276

TANDEM HIGH-DOSE (HD) CHEMOTHERAPY (CT) WITH VP-16, IFOSFAMIDE (IFM), AND CARBOPLATIN (CBDCA) WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR PATIENTS (PTS) WITH GERM-CELL TUMORS (GCT) OR GESTATIONAL TROPHOBLASTIC DISEASE (GTD).

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Thirthy-two pts with previously treated GCT or GTD entered a trial consisting of two 5-day courses of combined VP-16, IFM and CBDCA with ABMT, as previously described (J. Clin. Oncol. 9 :1860-1870, 1991). 20 pts had gonadal (testis, 16 pts; ovary, 4 pts) GCT (17 with previous resistance to CT, 3 with no proven resistance to CT), 8 pts had extra-gonadal abdominal and/or thoracic GCT (7 with prior resistance to CT, 1 with non proven resistance to CT), 4 pts had refractory GTD. Median age was 27 y (range, 18-47). All pts had prior CDDP containing regimens. The dose ranges (in mg/m2/d x 5 d) were VP-16 : 200-250, IFM : 1500-2500 and CBDCA : 175-225. 23 pts received the 2 planned courses, 9 received only one. The main toxic effects (WHO grades III-IV) were (in No. of episodes) : mucositis (22), renal toxicity (3) and diarrhea (22). 7 pts died of therapy-related complications. The median No. of days to attain 0.5 x 10 E9 PMN/L from the day of BMT was 20 d (range, 10-30) and 20 d (range, 3-40) for the first and the second course, respectively. The maximum tolerated doses were (in mg/m2/d x 5 d) 250, 1500 and 200 for VP-16, IFM and CBDCA, respectively. 29 pts (of whom 28 were refractory to CT) were assessed for response : 7 pts (24 %) (gonadal GCT, 5 pts; GTD, 2 pts) attained a CR of 2,2,5, 38+,52+, 58+,68+ mos, and 5pts (17 %) achieved a PR (median : 4 mos). This regimen is highly efficient in refractory gonadal GCT and GTD. No CRs were attained in pts with extra-gonadal GCTs.

277

FEASIBILITY STUDY OF HIGH DOSE IFOSFAMIDE (I) PLUS CISPLATIN (C) COMBINED WITH rh-GCSF EVERY 2 WEEKS IN ADVANCED SOLID TUMORS

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Dose limiting side effects of the combination of C and I are bone marrow toxicity and nephrotoxicity. Administration of rh-GCSF between courses can diminish the risk of granulocytopenia; administration of C in hypertonic saline diminishes the risk of nephrotoxicity. In this study 14 pts, 8 males and 6 females, median age 45 y(32-66y), non small cell lung cancer (NSCLC) 8, melanoma 6 pts, median WHO performance status 0 (0-1) were treated with I at a dose of 2000 mg/m^2 days 1-3 and C at a dose of 33 mg/m^2 days 1-3 every 2 weeks for a maximum of 6 courses. I is administered as a 4-hour infusion combined with mesna 3x 400 mg/m^2 followed by C in 250 ml 3% NaCl as a 3-hour infusion with standard pre- and posthydration. rh-GCSF is administered sc. at a dose of 300 ug from day 4 until day 12. In case of WBC < 2.5 x 10^9/l or trombocytopenia < 75x10^9/l on day 14 retreatment is delayed until recovery. Dose reductions are not made. Nine pts are evaluable for response and toxicity. Seven pts received 6 courses , two without any delays, 3 pts with once a delay of 1 week and 2 pts with 3 times a 1-week delay. One pt received 5 and 1 pt 3 courses because of PD. Toxicities observed: anaemia grade 1 in 1, grade 2 in 6 and grade 3 in 2 pts; except 2 pts all had at least one episode of granulocytopenia and trombocytopenia grade 3 or 4; of a total of 50 courses 11 courses were complicated by granulocytopenia grade 3 or 4 and 15 courses by trombocytopenia grade 3 or 4. There was 1 episode of neutropenic fever. Non hematologic toxicities: N/V grade 3 in 1 pt, neurotoxicity grade 1 in 2 pts, ototoxicity grade 2 in 5 pts. There was no nephrotoxicity. Three pts with NSCLC had a partial response. The dose intensity of C and I reached with this schedule is high. The study is ongoing.

