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Letter to the Editor

Cisplatin and Cytarabine Combination Chemotherapy of Advanced Non-Small Cell Lung Cancer: A Pilot Study

G.P.M. TEN VELDE, L.H. GREVE and G.H. BLIJHAM*
*Department of Pulmonology and *Oncology, University Hospital Maastricht, The Netherlands*

CISPLATIN has been reported as being active in non-small cell lung cancer (NSCLC) [1] with response rates of 15–20%, whereas early clinical trials of cytarabine (Ara-C) failed to demonstrate any antineoplastic activity in this disease [2]. *In vitro*, cisplatin and Ara-C have demonstrated synergistic cytotoxicity against human colon carcinoma cells, even though these cells were intrinsically resistant to the latter drug [3]. Cisplatin probably acts by cross-linking DNA; only the *cis*-isomer is cytotoxic, which suggests that intrastrand cross-linking of DNA is the most important reaction biologically [4]. Ara-C, after being metabolized to its nucleotides, acts as an inhibitor of DNA polymerase, and is also incorporated into DNA leading to a defect in ligation of fragments of newly synthesized DNA [5]. Synergism between the 2 drugs may result from Ara-C enhancing cisplatin-induced cross-linking or inhibiting the repair of cisplatin-induced DNA damage. Studies using continuous low-dose administration of Ara-C in combination with cisplatin have been associated with substantial neutropenia exceeding simple additive drug effects [6]. Administration of higher doses of Ara-C showed increased DNA cross-linking without appreciable inhibition of DNA synthesis and myelopoiesis.

Since previous experience using cisplatin in combination with continuous administration of low-dose Ara-C in NSCLC had been negative [7], we performed a pilot study combining standard dose of cisplatin with a short-term infusion of an intermediate dose of Ara-C in 20 consecutive patients, median age 62 years (range 48–75), UICC stage III (3) and IV (17), ECOG performance status I (10) and II (10 patients). Fifteen patients had squamous cell carcinoma, 4 adenocarcinoma and 1 large cell carcinoma. Treatment was given at 21-day intervals, with a minimum of 2, and a maximum of 5, courses.

Treatment was as follows: after pre-hydration cisplatin 80 mg/m^2 was given during a 4-hr infusion, immediately followed by Ara-C 500 mg/m^2 during 30 min, followed by post-hydration. Pretreatment evaluation included: chest X-ray, scintigrams, echoscopy or computertomography (CT) of tumor lesions as indicated, complete blood counts and blood chemistry. Measurement of the indicator lesions for response evaluation was done before each course with chest X-ray or, in patients with lesions only measurable with CT, after the fifth course. Response to therapy was defined as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD) according to standard criteria.

The number of patients to be treated was determined to the Gehan 2 step procedure. The lowest limit of therapeutic activity considered to be of interest was a response rate of 30%. Initially 9 patients were treated; on the basis of 1 response in these patients 11 more patients were accrued to a total of 20 patients. With this method the therapeutic effectiveness can be estimated with a

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Address for reprints: G.P.M. ten Velde, University Hospital Masstricht, P.O. Box 1918, 6201 BX Maastricht, The Netherlands.

standard error of 10%.

Two CR's, 2 PR's, 9 SD and 7 PD were observed after 2–5 courses, resulting in an objective response rate of 20%. The 2 CR's, also documented by repeated bronchoscopy, had undergone pneumonectomy for squamous cell carcinoma 6 and 3 years earlier, and presented with metastatic endobronchial tumor in the other lung. The duration of response for CR was 48 and 69+ weeks and for PR 48 and 26+ weeks. Toxicity was moderate. Three patients refused further chemotherapy after 2 courses because of side-effects. Hematological toxicity was very modest with only two patients showing WBC nadirs between 2.000 and 3.000/mm^3. Renal toxicity forced chemotherapy to be stopped in 1 patient after 2 courses and to be reduced in another 1. Mild diarrhea occurred in 3, anorexia and malaise in 11 and weight loss of more than 10% in 4 patients. Median survival of all 20 patients was 26 weeks (range 5–70+).

In conclusion, this cisplatin–Ara-C combination yielded a response rate of 20% (standard error 10%); the two CR's are encouraging, although this combination is therefore probably not synergistic to a clinically relevant degree.

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