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Citation: J Med Discov (2018); 3(3):jmd18030; DOI:10.24262/jmd.3.3.18030

Research Article

Phase I clinical trial of Photosan combined radiation and chemotherapy in advanced gastrointestinal tract malignant tumors

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Purpose: To evaluate the therapeutic effect of Photodynamic therapy (PDT) combined radiation and chemotherapy in advanced unresectable gastrointestinal(GI) tract tumors. Determination of the optimal laser doses of Photosan, evaluation maximum tolerated dose (MTD) of Photodynamic therapy combination with radiation and chemotherapy, adverse reaction and toxicity.

Experimental Design: In the 3+3 dose-escalation component of this phase I study, eligible patients with advanced tumors received Photosensitizer Photosan 1,1.5 and 2mg/kg dose, The energy density at 200J/cm2, combind with intensity-modulated radiation therapy and Cisplatin 30 mg/m2 once every week,total 5 weeks. Until confirmed progression, unacceptable toxicity, or trial withdrawal. The primary objective is to determine the safety and tolerated dose; Secondary objectives include adverse reaction and best overall response.

Results: Nine heavily pretreated patients with ECOG 0–2 have received Photosan Combined cisplatin and intensity-modulated radiation. Grade 2 treatment-related adverse events occurred in four patients (esophageal pains, bone marrow suppression , difficulty in swallowing). The MTD was not reached. There were signs of efficacy across all dose levels, including one ongoing confirmed complete response (esophageal cancer), two durable confirmed partial responses (PR; stomach cancer; esophageal cancer), one near-PR (gastroesoghageal junction cancer), four cases of stable disease and one PD in patients at study entry.

Conclusions: Photodynamic therapy (PDT) combined chemoradiotherapy has a manageable safety profile in patients with heavily pretreated advanced unable to surgical gastrointestinal tract tumors. Signs of efficacy are encouraging, and the recommended doses of Photosan in Phase II clinical trial is 2mg/kg.

Keywords: Photodynamic therapy; Maximum tolerated dose; gastrointestinal tract tumors; radiation; chemotherapy

How to cite: Zhang M et al., Phase I clinical trial of Photosan combined radiation and chemotherapy in advanced gastrointestinal tract malignant tumors. J Med Discov (2018); 3(3):jmd18030; DOI:10.24262/jmd.3.3.18030; Received July 1st, 2018, Revised August 6th, 2018, Accepted August 31st, 2018, Published September 17th, 2018.

Introduction

The GI tract malignant tumor occupies a large proportion in the malignant tumor (1), as it is too late when see the doctor. Most of the patients have lost opportunity of surgical therapy. In addition, due to insensitive to radiation and chemotherapy, most cases get to relapse, and this leads to the high morbidity and high mortality. As GI tract is one of the most important digesting organ, it strongly affect the life quality of patients who are with stricture or obstruction. How to solve it plagued clinicians. Improve the quality of life and prolong survival in patients has become a hot spot and focus in current cancer treatment. Photodynamic Therapy (PDT) is a new minimally invasive cancer treatment technology(2). It is based on a photochemical reaction between a light activatable molecule or photosensitizer, light, usually in the visible spectrum, and molecular oxygen. These three components are harmless individually, but the combination results in the formation of reactive oxygen (ROS) species that are able to directly induce cellular damage to organelles and cell membranes depending on where they are generated(3). Clinical data showed that PDT has certain advantages in the improvement of GI tract tumor stricture or obstruction, but it is limited by the scope of radiation depth (4). Due to the limitation of treating the advanced cancer, combinations of various therapeutic modalities with non-overlapping toxicities are among the commonly-used strategies to improve the therapeutic index of treatments in modern oncology. How to effectively combined variety of treatment methods is an urgent subject. There are few studies on

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combinations of PDT with standard antitumor regimens, especially in clinical trials(5-9). The aims of this trials will be: to analyze the effect of PDT combined radiation and chemotherapy in advanced unable to surgical gastrointestinal(GI) tract tumors. Determine the optimal laser doses of Photosan, evaluation maximum tolerated dose (MTD) of Photodynamic therapy combination with radiation and chemotherapy, adverse reaction and toxicity.

