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Intralesional beta-interferon in combination with radiotherapy in advanced soft tissue sarcoma

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Objective: Primarily inoperable or marginally operable soft tissue sarcoma show a poor prognosis, 5-year survival 30% with definitive radiotherapy and/or chemotherapy. Interferon-β (IFN-β) demonstrated to be radiosensitizing in soft issue sarcoma. Our own in-vitro data and the following results of a phase-2 study led to a multi-center study with intralesional IFN-β and radiotherapy in soft tissue sarcoma.

Materials and Methods: 16 patients with recurrent, pretreated and histologically confirmed soft-tissue sarcoma were included. Pretreatment: surgery 16/16, chemotherapy 13/16, radiotherapy 12/16 (median 60 Gy, range 40–90); age 42 (19–72), male/female 7/9. All patients received a combination of 5×10^6 IU IFN-β intralesional 3×/week and radiotherapy 32 Gy (26–64), 1.8 Gy 5×/week Duration of combined treatment: median 8 weeks (6–10).

Results: 14/16 patients responded to therapy, 3/16 CR (12+, 36+, 60+ month), 8/16 PR (median 12 month+, 2–36+), 3/16 SD (4, 8, 15 month), 2/16 PD progression-free intervall median 12 months + (10–36 mo). 2 patients were successfully reoperated (1 RO, 1 R1) with function keeping surgery. No serious toxicities were observed.

Conclusion: The combination of intralesional IFN-β and radiotherapy represents an interesting treatment for patients with locally advanced or recurrent soft tissue sarcomas, especially in whom limb-sparing surgery cannot be performed. These results should be further evaluated and confirmed to integrate this treatment option in a first-line treatment concept

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Multicentric randomized trials for high grade osteogenic osteosarcoma (OS). Cost-effectiveness?

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Purpose: These last 20 y. chemotherapy (CT) of patients (p.) with OS has been dramatically improved. Nevertheless dilemmas and controversies have continuously developed.

Methods: This study of the last 20 y. tries to evaluate the benefice of randomized trials in term of DFS for p. and cost effectiveness for the community.

Results: The literature demonstrates the following facts: 1) the multicentric trials to verify the effectiveness of CT in OS delayed the systematic use of CT for 3 or 4 y. 2) Preliminary results of COSS 77–82 which falsely concluded that amputed p. had more chances of DFS than others, delayed the conservative surgery for 5 y.. The definitive conclusions of these trials invalidated their preliminary reports. 3) the superiority of Rosen's protocols leas been continuously challenged for 15 y., by randomized studies. But these trials didn't respect the most important backgrounds of Rosen's protocol (delay between 2 courses of MTX, individualization of MTX dose upon evaluation of clinical efficacy, too large hydration of p. receiving MTX, too long preoperative phase, too low numbers of MTX courses, etc.). Furthermore, independent evaluation of T7 and T10 demonstrates, 15 y. later, that these protocols remain the most effective in OS DFS at 10 y. and the fundamental value of HDMTX became evident by macro-analysis of all published trials on this subject (Cancer, 08/1996).

Conclusion: In OS, multicentric trials led always to worse results than pilot studies performed in big centers. They served only to convince reticent medical community of the necessity of CT in OS. In the same time, many p. let their limb or/and their life because of these bad trials.

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Osteosarcoma in childhood – Improved survival with reduced toxicity

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Purpose: The outcome and toxicity of a neoadjuvant chemotherapy regimen for the treatment of childhood osteosarcoma with the aim of maintaining survival but reducing long-term toxicity is described.

Methods: Between 1988 and 1996, informed consent was obtained from 21 patients for treatment with the Bristol Resistant Tumour Protocol (BRTP), four with metastases at presentation. Chemotherapy comprised ten, three-weekly courses of CEEV (carboplatin 500 mg/sq m on day 1, epirubicin 50 mg/sq m days 1 and 2, etoposide 150 mg/sq m days 1 and 2; vincristine 2 mg/sq m (max 2 mg) day 1) alternating with IVA (ifosfamide 2.5 G/sq m days 1 to 3, actinomycin 0.9 mg/sq m days 1 and 2; vincristine as in CEEV). High-dose methotrexate (8 to 12 G/sq m) could be added after surgery (scheduled to follow the third course of chemotherapy) for poor histological response. Organ toxicity was assessed by regular echocardiography and chromium 51 EDTA determination of glomerular filtration rate (GFR).

Results: With median follow-up of 66 months, actuarial 5-year survival for non-metastatic osteosarcoma is 82% with progression free survival being 70%. Including the 4 metastatic patients, there have been only 4 deaths with 3 other progresssions, now disease free for 95, 31 and 16 months. Chemotherapy was well tolerated. 103/105 (98%) courses of CEEV and 101/105 (96%) courses of IVA were administered as planned. Severe but manageable haematological toxicity (WHO grade 3 or 4) was common. No clinical cardiac toxicity was observed although one patient had a reduction in echocardiographic fractional shortening and ejection fraction measurements. The last 2 doses of epirubicin were omitted and subsequent echocardiography has returned to normal. Four of twenty-one patients (19%) required long-term electrolyte supplementation but this was not related to changes in GFR in all of them.

