

included vinorelbine, cisplatin, etoposide, docetaxel, mitomycin, vinblastine and radiation therapy. All combination regimens have been well tolerated with no evidence of AG3340-related enhancement of toxicity. Accrual to these Phase III studies and studies in other diseases continues.

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PUBLICATION

Preliminary results of a dose-intense phase II study of a combination chemotherapy regimen with cisplatin (CDDP) and epirubicin (EPI) including medroxyprogesterone acetate (MPA) and recombinant interleukin 2 (rIL-2) in patients with inoperable primary lung cancer

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Based on our previous experimental and clinical data (G. Mantovani et al. *Semin Oncol* 25 (suppl 6): 45–52, 1998), we carried-out an open, dose-finding phase I study of a combination chemotherapy regimen (weekly CDDP + EPI) including rIL-2 and MPA for 6 weeks in 16 patients (pts) with stage IIIB–IV inoperable primary lung cancer. The maximum tolerable dose (MTD) was: CDDP 40 mg/m²/week (w) and EPI 40 mg/m²/w. A phase II study in the same patient population was designed with clinical response and toxicity as primary endpoints. The treatment schedule was: CDDP 40 mg/m²/w on day 1, EPI 40 mg/m²/w on day 1, MPA 1 g/day orally on days 1 to 7 starting 1 week before the 1st cycle and rIL-2 1.8 MIU administered subcutaneously (SQ) on days 2 to 6, for 6 weeks. G-CSF support 300 µg SQ was administered on days 2 to 5. From March to December 1998, 29 pts were enrolled: all were evaluable for toxicity and 22 of them for response as at February 1999 (M/F: 19/3, mean age: 68, range: 37–76). All patients but 3 had Stage IIIB–IV primary lung cancer (21 pts NSCLC and 1 pt SCLC). 90% pts had ECOG-PS. The body weight, appetite and QL (Therapy-Impact Questionnaire) were also evaluated. After 6 weeks, 10/22 patients (45.5%) had PR, 10/22 (45.5%) SD and 2/22 (9%) PD: the ORR was 45.5%. ECOG PS and body weight did not change significantly after treatment, whereas appetite showed a slight increase. Toxicity was only hematological. Grade 3/4 toxicity recorded were: 4 Grade 3 anemia and 2 Grade 3 leukopenia. One acute myocardial infarction occurred. Among the cytokine studied (IL-1β, IL-2, IL-6, TNF α), only IL-1 β serum levels were decreased after treatment. The study is in progress. *Work supported by C.N.R., Rome, A.P. "A.C.R.O." Contract no. 96.00588.PF39.*

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PUBLICATION

A phase II study of gemcitabine plus oral etoposide (GOE) in treatment of advanced non-small cell lung cancer

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Purpose: We have designed a new non-cisplatin based chemotherapy regimen to capitalize on the mild toxicity of gemcitabine (a novel antimetabolite) in treatment of advanced non-small cell lung cancer (NSCLC). This combination chemotherapy is intended to be relatively non-toxic and simple in administration. In this phase II study we report the response rate, toxicity, time to disease progression and survival.

Methods: Inclusion criteria: age 18 to 75; histologically confirmed NSCLC; stage IIIB or IV disease; bi-dimensionally measurable; chemotherapy naïve; no radiotherapy within 3 weeks of enrollment; ECOG performance status of 0 to 2; and informed consent. Patients with CNS metastasis, hypercalcemia, abnormal renal function and life threatening medical condition were excluded. Eligible patients were treated with gemcitabine 1000 mg/m² IV at day 1, 8, and 15 plus oral etoposide 50 mg daily from day 1 to 14 (GOE14) which was increased to 21 days (GOE21) if there was no WHO grade 3 toxicities in the first 2 cycles (28 days cycle).

