PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Phase I open label trial of Intraperitoneal Paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and Peritoneal metastases (IPGP study):study protocol
AUTHORS	Vatandoust, Sina; Bright, Tim; Roy, Amitesh; Watson, David; Gan, Susan; Bull, Jeff; Abbas, Muhammad; Karapetis, Christos

VERSION 1 - REVIEW

REVIEWER	Paolo Sammartino MD PhD Department of Surgery Pietro Valdoni University Sapienza Rome Italy
REVIEW RETURNED	07-Nov-2018

GENERAL COMMENTS	1) Regarding the use of intraperitoneal chemotherapy the Authors selected references 28,29 that were published seven or eight years ago..("recent studies.." !). Recent studies are Y Yonemura EJSO 42 2016 1123-1131 and Ann Surg Oncol 2017 24 478-485 2) In my opinion a precise definition about which class of patients must be included is lacking. It is well known that chance of treatment and prognosis are completely different between synchronous and metachronous peritoneal involvement in gastric cancer. Furthermore a reliable application of normothermic peritoneal chemotherapy is possible only in synchronous peritoneal spread in patients not yet surgically treated. 3) The endpoints of the study are not clear. The only valuable endpoint is the possibility of a gastrectomy including cytoreduction of peritoneal metastses after a neoadjuvant treatment. The response rate with RECIST criteria is questionable without including laparoscopy in the study. The only valuable criteria in the evaluation of the response rate is the peritoneal cancer index.

REVIEWER	Antonio Sommariva Unit of Surgical Oncology of the Esophagus and Digestive Tract, Castelfranco Veneto (TV), Veneto Institute of Oncology IOV-IRCCS Padua, Italy
REVIEW RETURNED	26-Nov-2018

GENERAL COMMENTS	No specific comment. Good protocol

REVIEWER	wim ceelen Department of GI Surgery, Ghent University Hospital
REVIEW RETURNED	30-Nov-2018

GENERAL COMMENTS	The authors propose a phase I trial of IV cis/5FU combined with IP paclitaxel in patients with gastric cancer with synchronous peritoneal metastasis (PM). In the Far East, the combination of systemic treatment with IP pac has resulted in impressive response rates. This would be one of the first trials to evaluate IP pac in combination with a regimen that is considered the standard of care in Western countries. Major remarks - the authors propose three dose levels of IP pac: 10-20-30 mg/m2. Why is a linear escalation chosen instead of the more common modified Fibonacci series? Also, most studies that have tested IP pac report safe dose levels up to 90 mg/m2. Therefore, there is a concern of undertreatment. - It is unfortunate that the authors do not include any translational endpoint. Tissue banking is mentioned, but no molecular/genetic research plan is given. - Are patients with metachronous PM excluded? Will surgery be offered to patients with excellent response and resectable disease? Minor remarks - Page 3, Limitations: the fact that the proposed study will not answer efficacy (survival) is not a limitation, this is just not the aim of phase I studies - Page 5, line 12: the word 'in' is misplaced - Page 6, line 2: the word 'in' is missing before 'Japan' - page 7, line 20: '>1 area of metastasis': unclear what this refers to - Page 9, line 42: endoscopic biopsies at the time of catheter placement: I assume that included patients already underwent gastroscopy/biopsies. Will this be done twice? - Page 9, line 51: diluted in saline or 5%D: I would strongly argue against using two carrier fluids since these are known to potentially affect not only drug pharmacokinetics but also peritoneal host defence. I would not use 5%D IP.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Paolo Sammartino MD PhD

Institution and Country: Department of Surgery Pietro Valdoni University Sapienza Rome Italy

Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below

1) Regarding the use of intraperitoneal chemotherapy the Authors selected references 28,29 that were published seven or eight years ago..("recent studies.." !). Recent studies are Y Yonemura EJSO 42 2016 1123-1131 and Ann Surg Oncol 2017 24 478-485

We would like to bring to the attention of the reviewers that this study protocol was designed in 2013/2014, approved by ethics committee in 2014 and the study was open to accrual in 2014.

Therefore the study design/protocol predates the mentioned literature and that is why these important studies were not mentioned in the protocol introduction. We have added the mentioned studies in the discussion section.

2) In my opinion a precise definition about which class of patients must be included is lacking. It is well known that chance of treatment and prognosis are completely different between synchronous and metachronous peritoneal involvement in gastric cancer. Furthermore a reliable application of normothermic peritoneal chemotherapy is possible only in synchronous peritoneal spread in patients not yet surgically treated.

This study is designed to include both metachronous and synchronous metastatic disease. We do agree that the prognosis of these patients may be different but given that the primary objective of this phase 1 study was to establish the treatment dose, the prognosis of patients was not thought to affect the primary objective. On the other hand, limiting the study to one group would affect accrual and potentially would have made it difficult to run the study on a practical level.

3) The endpoints of the study are not clear. The only valuable endpoint is the possibility of a gastrectomy including cytoreduction of peritoneal metastses after a neoadjuvant treatment. The response rate with RECIST criteria is questionable without including laparoscopy in the study. The only valuable criteria in the evaluation of the response rate is the peritoneal cancer index.

