTA CTT C-3′
We compared our findings with the literature findings.
Results: 30 cases of Kaposi's sarcoma underwent immunohistochemistry analysis. The primary antibiodies used included CD34; CD31; ki67; HHV8; cycline DI; CD45; CD20; CD3; CD68; CDI38; P53; BCL2.
Tumor spindle cells were positive for CD34, CD31, HHV8 and negative for KI67; Cycline DI; P53; BCL2. 20 cases were analysed by PCR and 18 cases show HHV8 sequences while there were two false negative.
Conclusion: There may be some molecular differences between "African" and "European" Kaposi's sarcoma. A comparative study between these two entities may be useful.

7511 POSTER

Safety and efficacy results of sunitinib from a worldwide treatment-use trial of gastrointestinal stromal tumour (GIST) patients (pts) with resistance or intolerance to prior imatinib therapy

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Background: Sunitinib malate (SUTENT®; SU) is an oral, multitargeted tyrosine kinase inhibitor approved multinationally for the treatment of imatinib (IM)-resistant/-intolerant GIST. The main objectives of this ongoing study are to allow pts access to SU who were ineligible to participate in SU clinical trials or for whom SU is unavailable prior to regulatory approval in their country, and to obtain broad safety and efficacy data from a large number of GIST pts.
Materials and Methods: In this ongoing, open-label study, SU (50 mg/day) is administered in 6-week cycles (4 weeks on treatment, 2 weeks off) to pts with advanced GIST who had failed prior IM therapy and were unable to obtain SU otherwise. Safety, antitumor response (as per local standard of care) and overall survival (OS) are assessed.
Results: As of April 2007, 1022 pts had been enrolled in 96 centers in 33 countries. Pts (median age of 59) received a median of 4 cycles (range 1–18) with follow-up of 195 days. In the ITT population (received at least one dose of SU; N = 1012), 15% discontinued due to AEs and 29% due to lack of efficacy. SU dose reductions occurred (for any reason) in 33% of the ITT population. The most common AEs of any cause were fatigue (46%), diarrhea (42%), and nausea (33%). The most common grade 3/4 AEs were fatigue (9%), hand–foot syndrome (8%) and abdominal pain (8%). Hematologic AEs (total, grade 3/4) included anemia (19%, 7.4%), thrombocytopenia (16%, 4.5%) and neutropenia (15%, 5.8%). Estimating all median OS using the product-limit method, at time of data cutoff, 715 (71%) pts were still alive, with a median OS of 68.0 wks (95% CI: 60.3–NA). Median time-to-progression was estimated at 36 wks (95% CI: 35–42). The median OS for pts under 65 years was 91.1 wks (95% CI: 62.9–NA; n = 651), while pts 65 years and older had a median OS of 60.3 (95% CI: 50.7–73.1; n = 360). Pts who had lower-dose ($\leqslant$400 mg) prior IM treatment had a median OS of 80.4 wks (95% CI: 60.3–NA; n = 307). Those who had higher-dose (>400 mg) IM treatment had a median OS of 63.0 (95% CI: 59.1–76.1; n = 702). Data for other subgroups will be presented.
Conclusions: SU is generally well tolerated in pts with IM-resistant or -intolerant advanced GIST who are ineligible for other SU trials. The safety profile observed is similar to that seen with SU in other GIST trials. Consistent with the phase I–III data, SU is an effective treatment for pts with advanced GIST after IM failure.

7512 POSTER

Assessing the clinical impact of trabectedin in patients with leiomyosarcomas or liposarcomas (L-sarcomas) progressing despite prior conventional chemotherapy: clinical benefit rate, growth modulation index and tumor variation as parameters of treatment effect in a randomised international trial of two trabectedin dosing regimens

