1002 POSTER

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.

Conclusion: This novel treatment is well tolerated and highly active in limited SCLC.

1006 POSTER

The role of TC-99m tetrofosmin (T) SPECT in primary lung cancer (LC) detection

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Purpose: The aim of the study was to further evaluate the usefulness of Tetrofosmin-SPECT in identifying primary lung cancer.

Methods: After T injection, SPECT images of the chest were acquired in 122 pts with suspect pulmonary lesions at conventional imaging procedures. Scan data were analized qualitatively and semiquantitatively, the latter by calculating the Tumor/Background ratio (T/B) in the coronal slices, and were then related to histology.

Results: T-SPECT was true positive in 105/105 LC pts (sens. 100%) and true negative in 13/17 pts with benign pulmonary lesions (spec. 76.5%). T/B value was higher in malignant lung lesions than in benign ones (2.37 ± 0.84 vs 1.42 ± 0.24; $p < 0.05$). Considering a T/B cut-off value of 1.4, T-SPECT specificity increased to 88.2%.

Conclusion: T-SPECT appears a highly sensitive method in primary lung cancer detection since there was no false negative result in our cases. Moreover, the additional use of T/B seems to give more useful information in differentiating malignant from benign pulmonary lesions.

1007 POSTER

Chemoradiotherapy for advanced non-small cell lung carcinoma (NSCLC). Qualitative and quantitative evaluation of the literature

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Purpose: The treatment of unresectable stage III NSCLC by chest irradiation with or without chemotherapy remains controversial. In order to clarify the role of each therapeutic modality, we performed a systematic review of randomised trials on this field.

Methods: We assessed the selected studies for their quantitative therapeutic results. A qualitative overview was carried out using two scales: the Chalmers and the ELCWP (Lung Cancer 19:141;1998) scores. The ELCWP score includes 15 groups of items, 7 on internal validity and 8 on external validity (maximal theoretical score of 110 points).

Results: Ten studies were eligible for our analysis, including 1749 eligible patients. Five were significantly in favour of combined treatment. Overall median ELCWP and Chalmers scores were respectively 63.2% (range: 36% to 85%) and 49.2% (range: 29.3% to 71.6%). However, no statistically significant difference in methodology was found between negative ($p > 0.05$ on survival curves) and positive trials ($p \leq 0.05$ on survival curves) as well for the ELCWP or the Chalmers scores. No difference could be detected according to the number of eligible patients, the date of first registration or publication.

Conclusions: These methodological similarities allows to aggregate the results of the tested treatments.

1008 POSTER

Extensive clinical experience with Taxotere® (T) in 1st and 2nd line treatment at 100 mg/m² in locally advanced or metastatic NSCLC

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100 centers from Europe, Middle East, Asia and South America participated in NSCLC study with broad inclusion criteria (1st + 2nd line) to establish the toxicity and efficacy profile of docetaxel at 100 mg/m² in worldwide clinical practice. 754 patients (pts) have been treated, 585M/169F. 3023 cycles have been administered, median: 3 (1–12). Median age was 59 yrs (25–83), median WHO PS: 1 (0–3), Median number of organs involved: 2 (1–6). Adenocarcinoma: 313 pts, squamous cell: 235 pts, large cell: 35 pts, other: 171 pts.

Results: To date 536 patients are evaluable for reponse, the overall response rate in first line is 27.9% (95% CI [17.5–29.8]). Safety profile: neutropenia gr. 3/4: 55% of pts, non hematologic toxicities gr 3/4: infection 5%, diarrhea 4%, pulmonary 3%, skin 2%, stomatitis 2%, neurosensory 3%

Conclusion: The safety and efficacy reported in more limited studies is maintained in a broad population.

1009 POSTER

Bendamustin in untreated small cell lung cancer (SCLC): Efficacy and toxicity

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Purpose: High response rates can be induced in patients (pts) with SCLC by different cytostatic treatment regimens. Durable remissions, however, are rare, even after aggressive and toxic combinations. Therefore, at least equally effective but less toxic first line treatments are warranted.

Methods: Twenty-six pts with extensive disease (ED) SCLC and no prior treatment received Bendamustin 120 mg/m² as an one-hour infusion on two consecutive days. The treatment was repeated every three weeks. If a complete (CR) or partial (PR) remission was achieved, six treatment cycles were given. In case of "no change" (ND) therapy was terminated after 4 cycles. It was immediately stopped, if disease progression (PD) could be demonstrated at regular tumor evaluations prior to every new treatment cycle.

Results: So far, 22 pts are evaluable for response and toxicity. Two pts (9%) showed CR, 8 pts (36%) PR and 4 pts (19%) NC. Another 8 pts (36%) had PD. The median remission duration is 3+ months (range, 1+–5). The median survival time is not achieved. Side effects (preferably WHO grade 1 and seldom 2) restricted to myelosuppression and gastrointestinal toxicities.

Conclusion: Bendamustin is a very effective and well-tolerated agent in ED SCLC. Remission durations are comparable to more aggressive and toxic cytostatic combinations.

1010 POSTER

Unresectable non-small cell lung cancer (NSCLC) as a target for clinical trials of AG3340, a selective inhibitor of matrix metalloproteases (MMPs), in combination with standard chemotherapies

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While treatment of newly diagnosed, advanced stage NSCLC with combination chemotherapy commonly results in patient benefit, therapies that enhance outcome are needed. MMPs are a family of enzymes that degrade the matrix between cells. Several of these enzymes have been shown to facilitate tumor angiogenesis, invasion, and metastasis. AG3340 is a potent and selective inhibitor of MMPs designed using X-ray crystallography. AG3340 inhibits MMP-2, -9 and -14 with Ki values of 30–330 pM, but is less potent against the enzyme believed to be responsible for maintaining function in the joints (MMP-1, Ki 8300 pM). Preclinical experiments conducted in xenograft tumor models demonstrated antitumor effects of single agent AG3340 and enhanced efficacy of chemotherapy and radiation therapy when administered in combination with AG3340. The pharmacokinetics of AG3340 in volunteers and patients are similar and linear, the free fraction in plasma is high (31%), and the minimum effective concentration identified in preclinical models is easily exceeded with well-tolerated doses of AG3340 administered twice daily. Two randomized, double-blind, placebo-controlled Phase III studies in patients having newly diagnosed Stage IIIB/IV or recurrent NSCLC are underway in North America, Europe and Australia. AG3340 or placebo is administered beginning on Day 1 of the study in combination with standard doses and regimens of gemcitabine/cisplatin or paclitaxel/carboplatin. Because AG3340 might be expected to slow the rate of tumor growth beyond an arbitrary definition of progression, patients may continue treatment with study tablets (AG3340 or placebo) in combination with the investigator's choice of subsequent therapies, in hopes of providing additional survival benefit. As of March, 1999, 400 patients have been accrued at over 50 participating institutions. Therapies used subsequent to first-line therapy and in combination with study tablets have