Intraarterial Chemotherapy with Polyoxyethylated Castor Oil Free Paclitaxel, Incorporated in Albumin Nanoparticles (ABI-007)

Phase I Study of Patients with Squamous Cell Carcinoma of the Head and Neck and Anal Canal: Preliminary Evidence of Clinical Activity

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BACKGROUND. This study was designed to determine the feasibility, maximum tolerated dose, and toxicities of intraarterial administration of paclitaxel-albumin nanoparticles in patients with advanced head and neck and recurrent anal canal squamous cell carcinoma. Antitumor activity also was assessed.

METHODS. Forty-three patients (31 with advanced head and neck and 12 with recurrent anal canal squamous cell carcinoma) were treated intraarterially with ABI-007 every 4 weeks for 3 cycles. In total, 120 treatment cycles were completed, 86 in patients with head and neck carcinoma (median, 3 cycles; range, 1–4) and 34 in patients with anal canal carcinoma (median, 3 cycles; range, 1–4). ABI-007 was compared preliminarily with Taxol® for in vitro cytostatic activity. Increasing dose levels from 120 to 300 mg/m^2 were studied in 18 patients. Pharmacokinetic profiles after intraarterial administration were obtained in a restricted number of patients.

RESULTS. The dose-limiting toxicity of ABI-007 was myelosuppression consisting of Grade 4 neutropenia in 3 patients. Nonhematologic toxicities included total alopecia (30 patients), gastrointestinal toxicity (3 patients, Grade 2), skin toxicity (5 patients, Grade 2), neurologic toxicity (4 patients, Grade 2) ocular toxicity (1 patient, Grade 2), flu-like syndrome (7 patients, Grade 2; 1 patient, Grade 3). In total, 120 transfemoral, percutaneous catheterization procedure–related complications occurred only during catheterization of the neck vessels in 3 patients (2 TIA, 1 hemiparesis) and resolved spontaneously.

CONCLUSIONS. Intraarterial administration of ABI-007 by percutaneous catheterization does not require premedication, is easy and reproducible, and has acceptable toxicity. The maximum tolerated dose in a single administration was 270 mg/m^2. Most dose levels showed considerable antitumor activity (42 assessable patients with 80.9% complete response and partial response). The recommended Phase II dose is 230 mg/m^2 every 3 weeks. ***Cancer* 2001;92:2592–602.**

KEYWORDS: taxanes, paclitaxel, intraarterial chemotherapy, squamous cell carcinoma.

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Paclitaxel was the first taxane to be introduced into clinical practice, but because of its poor solubility in water it must be formulated with polyoxyethylated castor oil and ethanol (Taxol®). Polyoxyethylated castor oil can cause allergic reactions; therefore, patients must receive premedication with dexamethazone, diphenhydramine, and cimetidine before paclitaxel administration. In addition, special precautions for the intravenous administration set are necessary, and it is advisable for infusion to be given over 3–24 hours.[1,2] Despite these measures, severe hypersensitivity reactions are reported in 1.5–3% of patients, and more modest reactions are observed in almost half of patients.[3] A recently published article highlights this problem and suggests changing patients with allergic reactions to another taxane, docetaxel.[4]

Intraarterial administration of taxanes has been considered only sporadically up to now.[5,6] The presence of alcohol in the commercial formulation and the problem of hypersensitivity reactions represent an obstacle to administration by this route, unless the drug is diluted considerably. A new polyoxyethylated castor oil free formulation of paclitaxel provided the opportunity to assess intraarterial chemotherapy with this cytostatic agent in squamous cell carcinomas of the head and neck and of the anal canal.

Few studies have been conducted to date on the activity of systemically administered taxanes in advanced head and neck carcinoma. In these studies, intravenous paclitaxel as a single agent has shown superior activity to that of the standard combined chemotherapy (cisplatin, 5-fluorouracil) in recurrences of these cancers, but the improvement was not very great. Overall, when more recent taxanes such as docetaxel are included, objective response rates (complete and partial clinical-radiologic) range from 30% to 42% in recurrences.[7–9]

Less than 30% of patients with locally advanced disease (American Joint Committee on Cancer [AJCC] TNM Stage III/IV) can be cured with surgery and/or radiotherapy. The chemotherapy regimen that achieves a complete clinical response of 30–50% and greater is the combination of cisplatin and fluorouracil given at initial presentation of the disease. Combination with radiotherapy improves the results but at the cost of greater toxicity.[10–12] Despite this result, neoadjuvant chemotherapy has not brought an improvement in survival, which depends more on locoregional recurrence than on distant metastases. A high T classification makes local recurrence more likely and is less amenable to clinical response and even less to complete pathologic response. Efforts to improve the results of neoadjuvant chemotherapy in advanced carcinoma of the oral cavity and hypopharynx are justified by the possibility of achieving definitive local treatment by surgery or radiotherapy while maintaining an acceptable quality of life, including organ preservation.