Patients and Methods

Study design and patients

This is a dose-escalation and dose-expansion trial of Photosan combined radiation and chemotherapy in patients with heavily pretreated advanced unable to surgical GI tract tumors. Patients had histologically or cytologically static or locally advanced solid tumors for which no effective standard therapy existed or standard therapy had failed. All patients had an ECOG performance status of 0-2, preserved organ function, and evaluable or measurable disease. Exclusion criteria: pregnancy, nursing mothers, or fertility but not women using contraception; Patients can't tolerate radiotherapy, chemotherapy and PDT; Drug allergy for examination or of suffering from disease of puling was not allowed. The study was conducted in accordance with all applicable regulatory requirements, and the protocol was approved by the Institutional Review Board of the Center for Cancer Research at Hebei General Hospital. Each patient provided signed informed consent before study enrollment.

Procedures

In the dose-escalation component, patients received Photosan as a 1-hour intravenous infusion at dose levels of 1, 1.5, 2mg/kg; then Photodynamic therapy was used after 48 hours.In the time of six hours before therapy, it was forbidden to drink water and eat food .In order to cover fully the irradiated sccpe of disease, the irradiated section should be more 1-2cm than side of tumour. In case of longer scope,it was irradiated part by part. Every part could have a superimposed image of 1cm. The irradiated density of energy was selected as 200J/cm^2. Time of every part was about 15-20min.After therapy, Patients should be prohibited to drink water and eat food for 24 hours.In the same time, cisplatin was used at dose of 30 mg/m2 through intravenous infusion avoided from light once every week (Q1W), total 5 weeks.From a week after photodynamic therapy, Patients received radiationtherapy. The Radiation dose was 50 Gy in 25 fractions for carcinoma of esophagus and 45 Gy in 25 fractionsfor carcinoma of stomach. Radiation therapy was given using 3-dimensional conformal radiation therapy or intensity modulated radiation therapy. Patients were advised to avoid light one month. After one month of treatment, patients were for whole reexamination.Patients With good-reaction,will check by endoscope once a month. In addition, Patients were in Follow-up examination for three months in order to observe the the reaction of carcinoma.

Outcomes

The primary objective of this study was to determine the safety, tolerability, and maximum tolerated dose (MTD) of Photodynamic therapy (PDT) combined with chemoradiotherapy; Secondary objectives included treatment-related AEs and best overall response.

Safety

Safty was evaluated according to NCI CTCAE v4.03. For dose-escalation purpose, a dose-limiting toxicity(DLT) was defined as any grade≥3 toxicity considered by the investigator to be related to Photosan that occurred during the DLT assessment window 21 days after the first administration of Photosan, with the following exceptions: grade 3 infusion reaction or fever; grade 3 fatigue, headache, nausea, or emesis within 24 hours; grade 3 anemia resolving to 9 g/dL within 14 days without blood transfusion or use of erythroid growth factor. The design evaluated MTD in terms of the number of patients experiencing a DLT (vs. the number of DLT events experienced by an individual patient): more than one of six patients within a dose level experiencing a DLT would suggest that the MTD had been exceeded; in such case, the MTD would be defined as the highest dose level at which no more than 1 of 6 patients treated in a cohort and evaluable for DLT determination experienced a DLT.

Results and Discussion

Baseline demographics

From September 1, 2015 to October 21, 2016, 9 patients were enrolled at the Department of Radiation Oncology, Hebei General Hospital. Patients received Photosan at dose levels of 1mg/kg(n=3), 1.5mg/kg(n=3), 2mg/kgmg/kg(n=3); No patient in the 2mg/kg cohort was evaluable for DLTs. Patient baseline and disease characteristics are shown in Table 1. All patients had an ECOG performance status of 0-2, and a variety of primary tumor types were represented.

