European Journal of Surgical Oncology 45 (2019) 400–402

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

HIPEC with oxaliplatin for colorectal peritoneal metastasis: The end of the road?

Wim Ceelen*

Department of GI Surgery and Cancer Research Institute Ghent (CRIG), Ghent University Hospital, B-9000, Ghent, Belgium

ARTICLE INFO

Article history:
Accepted 30 October 2018
Available online 31 October 2018

Keywords:
Colorectal
HIPEC
Peritoneal
Metastasis

ABSTRACT

In patients with colorectal peritoneal metastases (PM), the use of cytoreductive surgery (CRS) and HIPEC with oxaliplatin (OX) is increasingly used. The results of the recently reported randomized Prodige 7 trial failed to show a difference in overall survival between patients undergoing CRS alone versus CRS combined with HIPEC using high dose OX. The trial was not designed or powered, however, to detect a potentially clinically meaningful benefit in locoregional disease control. Here, I address some potential explanations for the lack of benefit in the Prodige 7 trial, including OX efficacy issues, adverse effects of intraperitoneal high dose glucose, and potential drawbacks of the use of hyperthermia.

Introduction

Colorectal cancer (CRC) is one of the commonest causes of cancer related death in developed countries. Peritoneal carcinomatosis is present in 25–30% of patients with recurrent or metastatic colorectal cancer; in approximately 3% isolated peritoneal disease without systemic spread is observed [1]. These patients are amenable for locoregional therapy consisting of surgical cytoreduction followed by intraoperative hyperthermic intraperitoneal chemoperfusion (HIPEC). The combined approach results in a median survival of more than 30 months [2,3]. Historically, several chemotherapeutic drugs including the platinum compounds, mitomycin C, fluorouracil, and irinotecan have been used in HIPEC, either as a single agent or as a combination regimen. Since its introduction by Elias et al., in 2002, many centers have adopted oxaliplatin (OX), the standard of care in the adjuvant and palliative chemotherapy treatment of CRC, as the drug of choice in HIPEC treatment [4]. The available evidence from retrospective and non-randomized studies in CRC suggests that the survival benefit from CRS and HIPEC is independent from the type of intraperitoneal (IP) drug regimen used [5].

The recently presented Prodige 7 trial, which compared cytoreductive surgery (CRS) alone with CRS combined with HIPEC using OX, failed to demonstrate an overall survival advantage in the HIPEC arm, while the 60 day complication rate was significantly higher [6]. Here, I suggest possible explanations for this lack of benefit and propose an approach to further evaluate the use of intraperitoneal drug delivery in CRC.

What did the prodige 7 trial show?

Patients with histology proven peritoneal metastases (PM) from CRC, with a peritoneal cancer index (PCI) < 25 and who underwent optimal surgery (residual tumor ≤1 mm), where randomized to either no HIPEC or HIPEC with OX. The primary endpoint was overall survival (OS). Over a six-year period (2008–2014), 265 patients were randomized. The HIPEC arm patients developed more abdominal and extra-abdominal complications. Overall survival was unexpectedly high in both groups, but did not differ significantly (41.7 versus 41.2 months in the HIPEC and control arm respectively, hazard ratio (HR) 1.00 (95% confidence interval (CI): 0.73–1.37). Similarly, no statistically significant difference was observed in disease free survival (DFS, 13.1 versus 11.1 months, HR 0.91, 95% CI 0.69–1.19). The Kaplan Meier curves did show, however, a trend towards a better DFS in the first 18 months after surgery. In a subgroup analysis according to PCI, median OS was significantly better in patients with a PCI between 11 and 15.

* Department of GI Surgery, Ghent University Hospital, C Heymanslaan 10, B-9000, Ghent, Belgium.
E-mail address: Wim.ceelen@ugent.be.

https://doi.org/10.1016/j.ejso.2018.10.542
0748-7983/

Possible explanations for the Prodige 7 findings

Limitations of the study design

The most important explanation of the lack of benefit is, without doubt, the overestimation of the effect size in the design of the trial. Several studies have shown that HIPEC is ineffective when gross residual disease is present, and complete CRS is the major determinant of the efficacy of the combined treatment. The Prodige 7 investigators hypothesized a huge treatment effect of HIPEC alone: the estimated improvement in median OS was 18 months (from 30 to 48 months). To put this number in perspective, the desired improvement in median OS in systemic therapy trials is usually around 5 months [7]. Obviously, the magnitude of the estimated treatment effect was based on the limited sample size.

