Review Article on Appendiceal Malignancy and Colon Cancer

Hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal and appendiceal peritoneal metastases: lessons learned from PRODIGE 7

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The treatment for peritoneal metastases from appendiceal, colon and rectal cancer (MO1) has relied on cytoreductive surgery (CRS) to remove all visible evidence of disease plus a perioperative chemotherapy for the entire abdomen to eliminate microscopic residual disease. Using the results obtained from the PRODIGE 7 randomized controlled trial, methodological issues were discussed and possible improvements to the hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin were sought. Possible methodological and pharmacologic flaws were identified. Several methodological flaws included the sample size, cross-over option, neoadjuvant chemotherapy use and timing of the peritoneal disease evaluation. The sample size issue raised the question of what the minimal clinically relevant benefit we want in future trials. Neoadjuvant FOLFOX may have induced acquired drug resistance to oxaliplatin. Several pharmacological issues were identified including limited 5-fluorouracil exposure as well as limited oxaliplatin peritoneal exposure time. Insufficient 5-fluorouracil accompanied the oxaliplatin as only a bolus dose was used and continuous 5-FU infusion has previously been an integral part of oxaliplatin treatment. Finally, only approximately one-half of the oxaliplatin entered body tissues or tumor. Three suggestions from the lessons learned from a critique of PRODIGE 7 were offered as adjustments to the HIPEC protocol. The Efficacy of HIPEC, a perioperative FOLFOX or a return to HIPEC with mitomycin C were described.

Keywords: Intraperitoneal chemotherapy; hyperthermia; 5-fluorouracil; irinotecan; early postoperative intraperitoneal chemotherapy (EPIC); cytoreductive surgery (CRS)

Submitted Jul 01, 2020. Accepted for publication Aug 31, 2020.
doi: 10.21037/jgo-2020-05
View this article at: http://dx.doi.org/10.21037/jgo-2020-05

Introduction

Management strategies with curative intent for peritoneal metastases from appendiceal and colon cancer have evolved over four decades. Successful treatments have always required a surgical procedure to remove from the abdomen and pelvis all visible disease. Then at the time of surgery perioperative chemotherapy to control microscopic residual disease is used (1,2). The surgical procedures are usually referred to as cytoreductive surgery (CRS) which requires peritonectomy procedures and visceral resections. Requirements for extensive surgical interventions have been well defined and a complete cytoreduction is the starting point for all successful management plans (3). Unfortunately, the perioperative chemotherapy regimens are not well defined or well standardized. The chemotherapy most commonly used as a planned part of the surgical intervention is hyperthermic intraperitoneal chemotherapy (HIPEC). This is a lavage of the entire

abdominal and pelvic space with a large volume of chemotherapy solution at elevated temperatures (4). Usually, the intraperitoneal fluid is maintained at 41–42 ℃ within the peritoneal space using heat to augment the cytotoxicity of the chemotherapy solution (5,6). However, many different HIPEC strategies exist and the methodologies at different institutions are surprisingly variable (7-9). One HIPEC regimen popularized by French surgeons is ultra-high dose oxaliplatin given over a short time interval at higher than usual temperature (43 ℃) of the chemotherapy solution. To test the efficacy of the Elias HIPEC regimen, the French multi-institutional collaboration in peritoneal surface oncology initiated the PRODIGE 7/ACCORD-15 trial (NCT 00769405). This phase III trial tested HIPEC oxaliplatin following complete CRS *vs.* CRS alone. It was reported at the ASCO 2018 Annual Meeting by Quenet *et al.* (10).

The results of this randomized trial were negative. As of now these data are not published as a peer-reviewed manuscript but as an American Society of Clinical Oncology abstract (10). Quenet and his French colleagues randomized 265 patients with colon (n=239) and rectal (n=26) patients who had peritoneal metastases to receive CRS plus HIPEC oxaliplatin (n=133) versus CRS alone (n=132). Early in follow-up, an improvement in relapse-free survival at one year was documented (P=0.049 by post hoc test). In fact, the curves are completely separated until 18 months when they converge. However, this beneficial effect of HIPEC was apparently not durable and did not translate into overall survival benefit. At median follow-up of 64 months, the median survival of the HIPEC group was 41.7 months and the non-HIPEC group was 41.2 months (P=0.995). The survival in both groups was unusually favorable for patients with peritoneal metastases from colon and rectal cancer but no added benefit was reported for HIPEC.

