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Raltitrexed ('Tomudex') and cisplatin in metastatic non-small cell lung cancer (NSCLC): Preliminary results of a Phase I dose-escalation study

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Introduction: Raltitrexed ('Tomudex'), a specific inhibitor of thymidylate synthase, has shown some activity in pts with NSCLC in a Phase II trial. Also, preclinical studies have suggested that a combination of raltitrexed and cisplatin may have synergistic or additive effects. The primary aim of this study was to determine the RD of raltitrexed and cisplatin in combination treatment.

Methods: Chemotherapy-naive patients with metastatic NSCLC (stage 4) were treated once every 3 weeks with raltitrexed (15-min iv infusion) followed by cisplatin (1–2 h iv infusion) at escalating dose levels. 3–6 pts are being recruited at each dose level, with a further 20 pts enrolled at the RD.

Results: 21 pts entered the study (M14/F7; median age 60 [47–70] years; ECOG-PS 1, 18 pts, 2, 3 pts). No DLT was observed at dose levels 1–4 or in the first 3 pts entered at dose level 5. However, the 1st pt entered at dose level 6 experienced severe toxicity including GIII diarrhoea and 3/4 further pts subsequently entered at dose level 5 also experienced DLTs (GIII diarrhoea [1 pt], GIII leucopenia and other GII and severe adverse events [1 pt], GIV diarrhoea, thrombocytopenia and neutropenia [1 pt]). Of 15 pts evaluable for efficacy, 2 had a partial response and 11 had stable disease.

Dose level	Raltitrexed (mg/m^2)	Cisplatin (mg/m^2)	No. pts entered	No. cycles	DLT
1	2.6	60	3	12	0
2	2.6	70	4	19	0
3	2.6	80	3	5	0
4	3.0	80	3	8	0
5	3.5	80	7	17+	3
6	4.0	80	1	4+	1

Conclusions: The MTD has been reached at raltitrexed 3.5 mg/m^2 and cisplatin 80 mg/m^2. Further pts are to be recruited at the RD (raltitrexed 3.0 mg/m^2, cisplatin 80 mg/m^2). This combination shows promising efficacy in patients with metastatic NSCLC. Phase II trials in head and neck cancer and gastric cancer, and a Phase III trial in malignant pleural mesothelioma are also planned.

'Tomudex' is a trade mark, the property of Zeneca Ltd.

1003 POSTER

Standards, options and recommendations (SOR) for clinical care of malignant thymoma

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Context: The SOR project, started in 1993, is a collaboration between the Federation of the French Cancer Centres (FNCLCC), the 20 French Cancer Centres and specialists from French Public Universities, General Hospitals and Private Clinics. The main objective is the development of clinical practice guidelines to improve the quality of health care and outcome for cancer patients. The methodology is based on literature review and critical appraisal by a multidisciplinary group of experts, with feedback from specialists in cancer care delivery.

Objectives: To develop clinical practice guidelines according to the definitions of SOR for the clinical care of malignant thymoma in adult.

Methods: Data have been identified by literature search using Medline (december 1998) and the expert groups personal reference lists. Once the guidelines were defined, the document was submitted for review to national and International independant reviewers, and to the medical committees of the 20 French Cancer Centres.

Results: The main recommendations for malignant thymoma management are that 1-the clinical diagnosis is based on appropriate clinical and radiological findings 2-the final diagnosis is pathological and made from a biopsy, except in cases of well-encapsulated tumors which are completely resected. The biopsy, via anterior mediastinostomy, should be performed by the surgeon who will subsequently perform the definitive surgery. 3-Surgical resection must be complete including thymus and perithymic fat and performed by an experienced surgeon. 4-The therapeutic strategy for malignant thymoma is based on the three current staging systems and involves surgery with radiotherapy given if the capsule is invaded or penetrated. Radiotherapy should be given in experienced centres. Inclusion of patients in prospective clinical trials is recommended in order to determine the usefulness of neoadjuvant chemotherapy and multimodality approaches. 5-Treatment of metastatic malignant thymoma is based on chemotherapy. Secondary surgery may be performed with the aim of achieving complete resection. Inclusion in clinical trials is recommended. 6- at the present time, there are no clear data on which to base guidelines for timing and duration of follow-up studies in this condition. Because of late recurrence, follow-up should be long.

1004 POSTER

Late phase II trials of topotecan (T) for relapsed small cell lung cancer (SCLC)

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T is a water soluble, semisynthetic analog of the alkaloid camptothecin, which is a specific inhibitor of topoisomerase I. Two late phase II studies were undertaken to evaluate activity and toxicity in patients (pts) with relapsed SCLC. T was administered as a 30-minute intravenous infusion for 5-consecutive-day at a dose of 1.0 mg/m^2/day every 21 days. Fifty-three pts were enrolled in each study. A total of 103 eligible pts were entered and 96 pts, who were treated with 280 courses, have been evaluated. The mean age of pts was 63 years (range 42 to 75), the majority of pts were P.S. 1 and had stage IV disease. All pts had received one prior chemotherapy and 63 pts received radiotherapy. Patients had completed initial therapy at least 8 weeks prior to study. In the 96 evaluable pts 1 CR (1%) and 24 PR (25%) were observed: the overall response rates was 26%. Results in each group were similar. Responses were observed in the primary lung lesions (11 PR) as well as lymph nodes (11 PR), liver (4 PR), metastatic lesions in lung (1 CR, 2 PR), adrenal (2 PR), brain (2 PR), and soft tissue (1 PR). 18 pts had received prior CPT-11; of these, 4 PR (22%) were observed. T was effective against stage IV SCLC because 1 CR and 14 PR (response rate: 24%) were observed in 63 pts. The major adverse reaction was myelosuppression: grade 3 or 4 leukopenia, neutropenia, thrombocytopenia and anemia were observed in 66%, 84%, 42% and 46%, respectively.

We conclude that T has promising activity in pts with relapsed SCLC and is well tolerated. We are therefore planning to investigate topotecan combination therapy in first-line SCLC.

1005 POSTER

Paclitaxel in combination with cisplatin, etoposide and thoracic radiotherapy for limited small cell lung cancer. A Phase II study

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Introduction: To investigate the feasibility, efficacy, and safety of adding paclitaxel to standard cisplatin/etoposide regimen and concurrent thoracic radiotherapy (TRT) in the treatment of limited small cell lung cancer (SCLC).

Methods: Patients received five courses of chemotherapy (paclitaxel 175 mg/m^2 as 1-hour IV infusion day 1, cisplatin 50 mg/m^2 IV day 1, etoposide 100 mg/m^2 IV day 1, and oral etoposide 100 mg bid (day 2–5) at three week intervals. TRT (42 Gy/15 fractions) to the tumour and mediastinum was adminstered between chemotherapy course 3 and 4. All patients achieving CR were administered prophylactic cranial irradiation (PCI).

Results: Of 39 included patients, there were 21 males and 18 females. Median age was 63 years. 35 patients have completed treatment, and median follow up after completion is 18 months (range 1–33). Overall response rate was 91% and CR rate 80%. Hitherto, 17 (61%) of 28 CR patients have relapsed (9/17 brain, 6/17 thoracic). Mild hypersensitivity reactions were reported in 5 patients. Grade 4 leukopenia in 28% of patients, but no grade 4 thrombocytopenia. There was one treatment related death due to severe neutropenia and septicemia.

Chemotherapy doses were reduced in 41% of the courses. Reversible grade 3 neuropathy was seen in two patients and grade 3 myalgia in one. Five patients developed grade 3 esophagitis during radiotherapy.