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MORBIDITY OF COMBINED SURGERY AND INTERSTITIAL AND EXTERNAL BEAM RADIOTHERAPY IN SOFT TISSUE SARCOMA WITH POOR PROGNOSIS AND RECURRENT FIBROMATOSIS.

Wijnmaalen A.J., Van Geel A.N., Meerwaldt J.H. and Levendag P.C.
Dr. Daniel den Hoed Cancer Center, Rotterdam, The Netherlands.

From 1988 until 1993 18 patients with soft tissue sarcoma or fibromatosis (9 primary, 8 recurrent, 1 lymph node metastases) have been treated with surgery and interstitial radiation (IRT). Fifteen patients received external beam radiation (ERT) as well.

The mean diameter of the tumours was 12 cm (range 4 - 30 cm) Eight tumours were located in the lower limb, 6 in the abdomen/pelvis, 3 in the trunk/neck, and 1 in the arm. The mean IRT-dose was 25 Gy (range 10-51 Gy); the mean ERT-dose was 48 Gy (range 40-50 Gy).

The mean follow-up period is 21 months (range 3 - 41 m). In 1 patient a macroscopic tumour recurrence developed and in 2 additional cases a microscopic recurrence was incidently found. In 9 patients distant metastases developed. One patient died of intercurrent disease and 5 of sarcoma. Grade 3 toxicity developed in 5 patients while grade 2 toxicity was found in another 5.

The results in terms of local control are excellent, in view of the poor prognosis, however, the complication rate is high. Based upon our experience we developed guidelines concerning the surgical procedure, postoperative care, and the application of IRT and ERT in the management of recurrent or locally advanced soft tissue sarcoma.

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NEOADJUVANT CHEMOTHERAPY WITH HIGH-DOSE METHOTREXATE (HD-MTX) IN THE TREATMENT OF MALIGNANT FIBROUS HISTIOCYTOMA (MFH) OF BONE

H. Hoekstra, H. Schraffordt Koops, W. Kamps, W. v.d. Graaf, W. Molenaar, J. Oldhoff.

Dept's Surgical Oncology, Pediatric Oncology, Medical oncology, and Pathology, Groningen University Hospital, The Netherlands.

Since 1980, 14 patients, 11 males and 3 females, median age 35 years, were treated for a MFH of bone. The tumor was located in the lower extremity in 11 pts (79%), upper extremity 2 pts (14%) and skull one patient (7%).
Nine pts (64%), median age 29 yrs (17-50 yrs) received neoadjuvant HD-MTX (12gm/m^2), vincristin, adriamycin, cyclophosphamide, bleomycine, and dactinomycin, or HD-MTX, 4-epiadriamycin and carboplatin. After 4 courses of polychemotherapy tumor resection (6 pts), or exchocleation and cryosurgery (3 pts) was performed. Effect of neoadjuvant chemotherapy was histologically graded: 3 complete responses (33%), 5 subtotal responses (56%), 1 minimal response (11%). After recovery of surgery 6 courses polychemotherapy including HD-MTX were administered. During a median follow up of 8 years (0.5-13 yrs) no local recurrence or distant metastases were diagnosed.
Neoadjuvant chemotherapy was contraindicated in 5 pts (36%), median age 55 yrs (21-67 yrs), due to age (3), cardiac insufficiency (1), or mental disorder (1). Treatment consisted of tumor resection (3), hyperthermic isolated limb perfusion with Cisplatin (1), and radiotherapy (1). Four patients developed recurrent disease (80%): one local recurrence after radiotherapy, and 3 distant failures (lung) after a mean follow-up of 9 months (3-15 months). The median overall survival was 33 months (6-51 months).
The only curative treatment option of MFH of bone is the combined modality treatment of HD-MTX based neoadjuvant polychemotherapy and tumor resection.

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HEART AND LUNGFUNCTION IN PATIENTS WITH PULMONARY METASTASES OF OSTEOSARCOMA TREATED WITH METASTATECTOMY AND 20 Gy POSTOPERATIVE IRRADIATION.