FIGURE 1. Electron microscope enlargement (original magnification ×34,000) of paclitaxel-albumin nanoparticles (ABI-007).

Cystostatic drugs have been given by intraarterial administration in the past, particularly since the introduction of cisplatin. The responses reported (clinical-radiologic, complete, and partial) range from 47% to 94% in patients with miscellaneous advanced disease at presentation or with recurrence. The rate of catheter-related complications was greater than 30%.[13–16]

The expansion of interventional neuroradiology techniques, which now have high reproducibility and an acceptable complication rate, has led to the availability of new materials for superselective catheterization, prompting renewed interest in intraarterial chemotherapy of the cervicofacial district.[17–19] However, in this reappraisal of intraarterial chemotherapy, the drugs used thus far have been the same as in the past, and in no case have taxanes been used.

ABI-007 is a new formulation of paclitaxel. Its novelty lies in the use of human albumin as a stabilizer in place of the usual excipients, polyoxyethylated castor oil and alcohol. The particles of the paclitaxel-human albumin complex have a dimension of 150–200 nm (Fig. 1), and the product takes the form of a colloid when suspended in saline solution. Animal studies have shown that the pharmacokinetic profile of ABI-007 differs from that of the commercial formulation (Taxol) in that it shows lower plasma levels and higher tissue levels with wider, more rapid distribution and slower metabolism. ABI-007 is 59-fold less toxic than Taxol and 29-fold less toxic than the excipients of Taxol.[20] Preliminary results of clinical intravenous and intraarterial use were presented recently.[21,22]

The decision to study intraarterial chemotherapy

with paclitaxel in albumin nanoparticles in patients with squamous cell carcinoma of the head and neck and of the anal canal was based on consideration of the mechanism of action of this drug and of the particular problems posed by these two carcinomas. The antitumor efficacy of paclitaxel is related to its ability to stabilize microtubules. Alterations of microtubule dynamics may be of relevance not only in the mitotic spindle, but also in cytoskeleton functions. Because cytoskeleton is involved in signaling pathways mediated by growth factor receptors, the pharmacologic effects of taxanes could be at least in part caused by their interference with signal transduction. Because squamous cell carcinomas of different tissue origin (lung, head/neck, cervix) are characterized by overexpression of epidermal growth factor (EGF) receptors, the efficacy of paclitaxel in the treatment of these tumor types could reflect an interference of this taxane in specific processes mediated by growth factor receptors. This hypothesis should be addressed by specific approaches of modulation of receptor function. A better documentation of this additional molecular effect could allow a more rational design of clinical studies with taxanes.[23]

Squamous cell carcinoma of the anal canal has a high curability rate at presentation when treated by a combination of chemotherapy, radiotherapy, and surgery, but no further systemic therapeutic regimen is available for effective management of recurrence.[24,25] The rationale of intraarterial administration is reinforced in this pathology by the critical nature of pelvic vascularization due to the previous treatments, which might make it difficult to achieve an effective local concentration of systemically administered cytostatic agents.

The principal goals of the current study were 1) to determine the feasibility of intraarterial administration of ABI-007, 2) to determine the maximum tolerated dose (MTD), 3) to determine the dose-limiting toxicity, 4) to establish the recommended dose for a Phase II study, and 5) to seek preliminary evidence of antitumor activity.