278

A PILOT STUDY OF ACCELERATED CEF PLUS G-CSF AS ADJUVANT THERAPY IN EARLY BREAST CANCER (EBC).

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In order to evaluate the feasibility of CEF_{14} (Cyclophosphamide 600 mg/m^2, Epidoxorubicin 60 mg/m^2, 5-Fluorouracil 600 mg/m^2, i.v. day 1) given every 14 days (d) for 6 cycles plus G-CSF (granulocyte-colony stimulating factor, Roche) 5 µg/kg s.c. d 4-11, from March to October 1992, 32 patients (pts) were treated. Main pts characteristics were: 59% age ≥ 50 yrs, 25% node negative, 94% T1-T2, 66% conservative surgery plus radiotherapy (RT). All but 5 pts completed 6 cycles of chemotherapy (CT): 4 pts stopped due to psychological reasons, one pt due to grade II anemia requiring blood transfusion, refused by pt. No grade IV toxicity was recorded. Grade III toxicity: 9% pts suffered from nausea/vomiting, 9% from stomatitis; alopecia was almost universal. Noteworthy, 66% pts received concurrently RT and CT without any increase in toxicity. G-CSF related toxicity was mild and no dose reduction or suspension was necessary. The mean duration of treatment was 71 d (planned 70). All drugs were administered at full planned doses. The mean Cyclophosphamide dose-intensity (D.I.) actually given was 278 mg/m^2/wk, which corresponded to 93% of planned D.I. (300 mg/m^2/wk). In conclusion accelerated CEF_{14} plus G-CSF is a feasible regimen and allows a 46% increase of D.I. compared to a standard CEF_{21} given every 21 d. A randomized study in EBC pts comparing this regimen to CEF_{21} is now in progress.

279

COMBINED SYSTEMIC CDDP-INTERFERON ALPHA (IFNα) IN ADVANCED PLEURAL MALIGNANT MESOTHELIOMA (MM).

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MM is a rare, chemoresistant tumor. CDDP and IFNα have shown low anti tumor activity (10-20%) in clinical trials and are synergistic in experimental MM models. Concomitant weekly administration may produce optimal and durable interaction. From 9/91 to 1/93 26 untreated patients (pts) were included in a phase I-II study of CDDP-IFNα (CDDP 60 mg/sq, IFN 3 mui x 4/w) given as 5 w on/3 w off (12 pts), 4 w on/ 4 w off (14 pts). Cycles (8 weeks) are resumed once at minimum (except early progression). Pts were : 22 males, 4 females, median age : 57 (30-70) ; median PS : 1 (0-2) ; pronostic factors = thrombocytosis : 7, weight loss >10% : 3 ; histologic subtype = epithelial : 14, sarcomatous : 3, biphasic : 9 ; UICC stage : II : 8 pts, III : 11 pts, IV : 3 pts ; asbestos exposure : 15 pts. Toxicity (WHO grade/pt) : 23 evaluable pts, 55 cy [median cumulative dose CDDP : 560 mg/sq (240-1200) ; median weight loss : 5.7% (0-20%) ; flu like syndrome 100% ; nausea/vomiting (N/V) : gr 2 : 9 , gr 3 : 4, gr 4 : 3 ; peripheral neurotoxicity : gr 1 : 6, gr 3 : 2 ; hematological : anemia gr 2 : 6, gr 3 : 6, gr 4 : 1, neutropenia gr 2 : 4, gr 3 : 5, thrombopenia gr 2 : 6, gr 3 : 6, gr 4 : 1, hypomagnesemia : 12, hypokalemia : 3, hypocalcemia : 4, hyponatremia : 5, 1 renal toxicity and 1 ototoxicity.
Results : 22 evaluable pts : 8 PR : 8,8,7,7+,6,6+,6+,2 (5 epithelial, 3 biphasic) ; 1 MR,3 SD, 10 PD.
This schedule is feasible with limiting toxicities being N/V and hematologic (both cumulative); treatment shortening (4w on, 4w off) provided better tolerance. Its encouraging activity, specially in epithelial subtype (6/9 evaluable pts), may be clinical confirmation of αIFN-CDDP positive interaction concept.