Nooy MA, Noordijk EM, Souhami R, Craft A, Hermans J, Bos vd B, Burgers JVM, for the European Osteosarcoma Intergroup. University Hospital, Oncology Dept. POB 9600, 2300 RC Leiden, The Netherlands.

Although prognosis of osteosarcoma patients has improved since the introduction of (neo)adjuvant chemotherapy, 40-45% of patients still relapse and half of them have pulmonary metastases only. Treatment of these metastases is preferably by surgery, but survival is still limited. Pulmonary irradiation might have an additive effect on survival. We have been doing a study to look whether irradiation after pulmonary surgery can safely be given in this chemotherapay pretreated group of patients.
Thirteen patients were treated: 12 male, one female. Mean age: 20.3 yr (range 13-29). Prior chemotherapy: Doxorubicin 13x, CDDP 12x, Ifosfamide 5x, other 4x. Number of thoracotomies before irradiation: 1,23 (range 1-3). Number removed lesions: 6.92 (range 1-41). Surgery: mainly wedge resection, lobectomy 1x, segmentectomy 1x. Irradiation: 20 Gy on both lungs after correction for lung density.

Lungfunction: % predicted	VC	mean	± SD	(range)	N=
before RT		80.0	± 16.6	(60-111)	8
after 8 months		76.0	± 4.0	(72- 80)	3
% predicted	TL Co				
before RT		81.6	± 13.3	(65- 98)	5
after 8 months		73.7	± 15.2	(60- 90)	3
% predicted	KCo				
before RT		99.8	± 18.7	(84-127)	4
after 8 months		80.0	± 8.5	(71- 88)	3
Ejection fraction LV (in rest)		mean	range		
before RT		0.68	0.50 - 0.75		5
after 4 monts		0.68	0.55 - 0.73		5

Although toxicity was the main topic of the study we looked after survival and disease free survival also. Median survival was: 16.8 months, median disease free survival: 5,4 months, median pulmonary metastases free survival: 5,4 months.
In conclusion: no severe lung nor cardiac toxicity was encountered. Pulmonary disease free survival is limited.

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CADOM (CYCLOPHOSPHAMIDE, ADRIAMYCIN, DACARBAZINE, VINCRISTINE AND METHOTREXATE) PROTOCOL FOR ADVANCED SOFT TISSUE SARCOMAS

Pfeffer M.R., Sulkes A., Catane R. Dept. Clinical Oncology and Radiotherapy, Hadassah University Hospital, Jerusalem 91120, Israel

Sixty consecutive patients with locally advanced or metastatic soft tissue sarcomas were treated with an aggressive chemotherapy protocol consisting of cyclophosphamide 600mg/m^2 d1, Adriamycin 30mg/m^2/d d1-2, dacarbazine 300mg/m^2/d d1-2, with vincristine 1.4mg/m^2 and methotrexate 200mg/m^2 followed by leukovorin rescue on day 15 of each 4-weekly cycle with planned dose escalation in the absence of hematological toxicity. Six (10%) patients achieved CR, 13 (22%) achieved PR, and 9 (15%) minimal response. Four of the patients achieving PR and 2 achieving MR were converted to CR following surgery or radiation therapy for a total CR rate of 20%. Median survival was 11 months (range 1-66 months). Thirteen (22%) of patients survived 30 months or more. The addition of high dose methotrexate with leukovorin, to the drugs of the CYVADIC protocol was feasible. Eight patients developed leukopenia associated fever and dose escalation was possible in only 4 patients. Nausea and alopecia was almost universal and stomatitis was common. The response rate was similar to our previous experience with CYVADIC. The percentage of long-term (>2½ years) survivors was increased. This may be due to a more aggressive surgical and radiotherapeutic approach following chemotherapy to patients with locally advanced or metastatic disease.