MATERIALS AND METHODS

Comparative In Vitro Cytotoxic Evaluation of ABI-007 and Taxol

A comparative study of the cytotoxic effects of Taxol and ABI-007 was performed in two human ovarian carcinoma cell lines, including a cell line sensitive to cisplatin (IGROV-1) and a subline selected for resistance to cisplatin (IGROV-1/Pt1), exhibiting a collateral sensitivity to taxane and in a squamous cell carcinoma of the cervix (A431) exhibiting overexpression of the EGF receptor. The cytotoxic activity

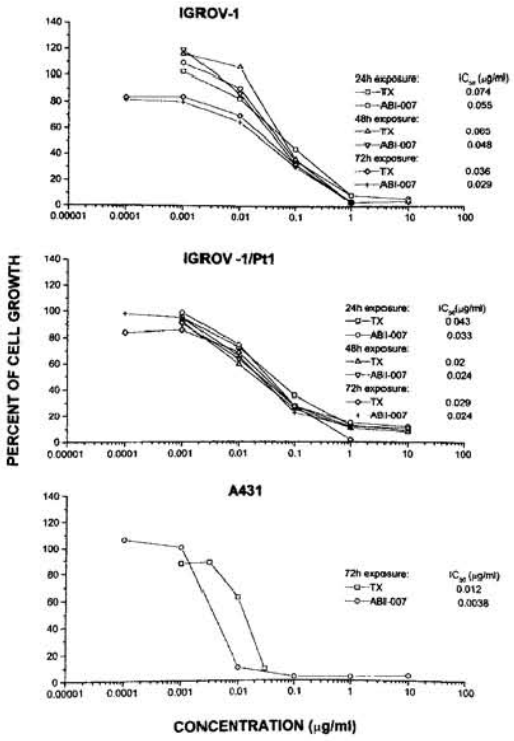

FIGURE 2. Comparison of cytotoxic activity of paclitaxel (TX) and ABI-007 in ovarian cell carcinoma IGROV-1, in a subline selected for resistance to cisplatin IGROV-1/Pt 1 and in cervical squamous cell carcinoma cells. Cells were exposed to the drug for 24, 48, or 72 hours as indicated. The antiproliferative effect was determined by the growth inhibition assay (cell counting 72 hours after the start of exposure). IC_{50} values refer to drug concentrations required for 50% inhibition of cell growth.

was evaluated using an antiproliferative assay (determination of the number of surviving cells 72 hours after drug exposure) and variable exposure times (24, 48, and 72 hours). The cell systems were chosen because the cytotoxic effect of paclitaxel was predictive of antitumor efficacy after in vivo treatment of tumor xenografts in athymic mice.

Because the drug formulation could interfere with cellular uptake of the drug, a comparative cellular pharmacology study was performed to examine the cytotoxic potential of the drug in various formulations using a panel of human tumor cell lines. The results are shown in Figure 2 as dose–response curves. It is evident that the cytotoxic activity of paclitaxel is retained completely in its formulation with albumin. Although the observed difference in cellular response should be regarded as marginal, an increased cytotoxicity of ABI-007 was consistently found in all experiments. A similar result was found in the A431cell line, which exhibited an increased sensitivity to taxanes.

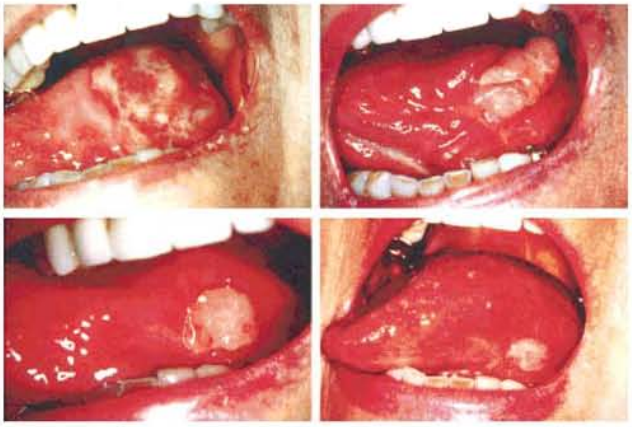

FIGURE 3. Carcinoma of left margin of tongue. At presentation (top left), after one cycle of ABI-007 into the lingual artery (top right), after two cycles (bottom left), after three cycles (bottom right). This patient received a fourth cycle of intraarterial chemotherapy, and no tumor was found at surgery. The patient also underwent total laterocervical lymph node resection with negative histology. The patient was disease free at last follow-up (10 months).