Conclusion: The BRTP is well tolerated and has resulted in excellent long-term survival for non-metastatic osteosarcoma in childhood. Long-term organ toxicity is confined to the kidney and is manifested as electrolyte loss. In all cases this has been easily controlled with oral supplements. Since these results are at least as good as those reported using more toxic regimens, a randomised comparison should be seriously considered.

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Proton radiation therapy for skull base chordomas and chondrosarcomas

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Objective: Local control, survival, and failure outcomes of 58 patients treated with fractionatel proton radiation therapy (PRT) were analyzed for treatment efficacy.

Methods: Between March 1992 and January 1998, 33 evaluable patients were treated for chordoma; 25, for chondrosarcoma. Following various surgical procedures, gross residual tumor was detected in 91%; 59% demonstrated brainstem involvement. Target doses ranged between 64.8 and 79.2 (mean: 70.7) Cobalt Gray Equivalent. Patients were followed from 7 to 75 (mean: 33) months.

Results: Ten patients (17%) failed locally, resulting in local control rates of 92% (23/25 patients) for chondrosarcomas and 76% (25/30 patients) for chordomas. Tumor volume and brainstem involvement influenced control. All tumors $\leq$ 25 ml remained locally controlled, compared to 56% of tumors >25 ml ($p = 0.02$); 94% of patients without brainstem involvement remained without recurrence versus 53% with involvement ($p = 0.04$). Three patients died of disease; one, of intercurrent disease. Actuarial 5-year survival rates were 100% (chondrosarcoma) and 79% (chordoma), respectively. Grade 3 and 4 late toxicities were observed in 4 patients (7%) and were symptomatic in 3 (5%).

Conclusion: High-dose PRT offers an excellent chance for durable tumor control and survival, with acceptable risks. All small- and medium-size tumors without demonstrable brainstem involvement have been controlled. Even patients with large tumors and disease abutting critical normal structures benefited.

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Functional results and complications after ablative and limb-saving therapy in lower extremity sarcoma of bone

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Purpose: The functional results and the complication rates after several limb-saving and ablative treatments because of lower extremity musculoskeletal sarcoma of bone were evaluated.

Methods: Seventy-seven surviving patients were evaluated according to the ISOLS functional rating system. Fifty-two patients had limb-saving and

25 had ablative surgery. Median follow-up in the salvage group was 97 months and in the ablative group 112 months.

Results: Functional results in the limb-saving group were significantly better than in the ablative group (p = 0.0001). Functional results in patients with tumors about the knee joint were significantly better (p = 0.0064) after limb-saving (endoprosthesis, knee arthrodesis, or rotationplasty) compared to after ablative surgery (hip or knee disarticulation, or above-knee amputation). No significant differences in functional outcome were found between the above mentioned three limb-saving procedures in tumors about the knee joint.

Complications were three-times more common after limb-saving procedures and four-times more common after endoprosthetic reconstructions compared to after ablative procedures. Complications after limb-saving therapy were fewest in tumors about the knee joint. In 3/28 patients the endoprosthetic reconstruction had to be converted to an amputation.

Conclusion: Functional results were significantly better after limb-saving compared to after ablative therapy. In tumors about the knee joint no significant differences in functional outcome were found between several limb-saving procedures, but functional results after limb-saving surgery were significantly better compared to after ablative surgery. Complications however were more common after limb-saving therapy.

1067 POSTER DISCUSSION

Desmoid tumours: A comparison between combined surgical resection and radiotherapy or surgery alone. An international analysis of 110 patients

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Purpose: An retrospective study of patients treated for desmoid tumours was performed to assess the value of combined surgical resection and radiotherapy.

Methods: After circulating a questionnaire concerning prognostic factors and treatment parameters, records of 140 patients could be analysed. Pathologic slides were reviewed. Adjuvant radiotherapy had 69 patients, 42 patients surgery only. Median radiation dose was 59 Gy.

Results: Histology was confirmed for 110 patients. Tumours were located in the head-neck region (7), extremities including hip and shoulder girdle (55), abdominal wall (23) and trunk including pelvis and breast (23). Relapse-free survival was best for tumours of head and neck region (100% for 5 and 10-years) and worse for tumours located in the trunk region (84% at 5 years: 61% at 10 years). Extremities could be preserved for all 41 patients treated with radiotherapy and for 80% (12/15) patients with surgery only. Recurrence-free survival was 95% at 5 year/90% at 10 years for patients treated with radiotherapy, 85% at 5 years/62% at 10 years without radiotherapy (p = 0.0135). No significant difference could be shown for radiation doses $\leq$50 or >50 Gy.

Conclusion: Patients with poor prognostic factors (localisation trunk) should receive radiotherapy after primary surgery. Postoperative radiotherapy should be added after first recurrence in any case and for preserving functional extremities.