Of course, the results of the PRODIGE 7 randomized controlled trial raises questions regarding the efficacy of HIPEC as part of the treatment for selected patients with appendiceal and colorectal cancer peritoneal metastases. However, an alternative interpretation to these negative results leads one to question the study design and particularly the choice of HIPEC regimen from the PRODIGE 7 protocol.

Although used extensively throughout Europe, HIPEC oxaliplatin was rarely used in North America. Needless to say, there are multiple different HIPEC regimens currently in use, most of which are markedly different from PRODIGE 7 HIPEC (11). In our opinion, HIPEC should not be declared ineffective until other promising HIPEC regimens have been tested in randomized controlled trials.

In this manuscript, we critically examine the HIPEC-oxaliplatin used in the PRODIGE 7 randomized controlled trial. Defects in the protocol design and implementation along with pharmacologic flaws will be suggested. Then, possible changes in HIPEC will be suggested along with experience to date with these revised HIPEC regimens.

Possible PRODIGE 7 methodological flaws

Sample size

There are several issues identified in the PRODIGE 7 trial. The first one is the sample size calculation used for the study. The estimated added survival benefit from HIPEC (apart from CRS) was set at 18 months, an increased median survival from 30 to 48 months. While this estimation is very optimistic, it also creates a problem. When designing a clinical trial, it is important to decide first what the minimal relevant benefit is. If one uses a larger benefit than the minimally relevant one, when the results are negative you are left wondering if a smaller benefit is still important. This is exactly what happened in the PRODIGE 7 trial. An 18-month benefit is definitely not a minimally relevant one. Future trials need to keep this in mind. If a negative trial comes then we want to be able to dismiss the treatment, not be left wondering if a clinically relevant smaller benefit still exists. Just for comparison, the QUASAR trial had 3,000 stage 2 colorectal cancer patients randomized to receive 5-FU adjuvant treatment for 30 weeks or no treatment with an overall survival endpoint increase from 75% to 80% (12). Considering 30 weeks of chemotherapy, this trial is definitely oversized, and the meaningful benefit has been questioned. We need not limit the added benefit to 5%, but we need to define within the HIPEC community what a relevant benefit of HIPEC should be.

Cross-over option

A second issue concerns the cross-over option used in the trial. This option was ethical and probably necessary in order to recruit patients to the trial; however, it makes for some very difficult interpretations of the overall survival results. Sixteen patients (or 12%) in the CRS only arm went on to receive CRS+HIPEC at the sign of first peritoneal

recurrence as recounted at the PSOGI 2018 presentation of the PRODIGE 7 study. Adjusting for this statistically is very difficult. In our opinion, it makes it difficult to make firm conclusions about the overall survival result. On the other hand, the relapse free survival is still relevant to evaluate as it does not take into account the cross-over patients. There does appear to be an early recurrence-free survival benefit up to 18 months. The hazard ratio was 0.90 (non-significant due to sample size). The 1-year recurrence-free survival rates were 46.1% *vs.* 59% (Fisher exact P=0.049, posthoc analysis). Even though it doesn't make it all the way through the rigorous standards for a randomized controlled trial, there is a relevant benefit here worth further exploration. Furthermore, there is a recent study in the ovarian cancer field where adding HIPEC to CRS and systemic chemotherapy was proven to have a significant survival advantage. As such, there is a proof of concept for the rational use of HIPEC. In this study, the survival advantage came at no extra morbidity (13).

