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ORIGINAL ARTICLE

Irofulven as first line therapy in recurrent or metastatic gastric cancer: a phase II multicenter study by the Cancer Therapeutics Research Group (CTRG)

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Abstract
Background The purpose of this study was to evaluate the tolerability and efficacy of irofulven, a DNA interacting acylfulvene analog, as first line therapy for patients with recurrent or metastatic gastric cancer.
Patients and methods Twenty-three patients with recurrent or metastatic gastric cancer received irofulven at a dose of 0.45 mg/kg administered intravenously over 30-min infusion (up to a maximum of 50 mg), on days 1 and 8, every 3 weeks.
Results The median number of cycles delivered per patient was 2 (range 1–6). Two patients (9%) had ≥ 1-week delay in administration of subsequent cycle of chemotherapy. For the day 8 chemotherapy, dose reductions were required in seven patients (30%); dose omitting occurred in five patients (22%). Grade 3/4 anemia and neutropenia occurred in 22 and 17% of patients, respectively. There was no grade 4 thrombocytopenia and no neutropenic fever was observed. Of the 20 evaluable patients, there were no responses observed, 3 patients had stable disease after 2 cycles of treatment which was not confirmed by a further assessment. Median overall survival was 6.05 months (95% CI 4.55–9.39).
Conclusions Irofulven was tolerated at the dose of 0.45 mg/kg on days 1 and 8, every 3 weeks but showed no evidence of antitumor activity in patients with advanced gastric cancer.

Keywords Irofulven · Stomach cancer · First line chemotherapy

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Introduction

Although there has been a decline in incidence in the Western world, gastric cancer remains one of the most common malignancies and the disease remains a major health problem world-wide [1]. In Asian region such as Hong Kong, gastric cancer represents the fourth major cause of cancer death [2]. Cytotoxic chemotherapy has been widely used in patients with

advanced or metastatic gastric cancer and has been demonstrated to be superior to best supportive care alone in terms of improvement in overall survival and quality of life in randomized trials [3, 4]. Although several cisplatin and fluorouracil-based combination regimens have been tested in phase II settings [5–10], the reported high objective response rates have not been confirmed by randomized trials [11–12]. Moreover, the therapeutic impact of these results on survival has been modest [11–12].

Irofulven (6-hydroxymethylacylfulvene; NSC683863, MGI 114), a DNA interacting acylfulvene analog, is a semi-synthetic derivative of the natural product illudin sesquiterpenoid, and is a novel cytotoxic agent related to mushroom-derived illudin toxins [13]. It rapidly enters cells and inhibits DNA synthesis, producing DNA lesions such as strand breaks that are difficult to repair. It also binds to other intracellular molecules. Radiolabeled irofulven localizes primarily in the nuclear compartment followed by the cytosolic and membranous compartments [14]. Intracellularly, more than 60% of the drug is bound to protein with the remainder bound to nucleic acids. Irofulven was active in vitro against numerous cell lines known to be resistant to alkylating agents, cisplatin, doxorubicin, topoisomerase inhibitors, and taxanes [15, 16].

The antitumor efficacy of irofulven has been demonstrated in vitro with potent growth inhibition against a variety of human and murine tumor cell lines and surgically derived human primary tumors. The agent has shown substantial in vivo antitumor activity against human gastric tumor xenografts, with complete tumor regression observed in some. The efficacy of irofulven has been compared with that of the other reference antitumor drugs, and overall, its efficacy was reported to be higher than or almost equivalent to that of other conventional antitumor drugs in gastric cancers [17].

Based on these findings, we designed a phase II study to evaluate the efficacy and toxicity of irofulven in patients with recurrent or metastatic gastric cancer.

Patients and methods

Eligibility

Eligibility criteria included: histologically or cytologically confirmed recurrent or metastatic gastric adenocarcinoma; adenocarcinoma of the gastroesophageal junction was considered eligible if the majority of the tumor bulk is below the junction; age over 18 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm with conventional techniques or as > 10 mm with spiral computed tomography (CT) scan; no prior chemotherapy for recurrent or metastatic disease (adjuvant or neoadjuvant chemotherapy was allowed provided that relapse occurred > 6 months from the treatment); life expectancy of greater than 3 months; absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, total bilirubin $\leq 1.5 \times$ institutional upperlimit of normal (UNL), aspartate/alanine transaminase $\leq 2.5 \times$ institutional UNL for patients without liver metastasis or $\leq 5 \times$ institutional UNL for patients with liver metastasis, alkaline phosphatase $\leq 5 \times$ institutional UNL, creatinine $\leq 1.5 \times$ institutional UNL; no previous or current malignancies at other sites for the previous 5 years from registration of this study, with the exception of adequately treated in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin; ability to understand and the willingness to sign a written informed consent document.

