1080 PUBLICATION

Chemoimmunotherapy with weekly cisplatin and etoposide plus S.C. rIL-2 plus oral medroxyprogesterone acetate (MPA) in stage IIIB–IV NSCLC: Preliminary results on clinical response and on immunologic assessment

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Purpose: MPA is widely used in oncology both in the treatment of hormone-related cancers and as supportive therapy in anorexia/cachexia syndrome (ACS), but conclusive data are not yet available to explain its anticachectic effect. Several cytokines, mainly interleukin (IL)-1, IL-2, IL-6 and tumor necrosis factor α (TNFα), are involved in the pathogenesis of ACS. In a previous study (Eur J Cancer, 1996 in press) we reported the effect of MPA on peripheral blood mononuclear cells (PBMC) from 10 cancer patients in advanced stage of disease (6 head and neck, 2 colon, 1 lung NSCLC and 1 ovary). Our study provided evidence that MPA is able to hinder the activity of some cytokines, such as IL-1β, IL-6 and TNFα, which have a key role in the pathogenesis of ACS by inhibiting their production and/or release. These experimental results prompted us to perform a phase II open clinical study of chemoimmunotherapy treatment of stage IIIB–IV inoperable NSCLC.

Methods: The treatment plan consisted of cisplatin (50 mg/m^2 i.v.) and etoposide (100 mg/m^2 i.v.), combination administered on day 1 weekly for 6 cycles, plus recombinant Interleukin-2 (rIL-2) 1.8 MIU s.c. from day 2 to 7 weekly for 6 cycles, plus MPA 1000 mg/daily beginning 7 days before the chemotherapic treatment and during all treatment period (6 weeks). Twenty-three patients (M/F 19/4) with NSCLC were enrolled, 14 of whom (mean age 65.2 years, range 52–74; 6 stage IIIB, 8 stage IV) were evaluable for response and 17 for toxicity.

Results and Conclusion: There were 7% CR, 21% PR (OR 28%), 36% SD and 36% PD. The toxicity was acceptable: 3 patients were withdrawn from study for hematologic (Grade 3 anemia) and 1 for renal (Grade 2) toxicity. An immunological study carried out on 9 of these patients (2 stage IIIB and 7 stage IV) showed that PBMC proliferative response to PHA, anti-CD3 monoclonal antibody or rIL-2 of patients didn't change significantly after the planned chemoimmunotherapy treatment compared to pretreatment values. Similarly, the serum levels of cytokines IL-1β, IL-2, IL-6, IL-10, TNFα and IFNγ and the production in culture of the same cytokines by PHA-stimulated PBMC of patients did not show any difference after treatment as compared to pretreatment values (only IL-2 production was significantly higher after treatment compared to values before treatment).
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1081 PUBLICATION

A phase II trial of radiochemotherapy with ifosfamide/mesna in patients with unresectable non small cell lung cancer (NSCLC)

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Radiotherapy with a dose of 60–70 Gy is the standard treatment of medically or technically inoperable non metastasised NSCLC. In a phase I study the feasibility of a combination regime consisting in radiotherapy and a chemotherapy with ifosfamide was already established. The purpose of the ongoing phase II trial is to investigate the efficacy and toxicity of the multimodal treatment.

The radiotherapy consisted of a total dose of 60 Gy with a fractination of 2 Gy/day 5 times weekly. Additionally ifosfamide was applied in week 1 and 5 of the radiotherapy at a dosage of 1500 mg/m2/day (5 days/24 h infusion). Mesna was applied at a dosage of 20% of the ifosfamide dose.

17 patients with NSCLC stage III were treated. In 11 of the 17 pts treatment was completed according to protocol. In 6 patients non therapy related complications occurred and treatment was modified.

No treatment modification because of esophagitis was necessary. A leucopenia WHO grade 3 and 4 occurred in 7/17 pts. Thrombocytopinia was not a clinical problem. Radiaton pneumonitis RTGO grade II was observed in 1 pt. In all pts who completed the treatment a tumor regression of 80% and more was observed.

Our phase II study indicates that simultaneous radiochemotherapy of NSCLC with ifosfamide/mesna leads to a good local tumor control with an acceptable heamatological toxicity.