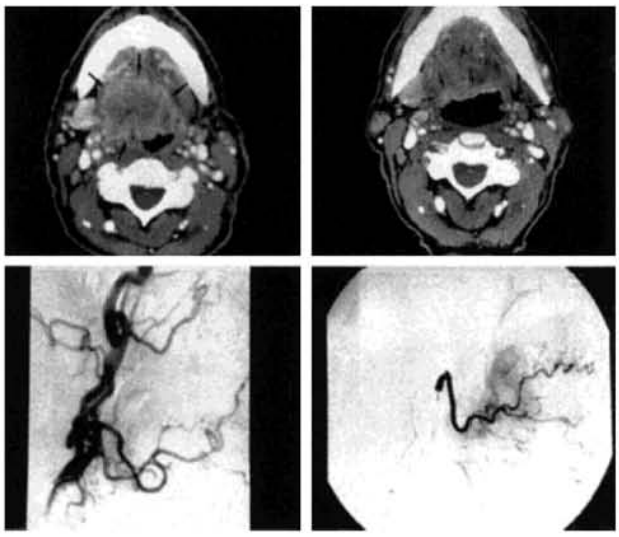

FIGURE 4. Carcinoma of the tongue. Computed tomography with contrast medium (top left); the arrows indicate the tumor margins. Result after three cycles of intraarterial chemotherapy (top right). Angiogram of right common carotid artery (bottom left). Catheterization and angiography of lingual artery (bottom right).

PATIENTS

Patient Selection

Patients considered eligible for this study were 1) those with histologic diagnosis of locally advanced squamous cell carcinoma of the head and neck with or without previous treatment; and 2) patients with recurrent squamous cell carcinoma of the anal canal. Inclusion criteria were age older than 18 years and younger than 75 years; Eastern Cooperative Oncology Group performance status of less than 2; previous chemotherapy, with exclusion of taxanes, completed at least 4 weeks before study enrollment; life expectancy longer than 3 months; and adequate bone marrow (platelet count $> 75{,}000 \times 10^9$ cells/L, absolute neutrophil count $> 1.5 \times 10^9$ cells/L), hepatic function (total bilirubin within normal limits, transaminases < 2 times normal), and renal function (creatinine < 1.5 times the upper limit of normal). Patients with formal contraindications or in whom transfemoral catheterization/angiography was not possible and those with severe cardiopathy were excluded.

Before enrollment in the trial, patients were required to sign the informed consent document to be enrolled in the trial, which was approved by the Ethical and Scientific Committee of the institution.

Dosage and Administration of ABI-007

ABI-007 was supplied by American BioScience, Inc. (Los Angeles, CA) in vials containing a lyophil equal to 30 mg of paclitaxel/albumin. The solution obtained by diluting each vial with 10 mL of 0.9% sodium chloride solution was administered over 30 minutes by selective percutaneous catheterization of the neck vessels in patients with head and neck carcinoma, with access from the femoral artery under local anesthesia, without premedication. A guiding catheter (Envoy H1 5F; Cordis/Johnson & Johnson, Miami, FL) first was positioned in the common carotid artery for digital angiography. Bilateral catheterization was performed for tumors that exceeded the median line. Intraarterial chemotherapy was performed by selectively or superselectively catheterizing the external carotid artery or its branches with coaxial microcatheters in a guiding catheter (Transit Infusion Catheter; Cordis/Johnson & Johnson).

In patients with recurrence of anal canal carcinoma, unilateral or bilateral transfemoral percutaneous catheterization of the internal iliac arteries was performed (Tempo 4 C3, 4F; Cordis/Johnson & Johnson) after pelvic aortography, with placement of a coaxial microcatheter (Rapid Transit; Cordis/Johnson & Johnson) distal to the gluteal artery. To prevent clotting within the catheter, we used a continuous washing set of our own design produced by SIDAM (Mirandola, Italy). Three treatment cycles were planned for both groups of patients, with a 4-week interval between cycles (in 2 patients 4 cycles were performed). The hospital stay was 3 days for each cycle.

The MTD was defined in this study as the dose level below that inducing dose-limiting toxicity in greater than a third of cycles at the same dose level (at least three cycles of a group of six).

The dose increase scheme was empiric and arbitrarily designed by us.