Patients were excluded if they had radiotherapy within 4 weeks prior to entering the study; known brain metastases; history of allergic reactions attributed to compounds of similar chemical or biologic composition to irofulven; uncontrolled intercurrent illness; on-going pregnancy or breastfeeding.

The institutional ethics committees of each participating center approved the study. The drug was supplied by the National Cancer Institute, Division of Cancer Treatment and Diagnosis (Bethesda, MD, USA).

Pre-treatment evaluation

Within 7 days of entry into the study, all patients underwent a complete medical history and physical examination, including a full neurological evaluation, assessment of ECOG PS, a complete blood count and blood chemistry profile. Within 28 days before the initiation of therapy, an electrocardiogram and a CT scan of the chest and upper abdomen or other disease sites were performed.

Treatment plan

Treatment was administered on an outpatient basis. Irofulven 0.45 mg/kg (up to a maximum of 50 mg) in 100 ml 5% dextrose USP, given as a 30-min infusion via central venous access device or peripherally inserted central catheter, on days 1 and 8, every 3 weeks. All patients received standard anti-emetic regimen consisted of intravenous dexamethasone and a

5-HT_3 antagonist. A complete blood count was performed weekly during treatment. Before each subsequent cycle, patients had a clinical history and physical examination, toxicity assessment, complete blood count and biochemical profile assessment.

Treatment was delayed if, on the scheduled day of drug administration, the ANC was $< 1.5 \times 10^9$/l or platelet count was $< 100 \times 10^9$/ml, and was resumed when these minimal levels were reached. Treatment was also delayed for grade 2 or 3 mucositis, dysphagia, and/or diarrhea, and was resumed when these toxicities abated. The planned dose of irofulven on day 1 of the subsequent cycle was reduced by 20% if any of the following events occurred at any time during the preceding cycle: platelets $< 25 \times 10^9$/l or $< 50 \times 10^9$/l associated with bleeding, ANC $< 0.5 \times 10^9$/l for 7 or more days, or $< 1.0 \times 10^9$/l associated with fever of > 38.5°C or infection; any non-hematologic toxicity of National Cancer Institute Common Toxicity Criteria (version 2) grade 3 or 4 with the exception of nausea, vomiting, and alopecia. The day 8 dose of irofulven was reduced by 25% if ANC was $1.0–1.49 \times 10^9$/l or if platelet was $50–99 \times 10^9$/l; the day 8 dose would be omitted if ANC $< 1.0 \times 10^9$/l; platelets $< 50 \times 10^9$/l, if the patient has fever, infection, or bleeding, or any non-hematological toxicity of grade 3 or 4 with the exception of nausea, vomiting, and alopecia. Patients with mild and acceptable toxicity with full hematological recovery maintained the same irofulven dose during the course of treatment.

Formal assessment of tumor response was repeated after 2 cycles. Treatment was continued provided that toxicities were tolerable or until one of the following criteria applied: disease progression; static disease after 4 cycles in the absence of clinical benefit, according to the judgment of the clinician; intercurrent illness that prevents further administration of treatment; unacceptable adverse events; patient decided to withdraw from the study; or in the judgment of the investigator, changes in the patient's condition that rendered the patient unacceptable for further treatment. Tumor response continued to be assessed every 2 cycles using the Response Evaluation Criteria in Solid Tumors Committee [18].

Statistical analyses

The primary end-point was treatment response and toxicity; the secondary end-point was overall survival. A two-stage phase II design as proposed by Fleming [19] was used in this study to test a null response rate of 10% versus an alternative response rate of 30% with a maximum sample size of 35 patients. The target number of patients to be enrolled in the first stage was 20, if ≤ 2 responses were observed, the study would be stopped and the treatment concluded to be ineffective; if ≥ 6 responses were observed, the study drug would be concluded to be active. Otherwise, another 15 patients would be entered into the second stage. If ≥ 7 responses were observed out of the total 35 patients, the study drug would be concluded to be active. This design provided a 92% power to detect an active treatment with 5.3% type I error.

