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COMBINATION CHEMOTHERAPY OF IFOSFAMIDE (IFX) / MESNA PLUS ETOPOSIDE (VP16) IN HUMAN BRONCHIAL CARCINOMAS XENOTRANSPLANTED INTO BALB/c-nu/nu MICE

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Two transplantable human non-small-cell bronchial carcinomas were included: Well-differentiated keratinizing squamous cell carcinoma 2045; mostly non-keratinizing squamous cell carcinoma 2089. The tumor 2045 forms extensive keratinizing cysts. It is monthly transplanted. Using the s.c. technique and the 12th-day subrenal capsule assay CTX, IFX, 5FU, ADM, VP16 cause a low sensitivity. The slowly growing tumor 2089 developing extensive fibrous regions is transplanted at two-monthly intervals. Its sensitivity pattern is comparable to that of 2045. Ongoing experiments are concerned with combination chemotherapy consisting of IFX/Mesna plus VP16. Using a computerized mathematical model for dosage scheduling (I.Fichtner and G.Steinhoff, Cancer Treat. Rep. 67, 621, 1983), it should be found out whether the two-component treatment causes synergistic therapy effects as compared to monotherapies with optimal doses. The evaluation of therapeutic parameters (Tumor growth as Δ Ocular Micrometer Units) and toxicologic parameters (Lethality; Body weight difference; Nadir of white blood cells) is performed.

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Ifo 28

IFOSFAMIDE, ETOPOSIDE AND THORACIC RADIOTHERAPY FOR SMALL CELL LUNG CANCER.

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137 patients without clinical evidence of CNS metastases, a Karnofsky Score (KS) > 20, and age 70 years or less were consecutively entered into the study.

66 patients were Limited Stage (LS), of whom 20% had ipsilateral neck nodes and 20% ipsilateral pleural effusions. Metastases in the 71 Extensive Stage (ES) patients were ipsilateral neck nodes 25%, effusions 24% contra-lateral neck nodes 16%, axillary nodes 20%, marrow 18%, liver 42%, bone 25% and other sites 45%.

Ifosfamide 5grams/m² with Mesna was given over 24 hours on day 1 with Etoposide 120mg/m² iv days 1 & 2 & 240mg/m² orally day 3. The courses were given at 3 week intervals for a total of 6. 3 weeks after the last course, 4 MeV thoracic XRT 3250 cGy, 8F over 10 days was started.

In ES, 329 courses of chemotherapy were given (61% of patients had all 6 courses) 84% of patients who responded did so within the first 2 courses. Treatment delays due to chemotherapy toxicity occurred on 14% of courses and on 5% iv antibiotics were given with 2 treatment related deaths. The overall response rate was 84% (24% CR). Median survival is 8 months of whom 16% are still alive.

In LS, 392 courses of chemotherapy were given (89% of patients had all 6 courses) 92% of patients who responded did so in ≤ 2 courses. Delays due to toxicity occurred on 8% of courses and on 2% iv antibiotics were given. There were 2 treatment related deaths. Median survival is 13 months of whom 42% are alive without recurrent disease. After therapy, 86% of LS patients had a KP of 80 or more compared with 11% initially and 62% of ES patients had a KP > 80 compared with 6% before chemotherapy.

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A RANDOMIZED TRIAL FOR ALTERNATING POLYCHEMOTHERAPY OF SMALL CELL LUNG CANCER

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In a randomized trial the value of a cyclic alternating chemotherapy was tested in patients with small cell lung cancer (SCLC). 305 patients from 14 institutions were randomized for two treatment arms A and B. Patients in A received a standard therapy (ACO = adriamycin 50mg/m², cyclophosphamide 1g/m², vincristine 1mg, on day 1), while patients in B were treated with a cyclic alternating chemotherapy (VPIV = VP-16 80mg/m², days 1-3; iphosphamide 1.5g/m², days 1-5; vindesine 3mg/m², on day 1. APO = adriamycin 60mg/m², on day 1, cisplatin 90mg/m², on day 1; vincristine 2mg, on day 1. CMCC=cyclophosphamide 1g/m², on day 1; methotrexate 15 mg/m², days 1,4 8,11; CCNU 100mg/m², on day 1). The final analysis of the trial showed that the alternating chemotherapy resulted in a higher response rate (by chest x-ray after two cycles of therapy) of 88% vs. 78%. The complete remission rate after eight (23% vs. 17%) and twelve (11% vs. 7%) months was higher in arm B than in arm A. The one year survival was 32% in arm A and 43% in arm B. Another result of this trial was that the response during the first two cycles according to chest x-ray was of great impact on survival in treatment arm A, but no in arm B. The trial also suggests that prognosis of non-responders to the 1st and 2nd cycle may be improved by the immediate switch to a non-cross resistant 2nd line therapy which would be a response-orientated individualized treatment form. To test this hypotheses we have started a second randomized multicentre trial.

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SEQUENTIAL POLYCHEMOTHERAPY FOLLOWING SURGERY FOR SMALL-CELL BRONCHIAL CARCINOMA IN A LARGE MULTICENTER COOPERATIVE TRIAL

K.Karrer and ISC (International Society for Chemotherapy)-cooperative group

In 1979 a randomized trial for patients with small-cell carcinoma of the lung (SCCL) was activated to compare a polychemotherapy (CT) given intermittently within 3 years after operation consisting of 13 courses of 3 infusions 12mg/kg cytoxan, 12mg/kg 5-FU, 0.5mg/kg MTX, 0.1mg/kg vinblastine with a sequential polychemotherapy (sq.CT) of 3 different drug combinations (A = 1500mg/m² cytoxan, 100mg/m² CCNU, 15mg/m² MTX; B = 1000mg/m² cytoxan, 40mg/m² adriamycin, 1mg/m² vincristine; C = 1,6g/m² ifosfamid, 120mg/m² VP-16) given alternating in 4 weeks intervals during the 1st year after operation (AA,BB,CC,AA,BB,CC). Observations on 25 patients showed that sq.CT is applicable, no unexpected side effects occurred. The life table curves indicate the improvement of the survival rate of patients receiving sq.CT compared with those of 31 patients receiving CT.

In October 1984 a new randomized cooperative ISC-trial for SCCL was activated and is joined at present by 36 departments and clinics. The protocol is comparing a combined chemotherapy (CT 1) as used in the ongoing trial No. 832 of the Lung Cancer Study Group of the USA and Canada consisting of 1000mg/m² cytoxan, 50mg/m² adriamycin and 1,4mg/m² vincristine, starting 1 week after surgery, given 8 times in 3 weeks intervals with a sequential chemotherapy (CT 2) comparable with the above mentioned sq.CT, each combination is given 2 times in 4 weeks intervals (A,B,C,A,B,C) within a half year. At the end of this period both groups receive prophylactic cranial irradiation , but only for disease free patients.

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