The starting dose of 120 mg/m^2 was increased by 30 mg/m^2 at each subsequent level. Each level consisted of a group of six cycles. In the first 4 cycles, Grade 4 hematologic toxicity occurred in 3 cases in the group receiving 300 mg/m^2. The MTD therefore was defined as 270 mg/m^2. The total number of cycles "necessary" to define the dose-limiting toxicity and the MTD was 40 (29 cycles for 12 patients with head and neck carcinoma and 11 cycles for 6 patients with carcinoma of the anal canal).

Of the 18 patients participating in dose escalation (5 of whom completed treatment after determination of the MTD, receiving 250 mg/m^2 for the remaining cycles), 1) 8 patients received 3 cycles; 2) 6 patients received 2 cycles (1 discontinued treatment because of progression, 1 withdrew despite evidence of complete clinical response, and 4 received the third cycle at the dose 250 mg/m^2), 3) 4 patients received only 1 cycle (1 completed the treatment at 250 mg/m^2, 2 discontinued it because of progression, 1 patient died after rupture of esophageal varices complicating concomitant cirrhosis).

To better define the importance of the intraarterial chemotherapy procedure and make a preliminary evaluation of the tolerability of the ABI-007 dose to be recommended for Phase II study, we enrolled an additional 19 patients with head and neck carcinoma and 6 with recurrence of anal canal carcinoma. Treatment with 250 mg/m^2 every 4 weeks for 3 cycles was planned for this additional group.

Dose-Limiting Toxicities

All toxicities were graded according to World Health Organization (WHO) toxicity criteria. The MTD, as already stated, was defined as the dose level below that which induced a limiting toxicity in at least three of six cycles. Grade 4 neutropenia lasting 5 days or longer, Grade 4 thrombocytopenia or anemia of any duration, and Grade 3 or 4 nonhematologic toxicities were considered as dose-limiting.

Pretreatment and Follow-Up Studies

Complete clinical history, physical examination, hematologic examination, serum electrolytes, and chemistries were performed at the time of enrollment and before each cycle. Complete blood cell counts were taken weekly while patients were on study. Radiologic studies (computed tomographic scans or magnetic resonance imaging) were performed at baseline and before each treatment cycle to assess tumor response, which was graded according to WHO criteria.

Pharmacokinetic Analyses

To study the pharmacokinetics of ABI-007, extensive blood samples were drawn in 11 patients, from the superior vena cava (5 patients with head and neck carcinoma), from the inferior vena cava (6 patients with anal canal carcinoma), and from peripheral veins (11 patients) at multiple times during each infusion (at 0, 5, 15, and 30 minutes) and up to 18 hours (at 35, 45, 60, 90, 150, 270, 510, 750, and 1080 minutes).

Whole blood paclitaxel concentrations were determined by high-performance liquid chromatography after solid phase extraction, as described by Willey et al.[26] with some modifications. Standard curves were obtained using paclitaxel C (Indena, Milan, Italy) as internal standard. The drug quantitation limit was 0.06 μmol/L and the linearity up to 30 μmol/L with a precision range between 8.1% and 18% and an accuracy that exceeded 85%. The recovery of paclitaxel was 95%. The same method was used to check the paclitaxel contents in administered ABI-007 solutions.

Pharmacokinetic modeling and parameters were performed using the nonlinear regression program Kinetica 2000 version 3.0 (Innaphase Co., Philadelphia, PA). The concentration versus time curves were fitted using a three-compartment open pharmacokinetic model.

The data were compared with pharmacokinetic profiles with intravenous infusion of ABI-007 (Ibrahim NK, Ellehorst JA, Theriault RL, et al. Phase I and pharmacokinetic study of ABI-007, a cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel, unpublished).

RESULTS

Thirty-one patients with head and neck carcinoma received a total of 86 cycles (median, 3). Twelve patients with recurrent anal canal carcinoma received 34 cycles (median, 3).

Patient characteristics are summarized in Table 1.

Toxicity

Tables 2 and 3 summarize the hematologic and nonhematologic toxicities of all grades observed in 12 patients with squamous cell carcinoma of the head and neck and in 6 patients with squamous cell carcinoma of the anal canal who participated in dose escalation to define the MTD of intraarterial chemotherapy with ABI-007.

Neutropenia was the main dose-limiting toxicity for intraarterial administration of paclitaxel. Of the three episodes recorded, two were short-lasting and did not require hospitalization. These episodes occurred in two patients with recurrent anal canal car-

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