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Background: A randomised international trial was performed to assess the efficacy of 2 trabectedin (T) IV regimes: 1.5 mg/m^2 24h/3wk (q3wk 24h) or 0.58 mg/m^2 3h weekly $\times$ 3/4 wk (qwk 3h) in 270 pts with L-sarcoma

progressing despite prior therapy with at least anthracyclines (A) and ifosfamide (I). Primary endpoint was time to progression (TTP) assessed by independent review; response rate (RR), progression-free (PFS) and overall survival were secondary endpoints. In the protocol-specified primary analysis, TTP ($p = 0.030$; HR 0.73) and PFS ($p = 0.042$; HR 0.75) were significantly better with the q3wk 24h T schedule, in spite of a modest 5.6% (12% per investigators) RR by RECIST. Acknowledging the limitations of RR by RECIST as a surrogate for clinical benefit in sarcomas, 3 supportive analyses were conducted: Clinical Benefit Rate (CBR), Growth Modulation Index (GMI) and Maximum % of Tumour Variation (MTV).
Methods: CBR was defined as the sum of CR+PR+SD?24 wks. MTV was calculated as: (minimum sum of longest diameters [SLD] of all lesions before or at PD date – SLD at baseline)/(SLD at baseline)·100 (212 pts evaluable). GMI (intrapatient-specific historical control) was calculated as: TTP with T / TTP with prior chemo for advanced/metastatic sarcoma (218 pts evaluable; data prospectively collected). A GMI >1.33 (TTP with $T \geqslant 33\%$ prior TTP) was judged as indicative of pt benefit.
Results: CBR and MTV were significantly better with the q3wk 24h T schedule. CBRs of 39% and 24% were achieved with the q3wk 24h and qwk 3h schedules (Fisher's; $p = 0.022$). MTV showed tumour shrinkage in target lesions in 51% pts in the q3wk 24h arm vs 32% in the qwk 3h arm (Mann-Whitney-Wilcoxon; $p = 0.0008$). Most pts (67%) had bulky tumours at study entry. GMI > 1.33 was achieved in 37% (q3wk 24h) and 31% (qwk 3h) of pts. Last prior chemo was A+I in 48% of pts, gemcitabine-based regime (17%), single-agent I (13%) and others.
Conclusions: The outcomes with the less efficacious qwk 3h arm support this T schedule as an active control. However, consistently better outcomes were seen with the q3wk 24h T schedule. Overall, these results add biological plausibility to the significantly better outcomes in the primary endpoint TTP seen with T q3wk 24h and provide confidence in the clinical relevance of the overall findings. CBR, GMI and MTV, if adequately applied, appear more useful endpoints than conventional RR per RECIST to detect clinical benefit in pts with advanced/metastatic sarcomas.

7513 POSTER

Impact of local management on long-term outcomes in Ewing's tumor of the pelvis: the University of Florida experience

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Purpose: Comprehensive reports of long-term outcomes are limited but nonetheless crucial to the debate regarding local management of pelvic Ewing's tumor. This retrospective analysis describes our 35-year experience with respect to disease control and functional status.
Patients and Methods: Thirty-five patients with localized Ewing's tumors of the pelvis were treated from 1970–2005. Twenty-six patients were treated with definitive radiotherapy (RT) and 9 patients were treated with combined local therapy in the form of surgery + RT (8 preoperative and 1 postoperative). The median RT dose was 55.2 Gy. The patients who received RT alone were more likely to be older males with larger tumors exhibiting soft-tissue extension. All patients received standard chemotherapy. Patients in the definitive RT group were more likely to receive etoposide and ifosfamide or undergo bone marrow transplant. Median potential follow-up was 19.4 years. Functional outcome was assessed using the Toronto Extremity Salvage Score (TESS).
Results: 5-year absolute rates of local control and cause-specific survival in the post-1985 era have increased by 2% and 24% respectively. The 15-year actuarial overall survival, cause-specific survival, freedom from relapse rate, and local control rates were 26% vs. 76% ($p = 0.016$), 26% vs. 76% ($p = 0.016$), 28% vs. 78% ($p = 0.015$), and 64% vs. 100% ($p = 0.087$), respectively, for patients treated with definitive RT and combined therapy. Overall, tumors <8 cm had significantly better cause-specific survival but this was unrelated to local control. The median TESS for the definitive RT and combined therapy groups were 99 and 94 respectively ($p = 0.19$). Six definitive RT patients (23%) had serious complications including two secondary malignancies, a pathologic fracture, and osteoradionecrosis requiring hip replacement. Bowel perforation was the only serious complication observed in the combined therapy group.
Conclusion: Despite improvement in cause-specific survival over the past 35 years, we have made little progress in terms of local control. A small subset of eligible patients may benefit from complete excision, but rates of disease control and complication are poor when it is necessary to treat Ewing's tumors of the pelvis with RT alone. Most patients have unresectable tumors and therefore innovative RT strategies are needed to improve long-term disease outcomes and minimize side effects while maintaining an acceptable functional result.