A second issue is the choice of the primary endpoint. It is well known that only a minority of CRC patients is cured after CRS and HIPEC, and most of them will receive multiple and diverse systemic treatments. The overall survival effect of HIPEC will therefore be obscured by the differences in systemic treatment and the associated response and toxicity. Since CRS/HIPEC is a locoregional treatment aimed at PM, peritoneal recurrence free survival or an equivalent endpoint may have been more appropriate.

Uncertain efficacy of oxaliplatin

The in vitro cytotoxicity of oxaliplatin on colorectal cancer cell lines is concentration and time dependent. The IC50 varies between 3 and 10 μg/mL in published studies [8]. The Prodige 7 investigators used a Dextrose 5% (D5%) perfusate volume of 2 L/m^2 and a dose of 360–460 mg/m^2, resulting in a peritoneal oxaliplatin concentration of 210–230 μg/mL, which far exceeds the in vitro IC50 threshold. In comparison, the standard iv dose of 85 mg/m^2 results in a blood concentration of approximately 35 μg/mL. However, although OX is considered as one of the standard drugs in the treatment of locally advanced and metastatic CRC, not all metastatic CRC patients respond to OX. In fact, in patients with a mucinous histology, which is more common in PM, response rates after first line therapy as low as 18% were observed [9,10]. In addition, previous chemotherapy regimens may induce alterations in the cancer cell genome and in OX sensitivity [11]. Whether the high peritoneal drug concentrations during HIPEC can overcome genetically determined resistance mechanisms in colorectal cancer cells is unclear.

A second important treatment parameter is drug exposure time. Although OX is a non cell cycle dependent agent, results from in vitro experiments and mathematical modeling suggest that, in addition to drug concentration, exposure time is a major determinant of the cytotoxicity of the platinum compounds. Levasseur and coworkers showed that the in vitro cytotoxicity of cisplatin can be modeled as a single Hill model, and that exposure time and drug concentration are equally important for the cytotoxic effect (in detail: $IC_{50} = (k/T)\exp^{(1/n)}$ with T = exposure duration, k = exposure constant and n = concentration coefficient) [12]. A recent study using ovarian cancer cell lines showed that prolonging exposure time to cisplatin from 1 h to 2 h was at least as effective as the addition of hyperthermia (42 °C) [13]. Exposure-response relationships and the effect of hyperthermia on oxaliplatin cytotoxicity in colon cancer cell lines were reported by Kirstein et al. [14] They found that incubation of SW620 colon cancer cells during 2 h at 37 °C or 42 °C resulted in similar dose-response curves. On the other hand, the mean IC50 for cells treated during 30 min was significantly higher compared to a treatment duration of 2 h (10.6 versus 2.8 μg/mL, P = 0.02). The authors concluded that cell kill effects are depending on treatment time, and that treatment for 2 h is superior to treatment for 30 min.

Possible adverse effects of the Carrier solution (Dextrose 5%)

Oxaliplatin is degraded rapidly in the presence of chloride ions to a monochloro–monooxalato complex [15]. As a consequence, oxaliplatin should be dissolved, according to the manufacturer's instructions, in chloride free solutions such as D5%. Theoretically, D5% has the advantage of being moderately hypo-osmolar (252 mOsm/L), resulting in an osmotic force that is directed from the peritoneal cavity towards the peritoneal (and tumor) tissue, and this may enhance drug diffusion. However, the use of D% is associated with clinical and theoretical drawbacks. First, D5% causes metabolic and electrolyte shifts including hyperglycemia and hyponatremia, which pose a challenge to the anesthesiologist and may exacerbate surgical morbidity [16,17]. Second, glucose and glucose degradation products (GDP) have adverse effects on the ultrastructure and function of the peritoneum. Exposure of the peritoneum to high glucose concentrations leads to production of transforming growth factor-beta1 (TGF-β1), which is implicated in the pathogenesis of peritoneal carcinomatosis [18]. Heat sterilization of commercial glucose solutions leads to the formation of significant amounts of glucose degradation products (GDP) [19]. These GDP's, in turn, are precursors of Advanced Glycation End products (AGEs), which result from a chemical reaction when reduced carbohydrates (such as glucose) react with amino acids or nucleotides. High levels of GDPs and AGEs are involved in oxidative stress, induce apoptosis in human leukocytes and cause degradation of mesothelial cells and the peritoneal membrane. Third, the acidic pH of D5% solution (3.2–6.5) adversely affects mesothelial cell production of interleukin-6 and prostaglandin, and may therefore interfere with peritoneal host defense [20,21]. Of note, recent findings suggest that chloride solutions *can* be used as carrier solution for OX. Mehta and coworkers measured OX and OX degradation products in vitro at 42 °C, after dilution in different carrier solutions [22]. They found that the fractions of intact oxaliplatin after 30 min and 2 h were 91.7% and 85.3% with PD 1.36% solution, and 89.3% and 79.2% with NaCl 0.9% respectively. Moreover, the relatively limited degradation resulted in the formation of $[Pt(DACH)Cl_2]$, which is in fact the active cytotoxic form of the drug.