1082 PUBLICATION

Phase II trial of i.v. navelbine (NVB) and cisplatin (CDDP) in inoperable locally advanced or disseminated NSCLC

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New drugs with promising activity have been identified for NSCLC treatment, and NVB has already been shown to increase the survival rate in randomised trials. Large European and American multicentre studies have shown that the results of NVB + CDDP combination had a statistically superior survival, compared with standard therapy (Le Chevalier/JCO 1994). Based on these results, this study has been conducted in South Africa in order to test this combination in our patients (pts): NVB 30 mg/m^2 D1 & D8 + CDDP 100 mg/m^2 D1, every 21 days, 6 cycles max. Thirty previously untreated pts were included from 09/95 to 12/96. To date, 24 pts are evaluable for response, 27 for tolerance, with the following characteristics: median age 55.8 y (42–68), 26 M/4 F; PS/0–1 = 77%, 2 = 23%; 56% squam. cell carcinoma, 28% adenoca, 16% large cell carcinoma. Stage IIIA = 17.2%, IIIB = 20.7%, IV = 62.1%. 116 courses were administered in total. The overall response rate was 41.5%: 1 CR/9 PR (95 CI 21.8–61.2%), 1 further patient obtained an objective response but was not available for confirmation. WHO G3/4 neutropenia in 9pts with only 3 G3 infections; 19% of cycles with WHO G3 nausea/vomiting, WHO G2–3 constipation in 8.7% of cycles (2 pts G3). Two pts presented G2 peripheral neuropathy. WHO G2/3 alopecia in 22% of pts, 2 episodes of G3 local phlebitis. Other side effects were uncommon. These preliminary results confirm that the combination of NVB + CDDP have major antitumour activity in NSCLC with a manageable tolerance.

1083 PUBLICATION

Gemcitabine and cisplatin for advanced non-small cell lung cancer (NSCLC)

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The aim of this phase II study was evaluate gemcitabine in combination with cisplatin in chemonaive patients (pts) with locally advanced or metastatic NSCLC at a higher gemcitabine dose. Gemcitabine 1200 mg/m2 was given on days 1, 8 and 15 of each 28 day cycle. Cisplatin 100 mg/m2 was given on day 15 before gemcitabine infusion. 23 consecutive pts were entered between January and October 1996: median age 60 years (range 39–73); 22 males and I female; performance status 0–2; histology: adenocarcinoma in 9 pts, squamous in 7 pts and large cell in 7 pts. 9 pts had stage IIIB and 14 pts stage IV. To date, 21 of 23 pts are evaluable. There were 1 CR and 5 PR (for an overall response rate of 28, 7%: 95% CI 14–50), 11 pts with stable disease and 4 pts with progresive disease. The median duration of response was 5.5 months and median survival have not yet been reached. The most important toxicity (WHO graded) over 93 cycles was: neutropenia 32.2% of the cycles at grades 1–2; anemia 58% grades 1–2; thrombocytopenia 19.3% grades 1–2; nausea and vomiting 21.5% grade 1. This preliminary findings suggest that the combination of gencitabine and cisplatin has promising activity in advanced NSCLC with mild to moderate toxicity.

1084 PUBLICATION

A pilot study of VIME-C/P or VIME, in patients with small cell lung cancer

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Purpose: To study the efficacy and toxicity of an intensive chemotherapy regimen containing VP16 (V) + Ifosfamide (I) + Mesna (M) + Epirubicin (E) +/– alternating cisplatin (C) – carboplatin (P). 27 pts, with histologically verified small cell lung cancer, 14 pts. with LD and 13 with ED, were treated. Median age 66 y.

Methods: Pts. were treated with V 80 mg/sqm d 1–3, I 2000 mg/sqm d1–3, Mesna 400 mg/sqm 0, 4, 8 h d1–3, E 60 mg/sqm d 1, alternating C 100 mg/sqm or P 300 mg/sqm d 1, q 3 w. 15 pts. recieved only VIME without platinum combination due to age or poor performance. Pts. in CR after 3 courses continued treatment for a total of 6 courses, pts. with LD not in CR after 3 courses received RT and thereafter 3 further courses of

CT. Patient in CR after 6 courses of CT received profylactic cranial irradiation.