Use of neoadjuvant FOLFOX treatment

A third possible design and implementation flaw with the PRODIGE 7 randomized controlled trial concerns acquired resistance to oxaliplatin HIPEC caused by neoadjuvant folinic acid, 5-fluorouracil (5-FU), oxaliplatin (FOLFOX) chemotherapy. Eighty-five percent of patients in this study were pretreated with 6 cycles of FOLFOX as neoadjuvant chemotherapy. The same drugs were used systemically as were then used for HIPEC. Was chemoresistance induced by neoadjuvant FOLFOX causing diminished oxaliplatin responses from HIPEC oxaliplatin? In order to test this hypothesis, we used an *ex-vivo* analysis of programmed cell death (EVA/PCD) to assess drug-induced cell death in fresh colon cancer specimens. Cancer cells were taken from patients without prior FOLFOX treatment and from those who had received prior FOLFOX treatment. In this apoptosis assay, the lethal concentration for 50% of the cells was 3.9 μg/mL of oxaliplatin in cells from previously untreated patients. This was compared to 6.0 μg/mL in cancer cells from patients previously treated by FOLFOX (P=0.002). The degree of resistance increased significantly for patients who had received FOLFOX treatments less than 2 months prior to the EVA/PCD (P=0.002). These data would suggest that neoadjuvant chemotherapy with FOLFOX may increase drug resistance to oxaliplatin and eliminate responses to oxaliplatin with HIPEC (14,15).

Our hypothesis that neoadjuvant FOLFOX reduced or destroyed any benefit from HIPEC oxaliplatin is supported by other data. Prabhu and coworkers performed chemosensitivity testing with a collagen gel droplet-embedded culture tool. Cancer cells from patients treated with neoadjuvant chemotherapy had altered responses to oxaliplatin (20/51 patients—39.2%) as compared to cancer cells from patients treated without oxaliplatin (16/24 patients—67%, P=0.02). These authors concluded that patients with oxaliplatin-based neoadjuvant chemotherapy were more likely to show chemoresistance to oxaliplatin at the time of CRS and HIPEC (Prabhu A, Brandl A, Satoshi W, *et al.*, personal communication).

Sluiter and coworkers observed that patients treated with CRS and HIPEC had an especially poor outcome if peritoneal metastases treatments were within 1 year following adjuvant chemotherapy. Patients who did not receive neoadjuvant FOLFOX chemotherapy had a more favorable overall survival with CRS and HIPEC (P=0.002) (16).

These observations regarding the effects of neoadjuvant treatment on the benefits of CRS and HIPEC may be of use in planning treatments for colorectal peritoneal metastases. PRODIGE 7 left the sequencing of neoadjuvant chemotherapy to the discretion of the individual investigators. Any new protocol must control for the systemic treatments of the cancer to enhance rather than inhibit the effects of potentially curative surgical intervention (CRS plus HIPEC). In patients with peritoneal metastases consider CRS and HIPEC (potentially curative) earlier in the course of the therapy when systemic chemotherapy (palliative treatment) has not induced drug resistance.

Extent of peritoneal metastases

A possible fourth flaw in design and implementation concerns an absence of pretreatment estimate of the extent of peritoneal metastases. As a matter of fact, the extent of peritoneal metastases prior to the initiation of the neoadjuvant FOLFOX chemotherapy is never mentioned in the PRODIGE 7 protocol results. The only peritoneal cancer index (PCI) that is reported was determined after the neoadjuvant chemotherapy and during the peritoneal exploration that must be a part of the CRS. This means that the PCI was determined after neoadjuvant chemotherapy in 84% of patients. Whether this post-treatment PCI has meaning or not in terms of survival with CRS and HIPEC treatments has not been determined. If the effects of the systemic chemotherapy were completely durable, a post-neoadjuvant chemotherapy PCI would be acceptable.

However, since the responses to FOLFOX chemotherapy are known to be transient, one would expect that the PCI after neoadjuvant chemotherapy has little meaning in terms of the assessment of long-term prognosis. The data from PRODIGE 7 gives us no information regarding the PCI of 84% of the patients. If we assume that neoadjuvant chemotherapy was used on patients because they had a high PCI and would not be protocol eligible without a response to neoadjuvant chemotherapy, it is possible that most patients in this trial have a PCI not thought to be curable by CRS and HIPEC. In future trials an assessment of PCI prior to rather than after the administration of neoadjuvant chemotherapy is essential; as well as stratifying the randomisation according to PCI since it may be the most important predictor of outcome.