Possible adverse effects of hyperthermia

Hyperthermic administration is based on in vitro and animal data that suggest synergism with the anticancer activity of OX. Atallah and coworkers found that the oxaliplatin IC_{50} in the Caco-2 cell line decreased from 35 μg/mL at 37 °C to 6.5 μg/mL at 42 °C after a 1 h exposure [23]. Possibly, this thermal enhancement is based on increased DNA cross-linking efficiency [24]. Others were unable to confirm thermally enhanced cytotoxicity of oxaliplatin in vitro [14]. There are at present no clinical studies in patients comparing normothermic with hyperthermic chemoperfusion. However, hyperthermia elicits the expression of heat shock proteins (HSP's), which were shown to exert antiapoptotic and proliferative effects, and induce resistance to chemotherapy [25,26]. Also, temperatures above 41 °C may cause scald injury to the peritoneum, which is already extensively damaged by the CRS [27]. Finally, the effects of hyperthermia on the patient's peritoneal immune environment is uncertain. Some have suggested that locoregional hyperthermia acts as a form of immunotherapy in metastatic cancer [28]. Others have shown, however, adverse effects of local heating on overall tumor immunity [29]. In general, hardly anything is known on the postoperative peritoneal immune environment, and how it is affected by the surgery itself and by the HIPEC treatment components.

Conclusions and implications for further research

- Given its limited power to detect a clinically meaningful benefit, the results of the Prodige 7 trial cannot exclude a potential benefit in locoregional disease control in the first 18 months after surgery. Even without any difference in OS, a decrease in peritoneal recurrence would be a sufficient ground for the continued use of HIPEC in CRC. This is comparable with the use of chemoradiation in locally advanced rectal cancer, which lowers local recurrence rate and is accepted as the standard of care even though an effect on OS has never been demonstrated.
- All patients undergoing CRS and HIPEC for CRC should, ideally, be included in prospective translational and clinical trials. These trials should study peritoneal recurrence rate as the primary endpoint, and include patient reported outcomes. The existing national and international collaborative groups such as the Peritoneal Surface Oncology Group International (PSOGI) should undertake prospective, multicenter, multi-arm, multi-stage pragmatic clinical trials with the support of trial methodologists [30]. These trials should, as much as possible, include translational endpoints that address the most important uncertainties: which drug for which patient? How do the treatment components and variables affect the peritoneal environment and natural immune defense? How can biomarkers predict and detect peritoneal recurrence?
- One of the major limitations of HIPEC is the short treatment duration. Preclinical data suggest that IP prolonged release formulations administered as *thermosensitive hydrogels* allow prolonged (up to 5 days) exposure of residual peritoneal cancer, and at the same time act as postoperative adhesion barriers [31–33]. Collaborative efforts should, by priority, aim to bring these new platforms to early clinical testing.

Acknowledgment

W Ceelen is a senior clinical researcher from the Fund for Scientific Research – Flanders (FWO).