Results: 22/27 pts. were evaluable for response. Evaluation after 3 courses; 7 CR, 13 PR, 1 SD, 1 PD, overall response rate RR 20/22 (91%). The main toxicity was bone marrow depression, 6/27 pts. required G-CSF support and 17 pts. received blood transfusions. Infections were seen in 16 pts. of whom 14 were hospitalized. One case of therapy related death occurred.

Conclusion: This chemotherapy regimen seems to be very effective, with considerable but manageable toxicity. In this small study, it seems like that the addition of alternating C/P treatment did not improve the response rate.

1085 PUBLICATION

Interim results of a sequential administration of docetaxel (TAXOTERE®) followed by cisplatin-vindesine in chemotherapy naive patients with locally advanced or metastatic non small cell lung cancer (NSCLC)

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Because of the potential lack of cross-resistance between docetaxel (D) and cisplatin-vindesine (PV) a phase II trial was initiated in order to give them at their optimal dose and scheduling: (Part A) (D) 4 cycles (100 mg/m^2 q3) followed by (Part B) (PV) 4 cycles (120 mg/m^2 d1 q4 weeks-3 mg/m^2 weekly), followed by (Part C) (D) 3 cycles. Main eligibility criteria: histologically proven NSCLC, KPS $\geq$ 60%, no previous chemotherapy, no brain involvement, no neurotoxicity NCI grade $\geq$1.32 patients (pts) have been included. To date 29 pts have been analyzed. Main pts'characteristics: 72% male; median age: 56 years (40–70); median KPS 100% (60–100); adenocarcinoma 41%; squamous cell 35%; large cell 24%; metastatic 83%. Main toxicities for 28 pts (147 cycles): Parts A, B, C: neutropenia G-3 39%, G-4 36%; febrile neutropenia 4%; allergy G-3 7%; severe asthenia 4%; stomatitis G-3 4%; transaminase elevation G-2 4%. Part B: neurosensory G-3 25%; creatinine elevation G-3 4%, G-4 4%; vomiting G-3 4%; neurohearing G-3 4%. No toxic death was observed. To date, 22 pts were off study and received a median number of 6 cycles (1–11). Six pts were withdrawn from study for adverse experience (neurological, hepatic or renal toxicity). Seventeen pts were evaluable for response: 4 PR (23.5%); 8 NC (47%). The response will be reviewed by an independent panel. The main non-hematological toxicity was neurosensory. Its incidence should decrease for the further pts as the dose of PV has been reduced. This sequential administration appears feasible (median number of 6 cycles administered) and seems to achieve a promising activity.

1086 PUBLICATION

The impact of vinorelbine in elderly (aged >70 years) with NSCLC: A preliminary report

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To assess the impact of chemotherapeutic treatment in obtaining better quality of life in elderly aged plus 70 years with inoperable NSCLC, since December 1996 we have submitted 15 patients (pts) to a "palliative" schedule with Vinorelbine 30 mg/mq i.v. days 1 and 8 every 3 weeks for at least 3 cycles.

To date the main features of the treated pts are: M/F ratio = 14/1; median age (years) = 70 (range 65–83); NSCLC stage IIIb = 7, stage IV = 8; all pts had one collateral disease (mainly COPD and diabetes).

All the pts were evaluated according to a MultiDimensional (MD) approach including cognitive state, daily activity functions, comorbidity, nutritional and clinical assessment, psycosocial condition. The MD evaluation was studied before, during and after the treatment.

12/15 pts received 3 cycles of Vinorelbine, 2 pts 2 cycles and are defined as too early to evaluate and 1 pt received only 1 cycle owing to early death (ED).

After 3 cycles, 3 pts have Partial Response and 6 Stable Disease but all the treated pts, excluding the ED, showed, at the MD evaluation, a better "status" of quality of life with less need at supportive care (steroid infusion and antibiotical drugs, mainly) and a good level of autonomous performance status.

The psycosocial examination revealed in 9/6 pts a higher level than before the treatment. The only toxic observed effect owing to Vinorelbine infusion, was phlebitis in the arm where the drug were infused 4/15 pts and hematological G1 in 1/14 pts. No neurological or gastrointestinal toxic effect was observed. Emesis was not recorded and anti-emesis protocol contained Ondansetron.

