Phase II trial of 13-cis-retinoic acid plus interferon-α in recurrent head and neck cancer

Narin Voravud¹, Scott M. Lippman¹, Randal S. Weber², Gladys I. Rodriguez³, Douglas Yee³, Isaiah W. Dimery¹, Charles L. Earley¹, Daniel D. Von Hoff³ and Waun Ki Hong¹

From the Departments of ¹Thoracic/Head and Neck Medical Oncology and ²Head and Neck Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, Texas; and the ³Department of Medical Oncology, The University of Texas Health Science Center, San Antonio, Texas, USA

Key words: interferon-α, retinoic acid, head and neck neoplasms

Abstract

13-cis-retinoic acid (isotretinoin) and interferon-α have limited activity as single agents in advanced cancer. Preclinical data indicate that these agents have different mechanisms of action and, in combination have greater activity (that is, the ability to modulate growth and differentiation) in a number of malignant cell types than either agent alone. In clinical trials, the new biological regimen of 13-cis-retinoic acid and interferon-α was shown to have major activity in advanced squamous cell carcinoma of the skin and cervix. We conducted a phase II trial of this regimen in recurrent squamous cell carcinoma of the head and neck. Of the 21 evaluable patients, none had a complete response, and only one had a partial response (5%). Two patients had minor responses, four had stable disease, and 14 experienced disease progression. Five patients developed grade 3 toxic effects, including skin toxicity, fatigue, headache, and anorexia/weight loss. The median survival duration was 25.5 weeks (range, 4–95). The combination of 13-cis-retinoic acid and interferon-α at this dose and schedule is ineffective for the treatment of recurrent squamous cell carcinoma of the head and neck.

Introduction

Squamous cell carcinoma (SSC) of the head and neck will account for an estimated 13,000 U.S. deaths in 1992 [1]. Systemic chemotherapy regimens now in use have not significantly prolonged the survival of patients with advanced local, regional, or metastatic head and neck cancer [2]; the median survival of patients with recurrent disease remains 4 to 6 months. The inability of current regimens to prolong survival indicates the urgent need for new drugs and drug combinations for this disease.

Single-agent 13-cis-retinoic acid (13cRA) or interferon-α has limited activity in advanced solid tumors, including head and neck SCC [3–8]. However, 13cRA has a significant chemopreventive effect in head and neck carcinogenesis [9,10]. In preclinical studies, the activity of the two agents was enhanced when they were combined [11–13] and their mechanisms of action and in vitro interaction were shown to be different [3,5,13–15]. Clinical use of this combination is further supported by the fact that the toxic effects of these two agents are nonoverlapping and reversible [3,5,14]. The chief side effect of 13cRA is mucocutaneous dryness, whereas interferon-α causes a flu-like syndrome and fatigue.

These findings provided the rationale for a phase II trial of 13cRA and interferon-α in 28 patients with advanced SCC of the skin. The overall response rate was an encouraging 68% [16]. These
positive data were the basis of a series of phase II trials of this new regimen in other advanced SCC, including those of the cervix, head and neck, and lung. The phase II trial in locally advanced cervical cancer has been completed with a striking 50% complete-plus-partial response rate overall and a response rate of over 50% in bulky tumors in which at least one lesion dimension is greater than 10 cm [17].

Based on these promising preclinical and clinical data, we designed a phase II study to determine the activity and toxicity of this new biologic regimen in recurrent SCC of the head and neck.

Methods

Patients with histologically or cytologically proven recurrent or metastatic SCC of the head and neck, who were at least 18 years of age and had a Zubrod performance status ≤2, life expectancy >8 weeks, WBC count >3,000/mm³, absolute granulocyte count >1,500/mm³, platelet count >100,000/mm³, bilirubin <1.5 mg%, serum creatinine <2.0 mg%, and bidimensionally measurable lesions were eligible for the study. This phase II trial was conducted in two institutions, and signed informed consent was obtained from all patients prior to enrollment according to the guidelines of each institution.

Before treatment, all patients underwent standard clinical evaluations, which included history and physical examination, complete blood count, urinalysis, SMA-12, electrolytes, lipid profile, chest x-ray, and computed tomography scan or magnetic resonance imaging as indicated to evaluate disease extent. Toxic effects, tumor measurements, and response were recorded every 4 weeks.

Hoffmann-La Roche, Inc., provided this study with the synthetic retinoid 13cRA (Accutane) and recombinant human interferon-α-2a (Roferon-A). Patients received 13cRA orally at 1 mg/kg per day and interferon-α 2a subcutaneously at 3 × 10⁶ units/m² per day. Treatment was administered on an outpatient basis.

Standard response criteria were used. Complete response was defined as the disappearance of all evidence of tumor. Partial response was defined as a decrease of 50% or more in tumor size (the sum of the products of the bidimensional measurements of all lesions). Progressive disease was defined as an increase of 25% or more in tumor size or the appearance of new lesions. Treatment toxicity was judged according to The University of Texas M.D. Anderson Cancer Center criteria, which incorporate the National Cancer Institute Common Toxicity Criteria [18].

Results

Patient characteristics

Twenty-eight patients were entered into the study. The median age was 59.5 years (range, 28–70) and 20 (71%) were male. Two patients were ineligible because of incorrect diagnosis (primary skin cancer). Ten patients received fewer than four weeks of therapy – 5 for progressive disease (evalu-