7514 POSTER

Long-lasting St. Jude Hospital protocol in adult Ewing sarcoma patients

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Background: Adult patients with Ewing sarcoma may achieve long-term survival with local treatment modalities and systemic chemotherapy. Although chemotherapy is effective in this setting, a standard chemotherapy regimen is not yet developed. In this study, the feasibility and the effectiveness of long-term ewing sarcoma protocol of St. Jude Hospital.
Materials and Methods: Twenty-five adult patients with ewing sarcoma (22 males, 3 females) received 41-week St. Jude Hospital protocol. The protocol consisted of induction chemotherapy applied within weeks 0 to 6 (ifosfamide 2 g/m2/day, days 1−3, etoposide 150 mg/m^2/day, days 1−3, cyclophosphamide 1.5 g/m2 day 5, doxorubicin 45 mg/m^2 day 5); on the 9th week surgical resection with or without radiotherapy was done, followed-by vincristin 1.5 mg/m^2, D-actinomycin 1.5 mg/m^2 within weeks 11 and 17 and the maintenance treatment within weeks 20 and 41 (ifosfamide 2 g/m2/day, days 1−5; etoposide 150 mg/m^2/day, days 1−5; cyclophosphamide 1/m2/day, days 1 and 2; doxorubicin 60 mg/m^2 day 1, as continuous infusion in 24 hours). All chemotherapy regimens were given every three weeks.
Results: The median age of the patients was 23 (range: 18−55). The initial stage of the disease was IIB in 20 cases, and IV in 5 cases. In 10 cases tumor was originated from the extremity, and in 14 cases from other bones from the extremities. Forteen cases underwent surgical resection and 22 cases were given radiotherapy for local control. All cases completed the treatment protocol. The median duration of chemotherapy was 44 weeks (range: 41−56). Twelve cases (48%) achieved complete response, 7 cases (28%) achieved partial response, whereas 5 cases (20%) had progression after the completion of the protocol. Thirteen cases (52%) developped myelotoxicity, 2 cases (0.08%) developped nefrotoxicity, 2 cases (0.08%) developed neurotoxicity, and 3 cases (12%) developed angina pectoris during the treatment protocol. No dose reduction or modification was made in the patients. In 11 patients (44%) G-CSF was used, 13 patients (52%) were given erytocyte transfusions. 4-year overall survival rates were 43% in stage II patients and 40% in stage IV patients, respectively. 4-year disease-free survival rates were 25% in stage II patients and 20% in stage IV patients, respectively.
Conclusions: In conclusion, the long-lasting St. Jude Hospital protocol was found similar to other chemotherapy protocols in regard to toxicity and survival in adult patients with Ewing sarcoma.

7515 POSTER

Prognostic factors in osteosarcoma. The arguments for risk adapted up-front treatment

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Background: The response to induction chemotherapy is the standard criteria for risk assessment in osteosarcoma. In order to evaluate the risk earlier, we have investigated several pretreatment tumor related characteristics.
Materials and Methods: The database included 593 patients treated at the N.N. Blokhin Russian Cancer Center. Between 1979 and 1986, preoperative treatment comprised one 72-hour IA infusion of DOX 90 mg/m^2 and radiotherapy 40 Gy. From 1986 to 1999 induction chemotherapy consisted of 3−5 monthly cycles of IA DOX 90 mg/m^2 or CDDP 120 mg/m^2. In both protocols 6 cycles of CAP (cisplatin 100 mg/m^2 + doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2) chemotherapy were administered after removal of primary. The last protocol consisted of 3−4 cycles of intensified induction chemotherapy with DOX 90 mg/m^2 and CDDP 120 mg/m^2 IV or IA, surgery at week 20 and 6 cycles of adjuvant chemotherapy with DOX, CDDP, IFO (standard dose) and VP-16. Cox regression was used for multivariate analysis.
Results: The following pretreatment factors were predictive for disease-free survival (DFS) in univariate analysis: stage by Enneking ($p < 0.00001$),