Table 1. Patient baseline characteristics

Group	Group1(1mg/kg)	Group2(1.5mg/kg)	Group3(2mg/kg)
Patient characteristics	N=3	N=3	N=3
Sex			
Male	2	1	1
Femal	1	2	2
Age,median(range)	61(48-71)	57(38-70)	56(45-65)
TNM Stage			
StageIII	2	1	0
StageIV	1	2	3
Pathological pattern			
Squamous	3	1	0
Adenocarcinoma	0	2	3
ECOG performance status			
0-1	2	0	1
1-2	1	3	2
Evaluation			
CR	0	1	0
PR	1	0	2
SD	0	2	2
PD	1	0	0

Treatment exposure

Nine patienls in our group, three patients was StageIII, and six patients was StageIV.The length of tumour in middle position was 3cm (2 to 6 cm). Four patients with a girth of less than one third and Five patients with a girth of one third to one half. Treatment-related AEs are shown in Table 2. The MTD was not reached at the highest dose level in this study 2mg/kg. No AEs led to death. In all groups, No infusion-related Photosensitization reaction occurred. No Bleed and Perforation occurred. As well as no toxicity of haematology with three degrees occurred. Eight patients occurred pain of esophagus. Four patients occurred condition of mild dysphagia. One patient(11.1 percent) to CR. Three patients(33.3 percent) to PR. Four patients (44.4 percent) to SD and one patient (11.1 percent) to PD.

Table 2. Treatment-related AEs

N（%）	Group1(1mg/kg)		Group2(1.5mg/kg)		Group3(2mg/kg)	
	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Photosensitization	0	0	0	0	0	0
Pyrexia	0	0	1	0	1	0
Pain	2	0	3	0	3	0
dysphagia	1	0	1	0	2	0
Gastroparesis	0	0	1	0	0	0
Nausea	3	0	2	0	3	0
Vomiting	2	0	3	0	2	1
Weight Decrease	1	0	2	0	1	0
Bleed	0	0	0	0	0	0
Perforation	0	0	0	0	0	0

Discussion

In recent years, Tumor treatment has entered the era of multi-disciplinary treatment model. How to effectively combind complex methods is also a hot spot in tumor field. Lower local controlling rate of digestive tract tumor as well as recurrence and distant metastasis are urgent clinical problems to be solved.

PDT is currently considered as a reasonable option for the treatment of a variety of malignant lesions especially In the case of the GI tract, for curative or palliative purposes by using either external or endoscopic irradiation approaches via non-coherent or laser light sources. PDT can combind with other therapies such as surgery, radiation, chemotherapy and Targeted drugs[10-14]. Combinations of various therapeutic modalities with non-overlapping toxicities are among the commonly-used strategies to improve the therapeutic index of treatments in modern oncology. Two general approaches may increase antitumor effectiveness of PDT: (i) sensitization of tumor cells to PDT; and (ii) interference with cytoprotective molecular responses triggered by PDT in surviving tumor or stromal cells. Any interactions between PDT and PDT-sensitizing agents will be confined to the illuminated area. Therefore, the potentiated toxicity of the combinations is not systemic[14]. This should be of special importance in elderly or debilitated patients who tolerate more intensive therapeutic regimes poorly. Moreover, considering its unique 1O2-dependent cytotoxic effects, PDT can be safely combined with other antitumor treatments without the risk of inducing crossresistance[15].

PDT and radiotherapy are both local therapy, combined them can increase the rate of local control. Chemotherapy, is mainly for subclinical lesions and distant metastasis. There is no clinical research reported about PDT in combination with radiation and chemotherapy in digestive tract malignant tumor, and the safty of combined all of them is unclear.

On the basis of this work, we conducted the first clinical trial to determine its safety, efficacy in 9 patients with heavily pretreated advanced solid tumors using a 3+3 dose-escalation design. The MTD was not reached at the highest dose level in this study 2mg/kg. No AEs led to death. In all groups, No infusion-related Photosensitization reaction occurred. No Bleed and Perforation occurred. As well as no toxicity of haematology with three degrees occurred. Eight patients occurred pain of esophagus. Four patients occurred condition of mild dysphagia. One patient(11.1 percent) to CR. Three patients(33.3 percent) to PR. Four patients (44.4 percent) to SD and one patient (11.1 percent) to PD.

In conclusion, these data from the phase I dose-escalation study show that PDT combination with radiation and chemotherapy appears to have a manageable safety in patients with heavily pretreated advanced solid tumors. In addition, Phase II clinical trial recommended doses of Photosan is 2mg/kg.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

Project was supported by Science and Technology Departmant of Hebei Province (15277728D)

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