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PHASE II STUDY WITH LIPOSOMAL MURAMYL TRIPEPTIDE PHOPHATIDYLETHANOLAMINE (MTP/PE) IN SOFT TISSUE SARCOMAS (STS)

Verweij J., Judson I., Steward W., A.van Oosterom. van Pottelsberghe C., van Glabbeke M. and Mouridsen H. for the EORTC Soft Tissue and Bone Sarcoma Group. Rotterdam Cancer Institute, PO Box 5201, 3008 AE Rotterdam, The Netherlands

MTP/PE is a liposomal encapsulated synthetic muramyl tripeptide, coupled to dipalmitoylphophatidylethanolamine, activating macrophages to tumoricidal state in rodents and dogs. In phase I studies toxicities included fever/chills, tachycardia, nausea/vomiting (N/V) and headache. The MTD was 6 mg/m^2 once or twice a week. The recommended dose for phase II studies was 4 mg, at which dose biological effects were observed. We performed a phase II study with MTP/PE at a dose of 4 mg iv once every week in patients with metastastatic STS, after failure at prior chemotherapy. Response evaluation was done after 8 weeks. Twenty patients (pts) were entered but one never started treatment. The others were 9 males and 10 females, median age 42 years (range 20-65), median WHO performance score 1 (range 0-2). Histological subtypes involved were malignant fibrous histiocytoma in 3 pts, leiomyosarcoma in 5 and miscellaneous 11. Nine pts had received prior radiotherapy. One Pt is inevaluable because of early non-toxic death at 4 weeks. Toxicity was scored according to WHO criteria. A total of 168 administrations were given, median per pt 8 (range 2-25). Most frequent side effects were N/V grade 1-3 in 8 pts (47%) and flu-like syndrome (chills, fever and headache) grade 1-3 in 14 pts (74%). There was no major hematological toxicity. In general treatment was well tolerated. Responses were not observed, 2 pts had SD for 20 and 25 weeks. MTP/PE at this dose and schedule is not an active drug in the treatment of metastatic STS but, in view of preclinical and animal data, may still be an interesting drug for adjuvant application.

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PHASE II STUDY OF A SHORT COURSE OF WEEKLY CISPLATIN (C) COMBINED WITH ORAL ETOPOSIDE (E) IN PLEURAL MESOTHELIOMA.

Planting A., Goey S., de Boer-Dennert M., Vecht Ch., Stoter G., Verweij J.
Rotterdam Cancer Institute, 3075 EA Rotterdam, the Netherlands.

Thirteen patients (pts) with pleural mesothelioma Butchard stage IIa, 12 males and 1 female , median age 49 years (range 42-69), median WHO performance status 1 (range 0-1) were entered in this phase II study. Previous treatments: pleurodesis 3; intrapleural IL-2 2 pts. All pts had measurable tumor masses on CT-scan. Chemotherapy schedule: C 70 mg/m^2/ weekly weeks 1+2+3 and 5+6+7 and E 50 mg orally days 1-15 and days 35-50. C was administered in 3% hypertonic saline as a 3-hour infusion with pre- and posthydration. All pts received $5HT_3$- antagonists as antiemetic. In case of bone marrow toxicity treatment was delayed until recovery, with a maximum of 2 weeks delay. Dose reductions were not made. After evaluation in week 8 all pts with stable disease or better continued treatment with E orally at a dose of 50 mg/m^2/day days 1-21 q 4 weeks for 4 courses. All pts are evaluable for response and toxicity. The median no. of C administrations was 6 per patient (range 4-6); the median C dose intensity was 60 mg/m^2/wk (range 47-60). A delay in C administrations was necessary in 4 of 76 C administrations. Toxicity was mainly haematological : anaemia grade 2 in all pts, leucocytopenia grade 3 in 1 and grade 4 in 1 pt, trombocytopenia grade 4 in 1 pt. Non hematologic toxicity: neurotoxicity grade 1 in 3 , ototoxicity grade 1 in 1 and grade 2 in 3pts, nausea/vomiting grade 3 in 4 pts; nephrotoxicity was not observed. Three pts obtained a PR (median duration 16$^+$ weeks); 6 pts had SD (median duration of 30 weeks). After the first response evaluation in week 8 only 1 pt improved further with E orally. We conclude that the combination of C with E has moderate activity in pleural mesothelioma.