ThT 06

CONCLUSIONS FROM THE COOPERATIVE OSTEOSARCOMA (OS) STUDIES COSS-80 AND COSS-82 FOR FUTURE THERAPEUTIC STRATEGIES

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In study COSS-80 113 evaluable patients (pts) received neoadjuvant preoperative chemotherapy (prop CT) with high-dose methotrexate (HD-MTX), doxorubicine (DOX) and either cisplatinum (DDP) or the triple drug combination bleomycine&cyclophosphamide&dactinomycine (BCD). Half of the pts received in addition fibroblast interferon following surgery in wk 12. The degree to which the histologic grade of tumor cell destruction (TCD) after prop CT correlates with freedom from metastatic disease was studied. By regression analysis according to the Cox' model, we found the following characteristics to be significant risk factors: poor response (TCD $\leq$ 90%) to prop CT ($p = .006$), tumor size of > 1/3 of involved bone ($p = .013$) and en bloc resection as opposed to more radical surgical procedures ($p = .03$).
In study COSS-82 128 evaluable pts received postoperative (pop) CT different from the prop CT in case of poor response. To examine in a controlled trial the possibility of sparing some of the pts from the more toxic drugs DOX and DDP, pts were randomized to receive, in addition to HD-MTX, either BCD only or DDP&DOX. The response in the BCD arm was found to be significantly inferior to that of the DDP&DOX arm (27 vs 48% with TCD > 90%, $p = .01$) and the use of DDP&DOX as pop salvage CT did not compensate for the initial poor response.
Future trials should incorporate all known potent drugs from the beginning. The poor risk pts with large tumors and/or not responding to prop CT should receive intensified CT complemented rather than replaced by second line drugs. The increased risk for developing metastases after limb salvage procedures suggests some benefit from an intensified local treatment, e. g. intraarterial CT and/or local radiotherapy, which might show an advantage also for pts undergoing ablative surgery.

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ThT 08

GPO - COOPERATIVE EWING'S SARCOMA STUDY 1981 (CESS 81): RESULTS AFTER 4 YEARS

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The CESS 81 trial of the German Society of Pediatric Oncology (GPO) incorporated following biopsy proven diagnosis 18 weeks intensive combination protochemotherapy with vincristine, actinomycin D, cyclophosphamide and adriamycin (VACA) prior to local control with surgery and/or radiation. Following local therapy chemotherapy is continued for an additional 18 weeks.
113 protocol patients were entered since Jan. 1, 1981, 78/113 pts. are under observation for longer than one year following diagnosis, the longest follow-up being 56 months. On Aug. 1, 1985, 47/78 pts. (60 %) were disease-free. Out of 31/78 pts. who relapsed, 7 presented with pulmonary disease, 5 with multiple bone disease and 19 with a local recurrence. 8 of these 19 pts. also presented with systemic disease at the time of the local failure or within four weeks thereafter. Cox regression analysis of factors influencing prognosis revealed tumor volume as most significant factor: 7/33 relapses (21 %) in pts. with small tumors ($<$100 ml tumor volume) compared to 22/33 relapses (69 %) in pts. with large tumors ($\geq$100 ml tumor volume). Pts. who underwent surgery were evaluable for histological tumor response to protochemotherapy: 4/34 (12 %) relapses in pts. with more than 90 % histological tumor necrosis compared to 10/17 relapses (59 %) in pts. with less than 90 % tumor necrosis showed the significant influence of tumor response to protochemotherapy on prognosis. Tumor response correlated with tumor size. The preliminary results of this ongoing study indicate that protochemotherapy in primary Ewing's sarcoma of bone is effective to lower the systemic failure rate and that compromising radical local control may jeopardize the treatment results.

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ThT 09

COOPERATIVE MEDULLOBLASTOMA TRIAL MED 84 OF THE GERMAN SOCIETY OF PEDIATRIC ONCOLOGY (GPO) AND THE INTERNATIONAL SOCIETY OF PEDIATRIC ONCOLOGY (SIOP) (BMFT 01 ZP 034)

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This study is based on the interposition of an intensive course of chemotherapy (vincristine-procarbazine-high-dose methotrexate) between surgery and irradiation in a highly malignant embryonal brain tumor. Such "sandwich" chemotherapy offers a number of theoretical advantages. Experience of the first SIOP study has shown that a delay by a few weeks of the onset of radiotherapy in medulloblastoma does not jeopardize overall treatment results. A previous GPO study had demonstrated that the administration of a similar chemotherapeutic regimen was well tolerated by the patients.
The joint study of both societies aims at testing the "sandwich" principle in a prospective, randomized fashion Half of the patients receive the combination chemotherapy as outlined above between surgery and irradiation, the other half receive immediate postoperative radiotherapy. Moreover, patients at high risk for relapse (i.e. incomplete resection of the tumor or proof of metastases at diagnosis) receive maintenance chemotherapy with vincristine and CCNU following radiotherapy for an overall duration of one year.
In a second part of the trial, about one half of the participatiing centers will randomize "low risk" patients (i.e.with complete macroscopic tumor resection and without metastases at diagnosis)into a group receiving reduced doses of radiotherapy (25gy instead of the usual 35gy) to the brain and spine and another one receiving conventional doses. The area of the primary tumor (posterior fossa) will continue to receive the maximum tolerated dose (50-55 gy) in both arms. This part of the study will test the hypothesis that such a dose reduction is possible without compromising survival and, hopefully, will lead to a reduction of deficits in long-term survivors. (Supported by Bundesministerium f.Forschg.u.Technol.)

ThT 10

UPDATE OF THE COOPERATIVE AML-STUDIES IN CHILDREN BFM 78 AND 83

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From 12/78 till 10/82 151 children with AML entered the cooperative study BFM 78. Therapy consisted of a 7-drug regimen together with cranial irradiation over a period of ten weeks, followed by maintenance over two years. 119 of 149 (80 %) patients treated achieved a complete remission (CR). 12 (8 %) died early of bleeding and/ or leukostasis, 5 (3 %) of infection. 13 (9 %) were nonresponders. - 54 relapses, with CNS involvement in 11 cases, have occurred after a median follow-up time of 4;10 years (2;10-6;7 yrs.). The life table analysis revealed a probability for event-free survival (EFS) of 37 % (SD 4 %) and for the event-free interval (EFI) of 47 % (SD 5 %) after 6;7 years. Only 3 relapses were seen after 2;5 years.

In the second study BFM 83 an 8-day induction with cytosine arabinoside, daunorubicin and VP-16 precedes the BFM 78 regimen. The results of 120 patients after a median follow up time of 1;8 years (0;3-2;8 yrs.) are: CR rate 80 %, probability of EFS 40 % (SD 10 %) and EFI 48 % (SD 12 %). The results of both studies indicate that the chances for long-term remission have been increased successfully.

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