Possible pharmacologic flaws of a 30-minute oxaliplatin HIPEC

Exposure time

The duration of the HIPEC treatment is a probable pharmacological issue. The short exposure time of cancer chemotherapy to peritoneal metastases within the abdominal and pelvic space may be a critical issue. Most HIPEC treatments are for 90 minutes or 2 hours in order to maximally utilize the drug administered directly into the peritoneal space. The PRODIGE 7 HIPEC greatly expanded this theoretical criticism of HIPEC in that the usual 90-minute lavage of the chemotherapy solution was reduced to only 30 minutes. If prolonged contact of cancer chemotherapy and cancer nodules are necessary for a therapeutic response, the PRODIGE 7 HIPEC may be predicted to be inadequate.

Hyperthermia

One of the major assumptions in the HIPEC strategy concerns the augmentation of cancer control as a result of hyperthermia. It is known that hyperthermia alone can cause the death of cancer cells (17-20). Also, hyperthermia augments the cytotoxicity of cancer chemotherapy. With some cancer chemotherapy agents, hyperthermia can markedly increase the chemotherapy-induced cytotoxicity (21,22). In the short course of HIPEC used in PRODIGE 7, the hyperthermia effects must be minimal and perhaps they are not active at all. Thirty minutes of hyperthermia, even at 43 ℃, will not induce cancer control *in-vivo*. Also, 30 minutes of hyperthermia is unlikely to have any *in-vivo* major result in the augmentation of oxaliplatin cytotoxicity. Most likely, hyperthermia in the PRODIGE 7 protocol was ineffective.

5-FU limited dosage

A second pharmacologic flaw concerns the insufficient use of 5-FU along with the HIPEC oxaliplatin. Oxaliplatin alone is not an effective chemotherapy agent for colorectal cancer. It has an approximately 20% response rate (23,24). The dose of 5-FU in combination with folinic acid that will increase the response rate from 20% to 60% is approximately 2 g/m^2. In the FOLFOX regimen, 5-FU is delivered by prolonged intravenous infusion over approximately 48 hours. The dose of 5-FU in PRODIGE 7 HIPEC oxaliplatin was only 400 mg/m^2. This is an inadequate dose of 5-FU to maximize the effects of this drug combination.

Oxaliplatin exposure time

The final pharmacologic flaw regards the lack of oxaliplatin diffusion out of the from the abdominal and pelvic space to cross the peritoneal-plasma barrier and penetrate cancer nodules. This results from the short time period for HIPEC. Over the 30-minute treatment, one-third to one-half of the drug crosses the peritoneal barrier to enter the body compartment (25,26). This means that the vast majority of the IP administered oxaliplatin is removed at the end of the 30 minutes and discarded. The potential efficacy of regional (intraperitoneal) chemotherapy is measured by the area under the concentration times time curve (AUC). Although the concentration of oxaliplatin is extremely high (460 mg/m^2 administered in approximately 3 L of chemotherapy solution), the time over which that chemotherapy dwells within the peritoneal space is extremely limited. Considering that up to 230 mg/m^2 (50% of the dose) does cross the peritoneal-plasma barrier into the body compartment and produces a systemic AUC that is twice that of a 130 mg/m^2 intravenous administration (26); there is no margin for increasing the exposure time with this high dose as it will increase systemic toxicity. A lower dose of oxaliplatin with a longer perfusion time will increase exposure time but lower dose intensity. In two carefully studied patients with less than half the dose (200 mg/m^2) and four times the exposure time (120 minutes), the AUC was increased as compared to HIPEC oxaliplatin in PRODIGE 7 (27).