280

TANDEM HIGH-DOSE (HD) CHEMOTHERAPY (CT) WITH VM-26, IFOSFAMIDE (IFM), AND CARBOPLATIN (CBDCA) WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR PATIENTS WITH STAGE IIIC-IV OVARIAN CANCER (OC).

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Thirthy-three pts with previously treated stage IIIC or IV OC (5 pts initially refractory to CT; 10 pts in relapse; 2 pts with stage IV in CR, and 3 pts with stage IV OC in PR; 13 pts with stage IIIC in CR after second-look laparotomy (n = 9) or (n = 4) with persisting tumor) were treated with two 5-day courses of combined VM-26, IFM, and CBDCA, with ABMT, as previously described (J. Clin. Oncol 9 : 1860-1870, 1991). All pts had prior CDDP and/or CBDCA containing regimens. The dose ranges (in mg/m2/d x 5d) were VM-26 : 150-200; IFM : 1500-2000; CBDCA : 175-200. 25 pts received the 2 planned courses, 8 received only one. The main toxic effects (WHO grades III-IV) were (in No. of episodes) : mucositis (31), oesophagitis (17, including 2 grade IV episodes) and diarrhea (22). 3 pts died of therapy-related complications. Renal toxicity consisted in 21 grade I and 11 grade II toxicities. The median No. of days to attain 0,5 x 10 E9 PMN/L from the day of BMT was 20 d (range, 9-30) and 21 d (range, 10-30) for the first and the second course, respectively. The maximum tolerated doses were (in mg/m2/d x 5d) 150, 1500, and 200 for VM-26, IFM and CBDCA, respectively. 16 pts with measurable disease were evaluable for response : 2 pts (12,5%) attained a CR (10-28+ mos) and 7 (43%) attained a PR (5-13 mos). Of the 15 pts without any perceptible tumor who received the treatment as consolidation therapy, 5 were in continuous CR at 4+,11+,16+,16+ and 34+ mos. Further randomized studies will be necessary to determine the impact of HD CT in advanced stage OC pts.

281

TREATMENT OF NON-RESECTABLE HEPATOCELLULAR CARCINOMA WITH CONTINUOS 5 D MITOMYCIN I.V. AND INTERFERONE ALPHA 2B S.C.

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Introduction: Hepatocellular carcinomas (HCC) are known as only moderate chemotherapysensitive aggressive tumors. Chemoembolization and intraarterial chemotherapy of the liver were described for subgroups of non resectable HCC. In 1992 we have started a prospective phase I study with Mitomycin continuos 5 day infusion i.v. and Interferone alpha 2b s.c.. **Patients:** Since now we have administered the therapy to 7 patients with pretreated (5 pats)/ previously untreated (2 pats) hepatocellular carcinoma. **Schedule:** 5 MIO I.E. Interferone alpha 2b were applicated three times every week (Mo,Wed,Fri) subcutaneously combined with 5d continuos i.v. infusion of 20 mg/m2 Mitomycin. First course with 50% dose reduction.
Toxicity: Since now 6 pats were evaluable for toxicity: leukopenia WHO III in 2 pat, WHO II in 3 pats, thrombopenia WHO III in 4 pats, anemia: WHO II in 1 pats, inappetence with weight loss >CTC 0 in 2 pats, diarrhea II in 2 pats,no WHO II/III alopecia was seen until now.In one patient we could observe an increased serum level of amylase and lipase.
Response: Since now 5 pretreated patients were evaluable for response. 1 PR, 4 SD, 1 PD could be confirmed with CT-scan.
Conclusion: The results for pretrated patients are so far very encouraging. A follow up will be presented.