Ann Surg Oncol (2024) 31:694–696
https://doi.org/10.1245/s10434-023-14258-w

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – GASTROINTESTINAL ONCOLOGY

Role of Iterative Normothermic Intraperitoneal Paclitaxel Combined with Systemic Chemotherapy in the Management of Gastric Peritoneal Carcinomatosis

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Gastric peritoneal carcinomatosis (PC) continues to be a major therapeutic challenge despite advances in systemic chemotherapy and targeted therapies. Because the effectiveness of systemic treatment for PC is limited due to poor penetration of the drug into peritoneal nodules as result of a plasma peritoneal barrier and poor intra-tumoral vasculature, delivery of high concentrations of chemotherapeutic agents through direct intraperitoneal (IP) administration offers a significant pharmacokinetic (PK) advantage.[1,2] Due to the PK advantage combined with the importance of systemic control in gastric cancer and possible synergistic effects of systemic and IP treatment, the combination of systemic and IP treatment, namely, the bidirectional approach, has been the focus of ongoing investigations to improve outcomes in gastric PC.[3,4] Iterative administrations of IP chemotherapy under various conditions, such as normothermia, hyperthermia, and pressurization with aerosolized chemotherapy, all are being studied in gastric PC with varied results.

The choice of IP approach also varies based on the geographic regions. Normothermic intraperitoneal chemotherapy (NIPEC) with paclitaxel is the most studied and uniformly accepted approach in the management of gastric PC in Asian countries. Paclitaxel as an IP drug has a distinct PK advantage because it is retained in the peritoneal cavity in high concentrations for prolonged periods due to its hydrophobic nature and large molecular weight (853.9 gm/mol).[5,6]

The largest randomized controlled trial to date that has tested the bidirectional treatment of gastric PC with NIPEC paclitaxel is the PHOENIX GC trial.[7] In this trial, 183 patients with gastric PC were treated with either systemic chemotherapy alone consisting of S1 and cisplatin or IP and intravenous (IV) paclitaxel with S-1. Although the study failed to meet the primary end point of improved overall survival, mainly due to imbalances between the groups, crossover to IP, and possibly a study design underpowered to detect an overall survival benefit, the exploratory analyses suggested likely clinical benefits with IP paclitaxel treatment. The 3-year survival rates of IP/IV paclitaxel and S-1 were respectively 21.9% and 6% with systemic chemotherapy alone. Because IV paclitaxel was not part of the control arm, it could be argued that the trial compared the efficacy of paclitaxel and that of cisplatin combined with S-1 in the first-line setting. Despite this, given the observed benefit, there is a continued interest in evaluation of NIPEC paclitaxel for the management of gastric PC.

The current study by Kobayashi et al.[8] titled, "Phase II Study of Intraperitoneal Administration of Paclitaxel Combined with S-1 and Cisplatin for Gastric Cancer With Peritoneal Metastasis," is a single-arm study in which 53 patients with macroscopic gastric PC were treated with systemic S1/cisplatin and paclitaxel NIPEC (20 mg/m^2) on days 1, 8, and 22 every 5 weeks. Treatment was continued until disease progression, unacceptable toxicity, investigator's decision, or patient refusal. The overall survival (OS) rates were 73.6% at 1 year, 39.3% at 2 years, and 20.4% at 3 years. The 1-year progression-free survival (PFS) rate was 43.6%, and the median PFS was 11.1 months (95% confidence interval [CI], 8.4–15.9 months). For the 16 patients (30%) who underwent gastrectomy, the median survival time was 42.1 months (95% CI 34.9–43.5 months), and the median PFS was 18.1

First Received: 22 August 2023
Accepted: 23 August 2023
Published online: 8 September 2023

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months (95% CI 14.8–29.3 months). This observation is extremely important because in a subset of patients who respond to IP therapy, as determined by negative cytology or a decrease in the size and number of peritoneal lesions, and for whom R0 resection is feasible, gastrectomy/cytoreduction is associated with better survival outcomes.

In a recent phase 2 study of paclitaxel NIPEC with FOLFOX/XELOX, Chia et al.,[9] reported a surgery rate of 36.1% (13/36) for patients with a median OS of 24.2 months (95% CI 13.1–35.3 months) and a 1-year OS rate of 84.6% for this group. Surgery rates higher than 50% have been reported in other IP paclitaxel studies.[10] In contrast, the surgery rate in the iterative hyperthermic intraperitoneal chemotherapy (HIPEC) study by Badgwell et al.[11] was 26%, with a median OS of 20.3 months.

The PK benefits of IP chemotherapy depend on the drug, concentration, and duration of exposure. Approaches to augment the cytotoxicity of intraperitoneal agents often include heat (HIPEC) and, more recently, pressurized aerosolized chemotherapy (PIPAC). However, both HIPEC and PIPAC require surgical interventions, making repeated administration cumbersome and expensive, with the inherent risks of surgical intervention. On the other hand, NIPEC is administered in outpatient settings similar to intravenous administration and can be repeated several times. The median number of IP cycles in most IP paclitaxel studies is 10. This practical advantage combined with the PK advantages of paclitaxel and the reported high surgery rates make NIPEC an attractive approach that warrants continued exploration in gastric peritoneal carcinomatosis.

The authors are to be applauded for conducting this important trial and adding further evidence for the role of IP paclitaxel in PC. As the authors appropriately acknowledge, S-1 is not available in the United States and European countries, which makes it challenging to expand the reported efficacy of this particular regimen to patients globally. Immune checkpoint inhibitors (ICI) combined with chemotherapy are currently the standard of care for metastatic gastric cancer, at least for PD-L1-expressing tumors. Although it is correct that patients with PC appeared to derive a smaller relative benefit from the addition of ICI in the ATTRACTION-4 and Checkmate 649 studies, the subset analyses of PC were not controlled for PD-L1 expression, which might have been a confounding factor.

Finally, novel targets in human epidermal growth factor receptor 2 (HER2)-negative gastric cancer have been identified and likely will lead soon to regulatory approval (e.g., zolbetuximab for Claudin18.2-positive tumors). Hence, moving forward, it would be advantageous to combine IP paclitaxel with modern regimens that are flexible and can be combined with targeted therapies. The other approach could be induction systemic treatment, with the most current and active regimen based on the tumor profile, followed by a switch to IP paclitaxel with continuation of the systemic regimen. The ongoing STOPGAP phase 2 clinical trial in the United States is testing sequential systemic chemotherapy combined with targeted therapies based on molecular markers followed by bidirectional treatment with NIPEC paclitaxel for gastric PC.[12]

In summary, the unique biologic features of PC, the ineffectiveness of systemic chemotherapy alone in treating PC, and the PK advantages of IP treatment, particularly IP paclitaxel, offer an important opportunity to develop new treatment approaches in the management of gastric PC. Randomized clinical trials comparing the bidirectional approach with systemic therapy are essential to understand the benefits from the addition of NIPEC, particularly in the era of improved systemic therapy with the addition of targeted agents.

DISCLOSURE Farshid Dayyani receives institutional research support from Astrazeneca, BMS, Merck, Exelixis, Taiho, Trishula, Natera, Amgen, Genentech/Roche, and Ipsen; honoraria from Exelixis, Sirtex Medical, Eisai, Astellas, and Servier; and consulting fees from Exelixis, Eisai, and Astrazeneca. Maheswari Senthil has no conflicts of interest.

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