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CLINICAL INVESTIGATION **Gastrointestinal Cancer**

PHASE II STUDY OF CONCOMITANT THALIDOMIDE DURING RADIOTHERAPY FOR HEPATOCELLULAR CARCINOMA

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Purpose: Thalidomide has been demonstrated to possess antitumor activity in patients with advanced hepatocellular carcinoma (HCC). The objective of the present study was to determine whether the combined treatment of thalidomide with radiotherapy (RT) is associated with acceptable toxicity and an improved clinical outcome in HCC patients.

Methods and Materials: A total of 24 patients were enrolled to receive RT combined with thalidomide. A total dose of 50 Gy was delivered in 2-Gy fractions within 5 weeks. Thalidomide was administered 100 mg twice daily starting 3 days before RT until the development of unacceptable toxicity or disease progression. Blood samples were collected before, during, and after treatment to measure the levels of angiogenic factors and cytokines. The results of patients receiving the combined therapy were compared with those from 18 HCC patients receiving RT only.

Results: No significant difference in the clinical parameters was noted between the two groups, except for the baseline interleukin-6 level, which was greater in the concomitant group ($p = .05$). The most common toxicities related to thalidomide use were skin rash (54.2%), somnolence (37.5%), and constipation (33.3%). No significant differences were seen in the response rate (55.6% vs. 58.3%, $p = .48$), median progression-free survival (182 ± 48.9 vs. 148 ± 6.2 days, $p = .15$), or median overall survival (258 ± 45.6 vs. 241 ± 38.6, $p = .16$) between those who received concomitant therapy and those who received RT alone. Thalidomide suppressed the serum basic fibroblast growth factor level significantly during RT ($p = .03$) and, to a lesser extent, the interleukin-6 and tumor necrosis factor-α levels. After adjusting for other potential prognostic factors in the multivariate analysis, only the baseline interleukin-6 level and stem cell-derived factor-1 during RT independently predicted the progression-free survival. A decreased serum stem cell-derived factor-1 level 1 month after RT completion was a significant predictor of the overall survival of HCC patients receiving RT.

Conclusions: Despite the acceptable toxicity, thalidomide provided no additional benefit for HCC patients undergoing RT. © **2012 Elsevier Inc.**

Hepatocellular carcinoma, Radiotherapy, Thalidomide, Angiogenic factors, Inflammatory cytokines.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, especially in Asian countries (1). Surgical resection has been considered the treatment of choice for long-term disease control. However, <20% of the patients will be surgical candidates at diagnosis (2). Nonsurgical treatments, such as transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection therapy, have achieved very limited success for unresectable HCC (3), and repeated treatments have often been necessary (4). HCC is characterized by an inherent resistance to all available chemotherapeutic agents; therefore, a search for more effective treatment modalities is mandatory.

External beam radiotherapy (RT) has historically played a minor role in the primary treatment of HCC (5). Although evidence has shown a tumor response to RT and despite the establishment of a radiation dose–response relationship (6), the limited radiation tolerance of the adjacent normal liver has prohibited the wider use of RT for HCC. Recent

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technological and conceptual developments in RT have provided the potential to improve RT by conforming the delivered radiation dose distribution tightly to the tumor or target volume outline and sparing the normal liver tissue. Combining improvements in tumor targeting with normal tissue sparing, RT dose delivery has the potential to provide a clinically effective and safe therapy for liver tumors such as HCC.

In general, the radiographic response rates of HCC to modern partial liver external beam RT have been approximately 50–70% (7, 8). The potential need for greater radiation doses to treat HCC has been documented by a small autopsy series (7 patients) that reported that HCC treated with doses of 50–70 Gy showed evidence of tumor regression, but not tumor eradication (9). Furthermore, several clinical studies have shown that a significant proportion of HCC patients undergoing RT subsequently developed intrahepatic and extrahepatic metastasis (10, 11).

Hepatocellular carcinoma is a hypervascular tumor. Angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and matrix metalloproteinases, are overexpressed in HCC tumor cells and the surrounding stroma cells. Elevated serum levels of angiogenic factors have also been found in patients with liver cirrhosis or HCC (12, 13). It appears that these conditions facilitate tumor proliferation and invasion of HCC (11, 14). Antiangiogenesis therapy is thus a reasonable choice for controlling this cancer.