References

[1] Ceelen WP, Flessner MF. Intraperitoneal therapy for peritoneal tumors: biophysics and clinical evidence. Nat Rev Clin Oncol 2010;7(2):108–15.
[2] Elias D, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28(1):63–8.
[3] Franko J, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer 2010;116(16):3756–62.
[4] Elias D, et al. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol 2002;13(2):267–72.
[5] Huang CQ, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival for peritoneal carcinomatosis from colorectal cancer: a systematic review and meta-analysis of current evidence. Oncotarget 2017;8(33):55657–83.
[6] Quenet F, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. J Clin Oncol 2018;36(18):1.
[7] Venook AP, et al. Effect of first-line chemotherapy combined with Cetuximab or Bevacizumab on overall survival in patients with KRAS wild-type Advanced or metastatic colorectal cancer: a randomized clinical trial. Jama 2017;317(23):2392–401.
[8] Kornmann M, et al. Oxaliplatin exerts potent in vitro cytotoxicity in colorectal and pancreatic cancer cell lines and liver metastases. Anticancer Res 2000;20(5A):3259–64.
[9] Catalano V, et al. Mucinous histology predicts for poor response rate and overall survival of patients with colorectal cancer and treated with first-line oxaliplatin- and/or irinotecan-based chemotherapy. Br J Canc 2009;100(6):881–7.
[10] Hugen N, et al. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol 2014;25(3):651–7.
[11] Andreou A, et al. Adjuvant chemotherapy with FOLFOX for primary colorectal cancer is associated with increased somatic gene mutations and inferior survival in patients undergoing hepatectomy for metachronous liver metastases. Ann Surg 2012;256(4):642–50.
[12] Levasseur LM, et al. Modeling of the time-dependency of in vitro drug cytotoxicity and resistance. Cancer Res 1998;58(24):5749–61.
[13] Facy O, et al. Comparison of hyperthermia and adrenaline to enhance the intratumoral accumulation of cisplatin in a murin model of peritoneal carcinomatosis. J Exp Clin Canc Res 2011;30.
[14] Kirstein MN, et al. Exposure-response relationships for oxaliplatin-treated colon cancer cells. Anti Cancer Drugs 2008;19(1):37–44.
[15] Alberto ME, et al. The degradation pathways in chloride medium of the third generation anticancer drug oxaliplatin. J Phys Chem B 2008;112(35):10765–8.
[16] Ceelen WP, et al. Safety and efficacy of hyperthermic intraperitoneal chemoperfusion with high-dose oxaliplatin in patients with peritoneal carcinomatosis. Ann Surg Oncol 2008;15(2):535–41.
[17] Tsukamoto JS, Belotto de Oliveira M, Peixoto RD. Tonic-clonic seizure following cytoreductive surgery with intraperitoneal oxaliplatin: a case report and review of the literature. Case Rep Oncol 2016;9(1):89–94.
[18] Lv ZD, et al. The cytotoxic effect of TGF-beta1 on mesothelial cells via apoptosis in early peritoneal carcinomatosis. Oncol Rep 2012;27(6):1753–8.
[19] Haybrard J, et al. Factors generating glucose degradation products in sterile glucose solutions for infusion: statistical relevance determination of their impacts. Sci Rep 2017;7(1):11932.
[20] Witowski J, et al. Effect of lactate-buffered peritoneal dialysis fluids on human peritoneal mesothelial cell interleukin-6 and prostaglandin synthesis. Kidney Int 1995;47(1):282–93.
[21] Kumar PS, et al. Glucose-based dialysis fluids inhibit innate defense against Staphylococcus aureus. Mol Immunol 2015;67(2 Pt B):575–83.
[22] Mehta AM, et al. Stability of oxaliplatin in chloride-containing Carrier solutions used in hyperthermic intraperitoneal chemotherapy. Int J Pharm 2015;479(1):23–7.
[23] Atallah D, et al. Thermal enhancement of oxaliplatin-induced inhibition of cell proliferation and cell cycle progression in human carcinoma cell lines. Int J Hyperther 2004;20(4):405–19.
[24] Halamikova A, et al. Biochemical studies of the thermal effects on DNA modifications by the antitumor cisplatin and their repair. Chembiochem 2007;8(16):2008–15.
[25] Kepenekian V, et al. Impact of hyperthermic intraperitoneal chemotherapy on Hsp27 protein expression in serum of patients with peritoneal carcinomatosis. Cell Stress Chaperones 2013;18(5):623–30.
[26] Grimmig T, et al. Upregulated heat shock proteins after hyperthermic chemotherapy point to induced cell survival mechanisms in affected tumor cells from peritoneal carcinomatosis. Cancer Growth Metastasis 2017;10.1179064417730559.
[27] Fujimoto S, et al. Prevention of scald injury on the peritoneo-serosal surface in advanced gastric cancer patients treated with intraperitoneal hyperthermic perfusion. Int J Hyperther 1991;7(4):543–50.
[28] Toraya-Brown S, Fiering S. Local tumour hyperthermia as immunotherapy for metastatic cancer. Int J Hyperther 2014;30(8):531–9.
[29] Bear AS, et al. Elimination of metastatic melanoma using gold nanoshell-enabled photothermal therapy and adoptive T cell transfer. PLoS One 2013;8(7). e69073.
[30] Wason J, et al. Some recommendations for multi-arm multi-stage trials. Stat Methods Med Res 2016;25(2):716–27.
[31] De Smet L, et al. Optimization of drug delivery systems for intraperitoneal therapy to extend the residence time of the chemotherapeutic agent. ScientificWorldJournal 2013;2013:720858.
[32] De Clercq K, et al. Genipin-crosslinked gelatin microspheres as a strategy to prevent postsurgical peritoneal adhesions: in vitro and in vivo characterization. Biomaterials 2016;96:33–46.
[33] Ohta S, et al. Intraperitoneal delivery of cisplatin via a hyaluronan-based Nanogel/in situ cross-linkable hydrogel hybrid system for peritoneal dissemination of gastric cancer. Mol Pharm 2017;14(9):3105–13.