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Epirubicin (EDX) 150 mg/m^2 – cisplatin (CDDP) versus epirubicin 180 mg/m^2 – cisplatin for advanced soft tissue sarcoma (STS); an interim report

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Purpose: In our previous study (Jelić S. Et al: EJC, 1997; 33 (2): 220–225) we have reported superiority of the EDX 180 mg/m^2 – CDDP combination over single drug EDX 180 mg/m^2 for advanced STS both in terms of response (54% vs. 29%, p = 0.025) and survival (p = 0.001). The aim of the present study was to establish whether decrease of EDX dosage to 150 mg/m^2 would result in the same activity with less marked hematological toxicity.

Methods: Pts. with advanced STS were randomized for either EDX 150 mg/m^2 – CDDP 120 mg/m^2 (arm A) or EDX 180 mg/m^2 – CDDP 120 mg/m^2 (arm B).

Results: *Arm A:* 80 patients evaluable, overall RR 23/80 (28%), 95% CI 19–38%, median survival 11 months, probability of survival at 1 year 0.42, gr. IV granulocytopenia present in 110/277 cycles, febrile neutropenia in 22/277; *Arm B:* 71 patients evaluable, overall RR 36/71 (51%), 95% CI 39–61%, median survival 14 months, probability of survival at 1 year 0.61, gr. IV granulocytopenia present in 124/284 cycles, febrile neutropenia in 26/284. *Differences:* for overall RR p = 0.004, power 83%; for survival p = 0.06; for gr. IV granulocytopenia p = 0.3; for febrile neutropenia p = 0.61.

Conclusion: Both regimens share the same toxicity but the EDX 180 mg/m^2 – CDDP seems more active in STS, indicating possibly a breakthrough for activity between EDX dosage of 150 mg/m^2 and 180 mg/m^2 in combination with CDDP.

1069 POSTER DISCUSSION

Myxoid liposarcoma – The frequency and the natural history of non-pulmonary soft tissue metastases

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Purpose: Myxoid liposarcomas (ML) comprise the major subset of liposarcomas and have a tendency to metastasise to other soft tissues (STM) in preference to lung. This has previously been described, however the natural history and the significance of STM in terms of survival are both poorly documented.

Methods: Review of the Royal Marsden Hospital,s experience over 10 years.

Results: There were 50 patients with a median age of 44 years (range 21–77 years) and a median follow-up of 43 months. Primary site was buttock or limbs in 41 cases, retroperitoneum in 5, trunk in 3 and soft palate in 1 case. The actuarial 5 year STM rate was 31%. The commonest sites of STM were to the retroperitoneum, abdominal wall and abdominal cavity with 9 of 12 cases having multiple sites of STM. In the 12 patients with STM there was a median interval of 23 months after original diagnosis to the time the first metastasis presented (range 0–142 months). Median survival following first metastasis was 35 months with 6 patients having died between 6 and 50 months. Four patients who had STM remained disease free at 15–59 months after the first STM. Any round cell component of ML was associated with significantly greater chance of metastatic disease (p = 0.02). Multimodality therapy was used for control of STM with 4 of 7 patients responding to chemotherapy and non cross-resistance between doxorubicin and ifosfamide noted in 2 cases. In this series the overall 7 year survival rate was 68%. Cases of ML with STM had 11 times greater mortality than those with no STM.

Conclusions: ML is usually an indolent disease but a subset of patients develop STM and have a significantly worse prognosis. STM can occur years after initial diagnosis and can be associated with medium-long term survival after they occur. They should be managed aggressively because of this.

1070 POSTER DISCUSSION

Importance of histological categorization in the therapeutic management of malignant pleuric mesothelioma (MPM)

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Purpose: To identify the subset of patients (pts) with MPM who could obtain a major clinical benefit from more aggressive treatment.

Pts and Methods: A retrospective series of 103 pts (78 M, 25 F) with MPM was reviewed. Median age was 60 yrs (range 33–86). Eighty-six pts had ECOG-PS <2. Stage according to IMIG was I in 39, II in 21, III in 24 and IV in 19 pts. Histotype was epithelial (Ep) in 77 cases, sarcomatoid (Sa) in 19, and mixed (Mx) in 7. Twenty-five pts had supportive care (SC) alone, 36 pleurectomy (P), 11 P and chemotherapy (Cht), and 31 pts Cht alone.

Results: One- and 2-yr FFP for the entire series are 22% and 3%; 1-yr and 2-yr OS are 41 and 15%. Pts receiving any treatment survived longer than pts treated with SC (1-yr OS 50% vs 18%, p = 0.003). One-yr OS with SC, Cht, P or P + Cht was 18%, 44%, 54% and 66% (p = 0.0001). Multivariate analysis adjusted for the main prognostic factors confirmed the independent prognostic value of treatment modality (p = 0.0026), PS (<2 vs. "2; p = 0.00016) and IMIG stage (I vs >I; p = 0.02). Histotype was nearly significant (Ep and Mx vs Sa; p = 0.15). The advantage for P + Cht was confirmed in the subset of pts with Ep or Mx MPM (p = 0.001), while therapy had no impact on OS in pts with Sa MPM (p = 0.29).

Conclusions: P + Cht seems justified in pts with Ep or Mx MPM with PS 0– 1. Experimental approaches should be encouraged in Sa MPM.