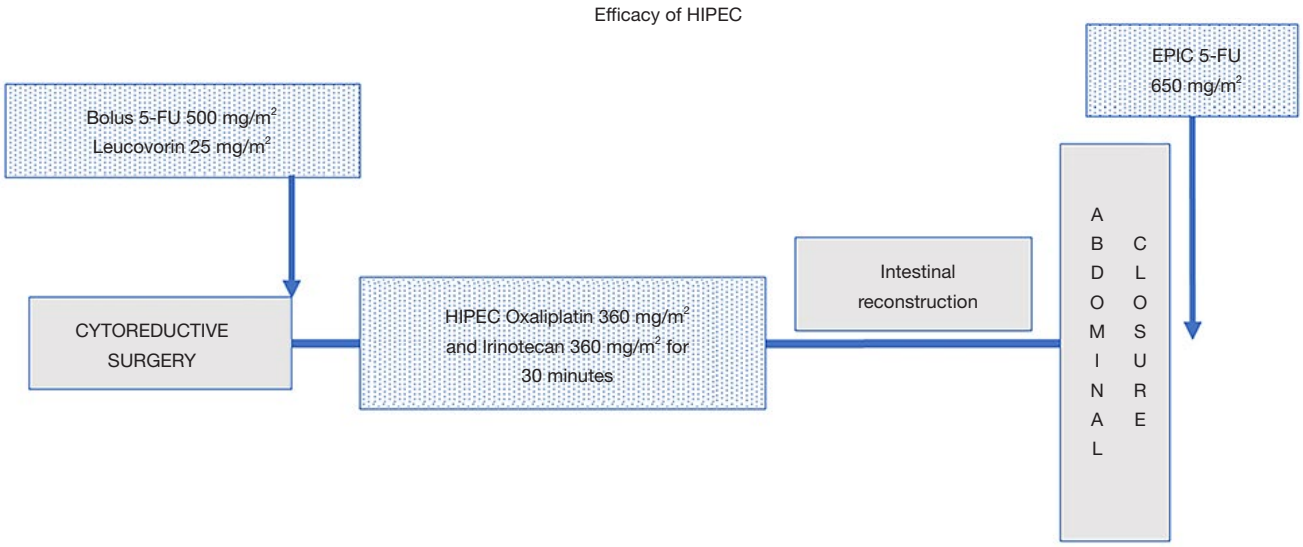

Figure 1 Efficacy of HIPEC perioperative regimen. In this treatment plan, 5-FU is given twice. Thirty minutes prior to the initiation of HIPEC an intravenous bolus of 500 mg/m^2 of 5-fluorouracil with leucovorin 25 mg/m^2 is infused. After the abdomen is closed, 650 mg/m^2 of EPIC 5-FU is instilled into the peritoneal space. The HIPEC is for 30 minutes. The chemotherapy solution contains oxaliplatin 360 mg/m^2 and irinotecan 360 mg/m^2. *, exact dose to be determined in a phase I trial.

Protocols to increase the efficacy of HIPEC oxaliplatin

As a result of lessons learned from PRODIGE 7, efforts to improve HIPEC oxaliplatin are indicated. Regardless of the shortcomings of the PRODIGE 7 study, it is clear that the HIPEC component benefit, if present, is smaller than expected. In lieu of this, suggestions to HIPEC oxaliplatin regimen improvement have developed. In our suggestion 1, this technology for HIPEC administration is fundamentally the same as in PRODIGE 7. However, the oxaliplatin is supplemented by a second drug, irinotecan, and more adequate doses of 5-FU are added to the treatment regimen.

In suggestion 2, the technology for HIPEC administration is changed in that the time interval is increased from 30 to 120 minutes. Also, a full complement of 5-FU is added to the treatment regimen.

In suggestion 3, HIPEC oxaliplatin is abandoned and a mitomycin C-based perioperative regimen is recommended. The change in HIPEC from oxaliplatin to mitomycin C may be most important in patients pretreated with neoadjuvant FOLFOX.

Suggestion 1

Cashin and colleagues in Sweden have attempted to improve the outcome in patients with HIPEC oxaliplatin by revising the PRODIGE 7 treatment plan. First, the oxaliplatin dose is reduced to 360–400 mg/m^2. Then 360–400 mg/m^2 of irinotecan is added to the HIPEC chemotherapy regimen. The same short treatment time period of 30 minutes is maintained. Also, the bolus dose of intravenous 400 mg/m^2 5-FU prior to HIPEC is maintained. However, at the completion of the cytoreduction/HIPEC procedure and after the abdominal incision has been closed, increasing dosages (500–800 mg/m^2) of 5-FU will be instilled into the peritoneal space as a 1-day early postoperative intraperitoneal chemotherapy (EPIC) treatment (*Figure 1*). This revision of the PRODIGE 7 HIPEC will be tested in a phase 1–3 clinical trial program in Sweden—the EFFIPEC (Efficacy of HIPEC) trials. The phase 1 study will be a dose titration study to evaluate what EPIC 5-FU treatment dosage is possible. Trial protocols are still pending completion.