Overall survival was calculated from the first day of treatment to the date of death. Survival curve was constructed using the Kaplan–Meier method. All patients entering the trial were included in the survival analysis.

Results

Patient characteristics

From July 2003 to January 2005, a total of 23 patients from six participating institutions in Cancer Therapeutics Research Group entered the study. One patient did not receive the study medication due to bone marrow involvement with rapid rise in alkaline phosphatase soon after enrolment to the study. Irofulven treatment was withdrawn within the first 2 cycles in two patients due to grade 3 skin toxicity in one patient and death after suicide attempt in the second patient. Therefore, 20 patients received at least 2 cycles of chemotherapy and were evaluable for response assessment.

Patient characteristics are shown in Table 1. Two (9%) had received fluorouracil-based and one (4%) received doxorubicin-based neo/adjuvant chemotherapy. Two (9%) patients had received adjuvant radiotherapy.

Toxicity

A total of 54 cycles of irofulven was administered to 23 patients (median 2 cycles per patient; range 1–6). Two patients (9%) had 1 week or more delay in administration of subsequent cycle of chemotherapy. For the day 8 chemotherapy, dose reductions were required in 7 patients (30%) and 7 cycles (13%); dose omitting occurred in 5 patients (22%) and 6 cycles (11%).

Toxicity was assessable in all 23 patients (Table 2). Hematological toxicities of grade 3/4 severity included anemia (5 patients; 22%), grade 3/4 granulocytopenia (4 patients; 17%). There was no febrile neutropenia.

Table 1 Baseline patient characteristics

Characteristics	No. of patients	%
No. of patients	23	100
Gender		
Male	16	70
Female	7	30
Age, years		
Median	50	
Range	29–74	
ECOG performance status		
0	18	78
1	5	22
Disease site(s)[a]		
Lymph nodes	18	78
Liver	14	61
Stomach	7	30
Ascites	3	13
Pelvic/ovarian masses	3	13
Omentum	2	9
Adrenal	3	13
Pleural effusion	2	9
Lungs	2	9
Pancreatic mass	1	4
Abdominal wall mass	1	4
Prior adjuvant/neoadjuvant chemotherapy[b]		
FU-based	2	9
Doxorubicin-based	1	4
Prior radiotherapy	2	9

[a] No. of patients with: 1 disease site (= 4), 2 disease sites (= 8), 3 disease sites (= 8), 4 disease sites (= 2), 5 disease sites (= 1)

[b] No. of patients received prior cisplatin-base chemotherapy

Non-hematological toxicities of grade 3/4 severity included dysphagia/esophagitis/odynophagia (2 patients; 9%), dehydration (2 patients; 9%), dyspnea (2 patients; 9%), vomiting (2 patients; 9%), nausea (1 patient; 4%), constipation (1 patient; 4%), raised alkaline phosphatase (1 patient; 4%), abdominal pain (1 patient; 4%), hyponatraemia (1 patient; 4%), hyperbilirubinaemia (1 patient; 4%), tumor pain (1 patient; 4%), prolonged partial thromboplastin time (1 patient; 4%), and proteinuria (1 patient; 4%). One patient (4%) had depression, depressed level of consciousness, and hallucination.

Response and survival

Twenty patients were evaluable for response. Stable disease was observed in three patients after 2 cycles of treatment; however, further evaluation was not performed in these patients as treatment was discontinued thereafter due to severe toxicities after 2 cycles in one patient, and patients' choice in two patients (after 2 and 3 cycles, respectively). Seventeen (85%) patients had progressive disease. In the absence of any observed response, the study has not proceeded to second stage. As of August 2005, 20 patients have died and 3 patients were still alive. The median overall survival was 6.05 months (95% CI 4.55–9.39).

Table 2 Hematological and non-hematological toxicities according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Grade 3/4 toxicities are listed first, followed by other toxicities with decreasing frequencies