These preliminary data indicate that even for elderly pts a chemotherapeutic approach is ethic when the aim is good level of quality of life.

Furthermore toxicity related to chemoterapeutic approach in elderly pts isn't so heavy as commonly retained if related not to the age of pts but to comorbidity.

1087 PUBLICATION

Carboplatin (CBDCA), ifosfamide (IFX) and etoposide (VP) in advanced non small cell lung cancer (NSCLC): A phase II trial

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Purpose: Assess efficacy, toxicity and changes of Karnofsky performance status (K) of CBDCA-IFX-VP (CIV) regimen in NSCLC neoadjuvant or palliation therapy.

Methods: Patients (pts) were required to have histologically proven locally advanced or metastatic NSCLC with measurable lesion, no previous chemotherapy and signed informed consent. They were treated in an outpatient setting with CBDCA 300 mg/m^2 on day 1 and IFX 1.5 gr/m^2 + Mesna and VP 60 mg/m^2 both on days 1–2–3 every 4 weeks.

Patients: For a total of 38 pts, 33 were males and 5 females, with a mean age of 59.6 years (33–74) and a median K of 80% (60–100%). 11 pts were stage IV disease, 14 stage IIIB and 13 stage IIIA. Histology were 28 squamous cell, 9 adenocarcinoma and 1 large cell.

Results: All pts were evaluable for response and toxicity. 227 cycles (cyc) were administered (mean 5.9/pts). Clinical complete response was achieved in 1 pts (2.6%) and partial response in 14 pts (36.8%), for an overall response (OR) rate of 39.5% (95% CI: 24%–55%). 16 pts (42%) had stable disease and 7 pts progression disease. K improved in 12 pts, remain unchanged in 13 pts and decreased in 13 pts. The principal toxic effect observed was myelosupression (M), particularly neutropenia. Median time to progression (mtp) was 7 months (mo) (95%CI: 6–13 mo) and median survival (ms) was 10 mo (95%CI: 8–18 mo). 10 cyc (4.4%) were not to be started as scheduled because M. When pts with and without dosage reduction were compared, mtp and ms were not different.

Conclusion: CIV combination is active in advanced NSCLC, with OR comparable to that achieved in other similar trials. Moreover, K improved or remained unchanged in 65.7% of pts. Prospective phase II studies are need to assess the role of dose intensity in advanced NSCLC.

1088 PUBLICATION

Navelbine (NVB), oral etoposide (VP16), in advanced non-small cell lung cancer (NSCLC)

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Methodology: Between 10/94 and 12/96, 25 patients (pts) with advanced/metastatic NSCLC were accrued to the NVB + VP16 phase II trial: pts with PS/ECOG $\leq$ 2, histologically confirmed and measurable disease were eligible for the treatment: NVB 30 mg/m^2 on D1 and NVB 35 mg/m^2 on D8, oral VP16 100 mg/m^2 over 5 days (D1–5) given on a 28-day schedule (maximum 6 cycles).

Results: Pts characteristics are as follows: 19 males (76%); median age 68y (39–75); PS 0, 1 and 2: 40%, 36% and 24% respectively; histology: adenocarcinoma – 11 pts (44%); squamous cell – 10 (40%); large cell carcinoma – 4 (16%). Stage: IIIb – 18 (72%); IV – 7 (28%). The incidence of Grade (G) 3 neutropenia was 12% and G2 neutropenic fever was seen in 2 pts.; non-haematological toxicity: G 2 nausea/vomiting 24%; G1 local phlebitis 4%; G3 alopecia 8%; G1–2 peripheral neuropathy 20%; G1–2 constipation 24%; 65% of pts experienced reversible and mild fatigue.

Response: Overall Response Rate: 72%; CRs: 4 pts (16%); PR: 14 pts (56%); the median TTP was 10 months. Moreover cancer related symtoms were improved as dyspnoea in 80% of pts; haemoptisis in 90%; cough in 60% and pain in 50%. At 1 year follow up 9/12 patients are alive.

Conclusions: This regimen produces encouraging response rates and an excellent tolerance profile in the management of inoperable NSCLC. This regimen should be assessed in the neoadjuvant setting in earlier stage disease.