Several important changes in the use of HIPEC with oxaliplatin are introduced with the Swedish trial. First, the patients will not have neoadjuvant FOLFOX prior to treatment with the exception of borderline resectable patients needing downstaging. Second, if acquired drug resistance to oxaliplatin has occurred, irinotecan is in this HIPEC regimen to maintain a response to perioperative chemotherapy. Third, the total dose of 5-FU is increased

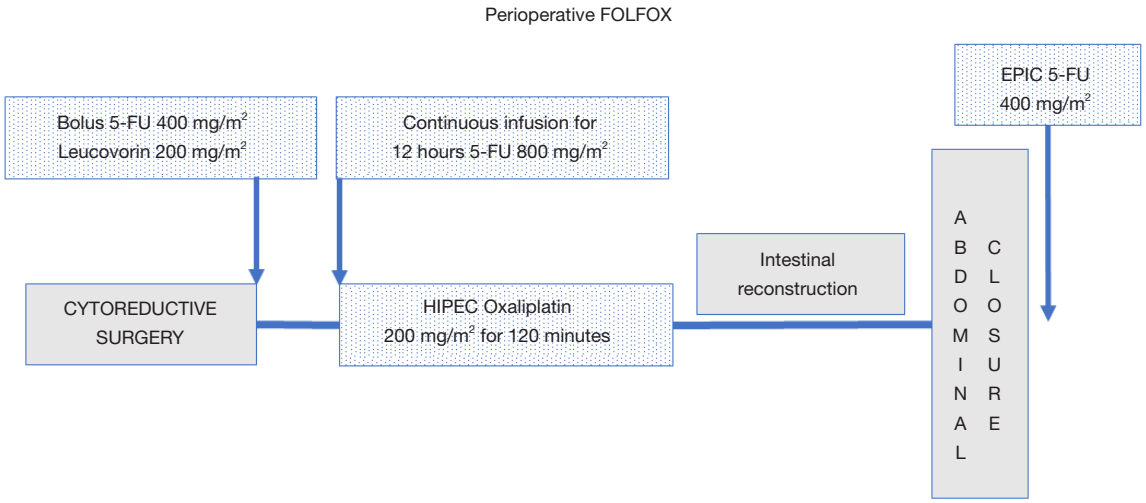

Figure 2 Perioperative FOLFOX as a HIPEC regimen. In this treatment plan, 5-FU is administered at 3 different time points. In order to saturate body tissues with 5-FU, a bolus of 400 mg/m^2 is administered approximately 30 minutes prior to the initiation of HIPEC. As HIPEC is started, a continuous intravenous infusion for 12 hours of 800 mg/m^2 of 5-fluorouracil is started. Then, after the abdomen is closed early postoperative intraperitoneal chemotherapy with 5-FU at 400 mg/m^2 in 2 L of peritoneal dialysis solution is instilled into the peritoneal space to remain for 24 hours. The HIPEC oxaliplatin is 200 mg/m^2 and the peritoneal lavage is continued for 120 minutes.

from 400 mg/m^2 in PRODIGE 7 HIPEC to 900–1,200 mg/m^2 (IV+IP together and depending on the phase 1 trial) The increased 5-FU dose is infused into the peritoneal space as EPIC. The EPIC 5-FU remains within the peritoneal space for 24 hours. The synergy of oxaliplatin and 5-FU has been restored with the Swedish Efficacy of HIPEC trials. The treatment package mirrors the FOLFIRINOX regimen.