Thalidomide has been intensively investigated as an antiangiogenesis agent. Using a corneal micropocket assay, D'Amato *et al.* (15) and Kenyon *et al.* (16) demonstrated that the angiogenesis induced by VEGF and bFGF can be inhibited by thalidomide. The effectiveness of thalidomide for treating neoplastic disorders has been confirmed in patients with refractory multiple myeloma (17) and in patients with human immunodeficiency virus-associated Kaposi's sarcoma (18). Hsu *et al.* (19) showed that thalidomide administered at low doses (200–300 mg/d) induced an objective tumor response in a few patients with advanced HCC.

A large body of experimental data has indicated that inhibitors of proangiogenic factors and antiangiogenic factors can all reduce the formation of new blood vessels (20), resulting in slower tumor growth or, even, tumor regression. However, in most cases, no permanent tumor control has been achieved. Therefore, the combination of antiangiogenic strategies with cytotoxic agents, such as ionizing radiation, represents a promising approach to increase the cure rates of solid tumors (21, 22). Preclinical studies have revealed a cooperative effect of thalidomide and RT in colon cancer and glioma models (23, 24). However clinical trials combining thalidomide with RT for brain metastasis or glioblastoma multiforme did not reveal additional benefit from thalidomide use (25, 26).

To assess the efficacy and tolerability of concomitant thalidomide with RT and to identify its mechanisms of action and potential biomarkers, we conducted a multidisciplinary study of thalidomide with RT for patients with advanced HCC. We assessed the candidate biomarkers' correlation with clinical efficacy by evaluating the association between the clinical outcomes and circulating biomarker levels involved in the angiogenic and inflammatory pathways (at baseline, after 2 weeks of RT, and at 1 month after RT completion). The clinical and cytokine analyses of the HCC patients receiving concomitant thalidomide and RT were also compared with those of the patients receiving RT alone.

METHODS AND MATERIALS

Patient eligibility

The patients (cases) for the present analysis were from a Phase II study of concomitant thalidomide with RT for advanced HCC that was started in March 2005. The controls were HCC patients who had undergone RT alone during the same period. Between March 2005 and February 2009, 88 patients had undergone local RT to HCC at our institute. Of these 88 patients, 46, noted to have a liver tumor size greater than one-half of the whole liver, were excluded from the study and underwent RT at a lower dose. Of the remaining 42 patients, 24 were enrolled to receive concomitant thalidomide and RT. Of the remaining 18 patients, 6 had refused concomitant thalidomide. The other 12 patients did not receive thalidomide because of failure from previous thalidomide in 5, unacceptable liver function in 4, and peripheral neuropathy or cardiovascular disease in 3. The diagnosis of HCC was determined by the histologic examination findings. For those who did not have a histologic diagnosis, enrollment was considered according to the presence of all the following criteria: chronic viral hepatitis infection and liver cirrhosis, hepatic tumor with imaging (ultrasonography, computed tomography [CT]) characteristics compatible with a diagnosis of HCC and without evidence of a gastrointestinal or other primary tumor, and a persistent elevation of the serum α-fetoprotein (AFP) level to $\geq$400 ng/mL (27, 28). To be eligible for the present study, the patients were required to have disease that was bidimensionally assessable using CT scans and that was not suitable for, or had experienced failure from, curative surgery or local treatment, such as TACE or percutaneous ethanol injection therapy. The judgment of TACE failure was determined by incomplete tumor filling of a lipiodol-adriamycin mixture or an increase in the size of soft-tissue density over the TACE lesion on the CT scan. The patients were required to have acceptable hepatic and renal function (bilirubin level $\leq$4.0 mg/dL, alanine transaminase $\leq$150 U/L, platelets $\geq 50 \times 10^9$/L, Child-Pugh's score $\leq$7, creatinine level $\leq$2.0 mg/dL). Disease staging was performed according to the TNM Classification System of the American Joint Committee on Cancer (29). The patients' liver function reserves were categorized according to the Child classification system (30).

Radiotherapy was begun $\geq$4 weeks after any previous therapy. The patients had a Karnofsky performance status of $\geq$60 and an estimated survival time of >8 weeks. No patient was pregnant or nursing, and all patients were willing to practice birth control during and for 2 months after treatment with thalidomide.

Study design

The CT scans for RT planning were done with the patients placed in the supine position with both arms raised above the head. The three-dimensional CT-based planning system was used to decrease the irradiation to the bowel, spare the normal liver and kidneys, and cover the tumor target adequately with 1.5–3-cm margins. If the nonirradiated liver volume was more than one-half of the whole