Toxicities	Worst grade (number of patients)		
	1–2	3	4
Neutropenia	3	4	0
Anemia	1	4	1
Transfusion of packed cells	0	4	0
Dysphagia, esophagitis, odynophagia	0	2	1
Vomiting	6	2	0
Dehydration	0	2	0
Dyspnea	0	2	0
Nausea	17	1	0
Constipation	2	1	0
Alkaline phosphatase	0	1	0
Abdominal pain	2	1	0
Hyponatremia	1	1	0
Hyperbilirubinaemia	1	1	0
Tumor pain	1	1	0
Mood alteration–depression[a]	0	0	1
Depressed level of consciousness[a]	0	1	0
Hallucinations[a]	0	1	0
Partial thromboplastin time	0	1	0
Proteinuria	0	1	0
Fatigue	14	0	0
Anorexia	7	0	0
Platelets	7	0	0
Insomnia	4	0	0
Headache	3	0	0
Alanine transaminase	3	0	0
Alopecia	2	0	0
Hypoalbuminemia	2	0	0
Edema	2	0	0
Weight loss	2	0	0
Aspartate transaminase	1	0	0
Chest pain	1	0	0
Cough	1	0	0
Diarrhea	1	0	0
Fever	1	0	0
Flushing	1	0	0
Hematuria	1	0	0
Hemoptysis	1	0	0
Hiccoughs	1	0	0
Hypokalemia	1	0	0
Hypophosphatemia	1	0	0
Injection site reaction	1	0	0
Mouth dryness	1	0	0
Myalgia	1	0	0
Neuropathy-motor	1	0	0
Neuropathy-sensory	1	0	0
Petechiae/purpura	1	0	0
Pulmonary–other[b]	1	0	0
Sweating	1	0	0
Taste disturbance	1	0	0
Vision–blurred vision	1	0	0

[a] These toxicities occurred in the same patient

[b] One due to sore throat and one due to sputum

Discussion

For patients with metastatic gastric cancer, recent advances in the treatment regimens incorporating agents such as taxanes, capecitabine, and camptothecin analogs have led to increase in response rates to the range of 40–50% [7–10, 20–23]. However, the prognosis remains poor, as the increase in response rates has not translated into improvement in overall survival; the median survival reported from most of the studies have been in the range of 10 months, and survival beyond 1 year has not yet been achieved in any randomized phase III study with combination chemotherapy [11, 12, 24, 25]. This could possibly be due to rapid development of acquired pharmacological resistance in this disease; thus, to improve the prognosis of these patients, novel agents are required.

Irofulven represents a new class of cytotoxic agent with significant antitumor activity against a number of pre-clinical tumor models. Previous studies using irofulven at daily schedules at 10–12 mg/m^2 for 4–5 consecutive days every 3–4 weeks in other tumor types have demonstrated promising activity, and clinical activities have been reported in the setting of heavily pre-treated ovarian cancer [26], androgen-independent prostate cancers [27], relapsed or refractory non-small cell lung cancer [28], and gemcitabine-refractory pancreatic cancer [29]. However, using the daily schedules, delayed thrombocytopenia was prevalent, and severe emesis with anorexia and asthenia had led to frequent treatment delays and/or discontinuations. This has led to the subsequent pharmacokinetic testing by intermittent administration of the agent, and the recommended two schedules for further evaluation in phase II studies have been: days 1 and 8 every 21 days and days 1 and 15 every 28 days [26]. The intermittent schedules have improved safety profile and patient tolerability while maintaining dose intensity over the daily schedule. On the other hand, intermittent administration, in particular, in patients receiving > 0.55 mg/kg/infusion, appears to associate with a higher likelihood retinal toxicity. It has thus been suggested that the intermittent dose of irofulven, using the above recommended scheduling, should be limited to $\leq$ 0.55 mg/kg/infusion and < 50 mg/infusion total dose, which represent a common dose intensity of 12 mg/m^2 week [26].

The present study is the first reported using irofulven for patients with recurrent or metastatic gastric cancer. By administrating with an intermittent dose scheduling at 0.45 mg/kg/perfusion on days 1 and 8 every 3 weeks, grade 3/4 toxicities that occurred in over 10% of the patients were anemia and neutropenia. Severe nausea, vomiting, anorexia, and fatigue were infrequent. Of note, no patients developed severe thrombocytopenia while grade 1–2 toxicity occurring in nine patients (39%). Mild fatigue was common and occurred in 57% of the patients. By limiting the intermittent irofulven dose to 0.45 mg/kg/infusion, only one patient experienced visual symptom that was of grade 2 and short-lived, which resolved after discontinuation of chemotherapy for progressive disease.

However, the present study revealed that irofulven has minimal activity in patients with advanced gastric cancer. As in the setting of endometrial cancers [30] and renal cell carcinomas [31], further evaluation of the agent in gastric cancers is unwarranted. Research into identification of novel agents for the treating of this malignancy is required.

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