Suggestion 2

A second effort to find increase efficacy in HIPEC oxaliplatin has been initiated by Sugarbaker (27). It is a modification of the HIPEC oxaliplatin regimen published by Stewart *et al.* (28). This is the "Perioperative FOLFOX" regimen. It is to be used in patients who have not been treated with neoadjuvant FOLFOX. In this HIPEC the dose of oxaliplatin is reduced to 200 mg/m^2. However, in order to maximally utilize heat and to maximally utilize the effects of chemotherapy absorbed through peritoneum and peritoneal metastases into the body compartment, the HIPEC treatment is continued for 2 hours. There is a bolus intravenous dose of 5-FU 400 mg/m^2 and folinic acid 200 mg/m^2 prior to initiating the HIPEC. During the HIPEC and for 24 hours afterwards, the patient receives a continuous infusion intravenously of 800 mg/m^2 of 5-FU. Prior to the patient leaving the operating theater 400 mg/m^2 of 5-FU is instilled into the peritoneal space as an EPIC chemotherapy. The intraperitoneal catheters remain clamped for 24 hours to maximize the regional effects of the EPIC 5-FU (*Figure 2*).

Important changes in Perioperative FOLFOX HIPEC are introduced. This management plan attempts to reproduce the FOLFOX regimen routinely used by medical oncologists in the operating room. The 5-FU total dose is increased from 400 to 1,600 mg/m^2 and 800 mg of this drug is given by continuous intravenous infusion. Therefore, the synergy of oxaliplatin and 5-FU should be restored. The dose of oxaliplatin is reduced from 460 mg/m^2 in PRODIGE 7 to 200 mg/m^2 in Perioperative FOLFOX but with a 120-minute dwell. As a result, 80–90% of the drug moves through the peritoneal surface from abdominal-pelvic space to the body compartment. Also, the 2 hours of hyperthermia should maximize by heat oxaliplatin cytotoxicity. The pharmacologic flaws of PRODIGE 7 are corrected by Perioperative FOLFOX HIPEC.

Suggestion 3

Another alternative to the HIPEC oxaliplatin used by PRODIGE 7 is to go back to mitomycin C-based

perioperative chemotherapy. This approach may be appropriate for patients who have been treated with neoadjuvant FOLFOX. This is what has been done in HIPECT4 trial which has recently completed its accrual in Spain (29). Also, mitomycin C alone is to be used in the CATCH trial not yet activated in the USA, a modification which is appealing because the HIPEC utilizes a doublet rather than monotherapy—mitomycin C and cisplatin HIPEC. This has been used with safety and efficacy for HIPEC in gastric cancer. These mitomycin C-based HIPEC treatments are usually a 90-minute heated lavage and a sensitizing dose of 400 mg/m^2 of 5-FU should be given approximately 30 minutes prior to the initiation HIPEC. A full dose of 5-FU with mitomycin C should be explored.

In summary, three different approaches have been suggested to improve the outcome in patients treated for peritoneal metastases from appendiceal and colorectal cancer. Both rely heavily on pharmacologic principles previously established for maximal drug effectiveness. In the Swedish protocol, irinotecan is used in order to combat possible chemoresistance due to previous oxaliplatin use and a 24-hour EPIC use is implemented to increase peritoneal exposure time to chemotherapeutic treatment. In the Washington Hospital Center protocol, the details of a FOLFOX chemotherapy cycle is introduced into the operating theater. The synergy of 5-FU and oxaliplatin are sought. Finally, HIPEC with mitomycin C alone or mitomycin C with cisplatin was suggested. Regardless of whether one of these protocols will prove themselves, further preclinical and translational validation is needed to continue to develop possible improvements to these locoregional treatments of colorectal and appendiceal tumors with peritoneal metastases.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*, for the focused issue "Intraperitoneal Chemotherapy for Peritoneal Metastases: HIPEC, EPIC, NIPEC, PIPAC and More". This article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-2020-05). The focused issue was sponsored by the Peritoneal Surface Oncology Group International (PSOGI). PHS served as the unpaid Guest Editor of the focused issue. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Cashin P, Sugarbaker PH. Hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal and appendiceal peritoneal metastases: lessons learned from PRODIGE 7. J Gastrointest Oncol 2021;12(Suppl 1):S120-S128. doi: 10.21037/jgo-2020-05

