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Phase II trial of oral β-all trans-retinoic acid in hepatocellular carcinoma (SWOG 9157)

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Summary

Twenty-nine chemotherapy-naive patients with primary hepatocellular carcinoma were treated with oral β-all trans-retinoic acid (retinoic acid, TRA 50 mg/m² tid) on a 3-week on/one week off schedule until progression or grade 3 or 4 toxicity. Eligibility requirements allowed abnormal liver function tests as long as the creatinine and bilirubin levels were normal. No responses were seen and the median survival was four months. Grade 3 side effects occurred in 11 patients and grade 4 in four and included a wide range of toxicities. The results indicate that oral TRA is ineffective against primary hepatocellular carcinoma and suggest that dose-modification of this retinoid may be required in patients with significant malignant hepatic involvement.

Introduction

Vitamin A and its natural and synthetic derivatives (retinoids) affect the growth and differentiation of normal and neoplastic cells. Retinoids prevent the development of second malignancies in patients with treated aerodigestive cancer and suppress cervical intraepithelial neoplasia and oral leukoplakia as well as other precancerous conditions [1]. TRA also produces profound effects on the differentiation and maturation of acute promyelocytic leukemia cells in the clinical setting, a response that is mediated by its interaction with the α-retinoic acid receptor (RAR) encoded on chromosome 17 and production of a fusion protein [2]. Garcia et al. have reported that in at least one hepatocarcinoma cell line HBV integration can result in RAR-β gene measurement with the resultant production of an oncogenic chimeric protein [3]. This retinoid receptor is encoded by a gene located on the p24 band of chromosome 3, an area that may be abnormal in hepatocellular carcinoma [4]. Several studies have also shown that retinoids slow the growth of hepatocellular carcinoma in culture and modulate expression of α-feto-protein [5,6]. We therefore hypothesized that the RAR-β/chromosome 3 relationship in hepatocellular carcinoma might be analogous to the RAR-α/chromosome 17 relationship and that the favorable effect of TRA on promyelocytic leukemia cells might occur on hepatocellular carcinoma cells as well. Therefore, a phase II trial of TRA was conducted in chemotherapy-naive patients with primary hepatocellular carcinoma. Eligibility criteria included: histologically proven diagnosis of hepatocellular carcinoma, presence of unresectable bidimensionally measurable disease, performance status 0-1 by SWOG criteria, no prior chemotherapy, no concurrent other therapy, and no prior malignancy. Twelve of the patients had metastatic disease in at least one site. Patients also had a pretreatment granulocyte count ≥1500/μl, platelet count ≥100,000/μl, and levels of serum creatinine and bilirubin ≤ institutional limits of normal. The level of other liver
function tests was not considered in the eligibility requirements. Written informed consent (approved by the IRBs of the involved institutions) was obtained before starting treatment. TRA was initially supplied by the National Cancer Institute and subsequently by commercial vendor (Vesanoid, Hoffman La Roche) when the oral formulation became available on the market during the course of the trial. Therapy consisted of oral retinoic acid 50 mg/m² tid for 21 days followed by a 7-day holiday. Dosage reductions for toxicity were based on SWOG criteria. Treatment was continued until progression or the appearance of grade 3 or 4 toxicity. Response to treatment was assessed after every two cycles. Patients with no evidence of disease were considered complete responders. Patients with disease that had decreased by at least 50% of the bidimensional product of the tumor mass were considered partial responders. Two assessments showing response in at least 4-week intervals were required to confirm a patient’s response. Patients with no evidence of progression but with less than a partial response were considered to have stable disease. Patients who at any time showed evidence of a new local tumor or distant metastases were considered to have progressive disease.

Survival was measured from the date of registration to the date of death or date of most recent contact. Survival curves were calculated using the Kaplan-Meier method.

Results

Twenty-nine eligible patients were accrued by 27 institutions. All patients had advanced unresectable or metastatic hepatocellular carcinoma. Hepatitis B antigen was positive in only 6 patients. The median duration of treatment for the 29 eligible patients was 36 days (range 5–202 days). Response assessment was not determinable in 11; 8 patients were discontinued due to toxicities before adequate response assessment; 2 patients refused further treatment before adequate response assessment; and 1 patient was removed from treatment before adequate response assessment due to worsening Alzheimer’s disease.

Toxicity was considerable with eleven grade 3 and four grade 4 toxicities (detailed in Table 1). Of 9 patients discontinuing treatment due to toxicity, the toxicities included some combination of headaches, fatigue, nausea and vomiting (7 patients), grade 4 mucositis (1 patient), and grade 3 neurotoxicity (1 patient, specified as “personality change”). In the 18 patients in whom response was assessable, there were no complete or partial responses and in 14 patients rapidly progressive disease was evident. One patient died early and three appeared to have stable disease after 2 months. One patient expired after 4 weeks on protocol due to pulmonary failure, which was unrelated to treatment. Median overall survival of all eligible patients was 4 months.

Discussion

Oral retinoic acid produced no objective responses in patients with advanced or metastatic primary hepatocellular carcinoma. This result indicates that TRA is unlikely to interact with RAR-β in hepatocellular carcinoma in a manner analogous to its interaction with RAR-α in acute promyelocytic leukemia cells. There was the general clinical impression that these patients progressed rapidly, raising the possibility that the TRA was having a promotional or progressive effect on the disease. However, the overall survival of 4 months is not different than that of other patients with hepatocellular carcinoma in SWOG phase II trials in which the overall survival was 4 months in one trial and 7 months in another [7, 8]. On the other hand, another retinoid, the acyclic derivative polypropenoic acid, has been shown to prevent the development of secondary primaries in patients with hepatocellular carcinoma resected for cure [9]. It is
difficult to compare the results of that trial with the current observations as the stages of disease and background etiologic factors (e.g., geographic location of patients, predominance of Asian vs. Caucasian ethnicity, high level of HBV antigen positivity) were different. Additionally, the mechanisms of actions of the two retinoids appear decidedly different, with the action of retinoic acid mediated via nuclear receptors [1,2] while polyprenoic acid probably produces its major effects via an apoptosis-mediated pathway [10].

Toxicity of the retinoic acid was also considerable. The reason for the extent and degree of side effects may have been a straightforward reflection of the extensive liver involvement. Even though the bilirubin was normal at the start of study, other liver function studies were abnormal. Considerable caution will need to be exercised in the use of these compounds in future trials in patients with hepatocellular carcinoma or with other tumors involving the liver.

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