Results: Between 5/97 and 7/98 we enrolled 46 patients and 44 were evaluable. Patient characteristics: mean age 53.4; male 37; female 7; stage IIIB 27; stage IV 17. One hundred and eleven courses of GOE14 and 100 courses of GOE21 were delivered. The incidence of grade 3 WHO toxicity is as follows: anemia 29.6%, leukopenia 29.5%, neutropenia 31.7%, thrombocytopenia 18.2%, nausea and vomiting 6.8%, mucositis 0%, and proteinuria 4.5%. Only 2 patients had neutropenic sepsis and both recovered promptly with antibiotic. No septic death was reported. Responses were

1 complete (CR 2.3%) and 19 partial (PR 43.2%). There were 12 stable disease (SD 27.3%) and 12 progressive disease (PD 27.3%). Median time to progression and median survival was 26 and 49.7 weeks respectively. One-year survival rate was 45%.

Conclusion: This new combination chemotherapy of gemcitabine and oral etoposide achieves high response rate. Comparing to historic data of other cisplatin-based regimens the toxicity of this combination is less and the survival is similar if not better.

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PUBLICATION

Accelerated hyperfractionation radiotherapy concurrently combined with chemotherapy for stage III non-small cell lung cancer

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Purpose: Stage III non-small cell lung cancers (NSCLC) were treated with concurrent accelerated hyperfractionation radiotherapy (AHFRT) and chemotherapy to evaluate its feasibility and efficacy.

Methods: Fifty-seven patients with stage III NSCLC who treated from 1992 to 1997 were enrolled in this study. They consisted of 53 males and 4 females, and ranged in age from 36 to 79 years (mean 65 years). Seven of them were stage IIIA and the others were stage IIIB. With the maximum dose of 60–72 Gy as a goal, AHFRT was performed twice per day at a dose of 1.5 Gy or 1.8 Gy for each irradiation. This was combined with chemotherapy using Cisplatin (80–160 mg/m²) or Carboplatin (300–600 mg/m²) as a principal anticancer agent.

Results: The treatment could be completed in 54/57 (95%). The major acute toxicity encountered was grade 3 or greater leukopenia (32/57; 56%) and esophagitis (7/57; 12%). In patients of 1.8 Gy group, esophagitis appeared frequently (6/27; 22%) as compared with patients of 1.5 Gy group (1/30; 3%). Grade 2–3 radiation pneumonia was encountered in 18/52 evaluable patients (35%). No grade 4 or greater radiation pneumonia was encountered. The primary effects in patients in whom the treatment was completed were rated as complete response in 2 (4%), as partial response in 44 (81%) and as no change in 8 (15%). Response rate was 85% in over all. The 1, 3 and 5-year rates were 63%, 25% and 16% respectively.

Conclusion: AHFRT (1.5 or 1.8 Gy at each irradiation for 60–72 Gy) concurrently combined with chemotherapy using Cisplatin (80–160 mg/m²) or Carboplatin (300–600 mg/m²) was appeared feasible with a tolerable degree of toxicity and is expected to contribute to the improvement of Stage III NSCLC.

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PUBLICATION

Vinorelbine, carboplatin and gemcitabine (VGC) in the treatment of untreated advanced/metastatic non-small cell lung cancer (NSCLC): A phase I study

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Background: Vinorelbine (VNR), Carboplatin (C) and Gemcitabine (GEM) are drugs which are active in the treatment of NSCLC. Administration of these three drugs can be a valid alternative to compounds containing cisplatin.

Purpose: To determine the maximum tolerate dosed (MTD) of C in association with fixed doses of VNR and GEM.

Methods: The study enrolled patients with Stage III B and IV, non-pre-treated, inoperable NSCLC that could not be treated with radical radiation therapy; age < 70, PS < 2 (ECOG), with normal hepatic, renal and hematological function, the patients gave informed consent. The patients were treated with increasing doses of C at day 1. Treatment cycles were repeated every 4 weeks. The dosage of C was calculated on the size of the AUC using Calvert's formula. The starting dose corresponded to AUC 4; doses of C corresponding to AUC 4-4.5-5-5.5 and 6 were tested without unacceptable toxicity.

Results: 24 male patients were enrolled, at 5 different dosage levels for a total of 78 cycles. The mean age was 60 years (47–70). Mean PS 1 WHO (0–2). Grade 3 neutropenia was found in 2 patients at AUC 5 and in 2 patients at AUC 5.5 of C. The MTD was found at AUC 6 with grade III–IV thrombocytopenia in 3 of the 6 patients treated.

Conclusions: The recommended dose of C for a Phase II study is AUC 5.5.