We respectfully disagree with the reviewer: This is a phase 1 study aiming at establishing the dosage. The primary objective of the study is documented as: “To determine the Maximum Tolerated Dose (MTD) of IP paclitaxel in patients with advanced gastric cancer and peritoneal involvement”. This is in keeping with the main purpose of phase 1 studies in general.

We do agree that important outcomes such as response should be further investigated for this treatment approach; however, such outcomes cannot be investigated adequately within this study and are going to be the objectives for a phase 2 study which our group is currently designing.

Reviewer: 2

Reviewer Name: Antonio Sommariva

Institution and Country: Unit of Surgical Oncology of the Esophagus and Digestive Tract, Castelfranco Veneto (TV), Veneto Institute of Oncology IOV-IRCCS Padua, Italy

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

No specific comment. Good protocol

Reviewer: 3

Reviewer Name: wim ceelen

Institution and Country: Department of GI Surgery, Ghent University Hospital

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The authors propose a phase I trial of IV cis/5FU combined with IP paclitaxel in patients with gastric cancer with synchronous peritoneal metastasis (PM). In the Far East, the combination of systemic treatment with IP pac has resulted in impressive response rates. This would be one of the first trials to evaluate IP pac in combination with a regimen that is considered the standard of care in Western countries.

Major remarks

- the authors propose three dose levels of IP pac: 10-20-30 mg/m2. Why is a linear escalation chosen instead of the more common modified Fibonacci series? Also, most studies that have tested IP pac report safe dose levels up to 90 mg/m2. Therefore, there is a concern of undertreatment.

We did start the initial dose at 10 mg/m2 and if we were to follow Modified Fibonacci sequence the following dose steps would be 20 mg/m2 and 33 mg/m2 which is very similar to the dose steps in our study.

We respectfully disagree with the second point made by the reviewer:

The published literature on intraperitoneal paclitaxel in this setting, mention treatment doses of 20 mg/m2 (Ishigami et al 2018) and Yamaguchi (2013). The phase 1 study published by Ishigami et al (2006) established IP Paclitaxel MTD at 30 mg/m2.

Higher dose of 80 mg/m2 was used in the study by Imano et al (2012) but this study used only a single intraperitoneal administration of paclitaxel which is different from our study design.

In our study design patients receive a combination of cisplatin and capecitabine which is one of the accepted standard treatments in advanced gastric cancer. These medications were both given at full dose and based on available evidence. IP paclitaxel is not part of the standard treatment of gastric cancer, therefore using low doses as part of the phase 1 design does not carry a risk of under-treatment as patients received the IP paclitaxel in addition to standard and adequate treatment for their disease.

- It is unfortunate that the authors do not include any translational endpoint. Tissue banking is mentioned, but no molecular/genetic research plan is given.

This is a phase 1 study and molecular/genetic studies/outcomes were not the primary objectives. However, in the absence of established biomarkers and with a view to future translational research, we have included Tissue banking for biomarker analysis as one of the secondary objectives of the study. Future translational research will be designed using these specimens to investigate potential biomarkers in this setting.

- Are patients with metachronous PM excluded? Will surgery be offered to patients with excellent response and resectable disease?

This was addressed in response to point 2 raised by reviewer 1

Surgery can be offered to patients with excellent response and resectable disease but this will not be part of the study design and will be decided on an individual basis by the involved surgeon.

Minor remarks

- Page 3, Limitations: the fact that the proposed study will not answer efficacy (survival) is not a limitation, this is just not the aim of phase I studies

We have now updated the manuscript to reflect this change.

- Page 5, line 12: the word 'in' is misplaced

We have now updated the manuscript to reflect this change.

- Page 6, line 2: the word 'in' is missing before 'Japan'

We have now updated the manuscript to reflect this change.

- page 7, line 20: '>1 area of metastasis': unclear what this refers to

This refers to >1 area of peritoneal metastasis.

- Page 9, line 42: endoscopic biopsies at the time of catheter placement: I assume that included patients already underwent gastroscopy/biopsies. Will this be done twice?

Diagnostic endoscopy with biopsy to be performed before the insertion of IP catheter. It will not be done twice. Biopsy to confirm peritoneal metastasis will be performed during laparoscopy.

- Page 9, line 51: diluted in saline or 5%D: I would strongly argue against using two carrier fluids since these are known to potentially affect not only drug pharmacokinetics but also peritoneal host defence. I would not use 5%D IP.

We acknowledge the concerns raised by the reviewer. Paclitaxel is compatible with both 5% Dextrose and Sodium chloride 0.9%. We used 5% dextrose with IP paclitaxel in the study for all patients and none of the patients had any significant issues.

VERSION 2 – REVIEW

REVIEWER	Paolo Sammartino MD PhD Department of Surgery Pietro Valdoni University Sapienza Rome Italy
REVIEW RETURNED	21-Feb-2019

GENERAL COMMENTS	Good paper and interesting field in which western Authors so far demonstrated scarce interest.

REVIEWER	wim ceelen Ghent University
REVIEW RETURNED	06-Mar-2019

GENERAL COMMENTS	The authors have adequately addressed the questions and issues that were raised.