Hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal peritoneal metastases: still a necessity?

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The management of peritoneal metastases (PM) remains one of the greatest challenges in patients with metastatic colorectal cancer (mCRC). While systemic chemotherapy renders good results in the treatment of colorectal liver metastases, it is poorly efficacious in the management of colorectal peritoneal metastases (CRPM). When treated with chemotherapy alone, five-year survival in patients with CRPM is less than five percent.¹ Verwaal et al² demonstrated in a randomised trial (RCT) that cytoreductive surgery (CRS) with mitomycin C based hyperthermic intraperitoneal chemotherapy offered a significantly improved survival compared to systemic chemotherapy alone (22.3 v 12.6 months). Subsequent studies utilised oxaliplatin as the HIPEC agent. Oxaliplatin had proven efficacy as first line systemic treatment in mCRC,³ and was found to be safe intraperitoneally.⁴ Studies reported a median survival of 27-32 months in selected patients when treated with CRS and oxaliplatin HIPEC.^{5,6} To date, there are no prospective studies comparing the efficacy of different HIPEC agents. With no accepted consensus on the preferred HIPEC agent, the choice of oxaliplatin or mitomycin C is being based largely on country and institutional preference.⁷

Recent evidence from three RCTs has raised significant doubts about the efficacy of HIPEC, particularly oxaliplatin HIPEC. The PRODIGE 7 RCT compared outcomes following complete cytoreduction alone, and with the addition of oxaliplatin HIPEC. It reported no survival benefit with oxaliplatin HIPEC in addition to successful complete cytoreduction (41.7 v 41.2 months). Sub-group analysis did suggest potential benefit with HIPEC in patients with a PCI of 11-15. Worryingly however, those receiving HIPEC had a significantly higher complication rate (24.1% v 13.6%, $p=0.03$). In the prophylactic setting, the ProphyloChip trial (NCT01226394)⁸ compared the utility of 'second look' CRS with oxaliplatin HIPEC versus standard surveillance for asymptomatic patients six months following primary tumour resection deemed high risk for peritoneal recurrence. High risk was defined as minimal CRPM resected with the primary,

ovarian metastases or perforated primary tumour. While CRPM were found in 52% of patients undergoing second look surgery, there was no difference in three-year disease free (DFS) or overall survival (OS) between the two arms (79% v 80%). The COLOPEC RCT (NCT02231086)⁹ compared the use of adjuvant oxaliplatin HIPEC with adjuvant systemic chemotherapy versus adjuvant systemic chemotherapy alone after pT4 or perforated primary tumour resections. There was no difference in peritoneal metastasis free survival (77% v 81%) by diagnostic laparoscopy at 18 months in either group, with no difference in DFS and OS.

Despite their limitations, these RCTs are landmark studies in a field with paucity of high quality evidence. These trials have led to significant debate on the role of HIPEC, with some experts calling for CRS alone to become standard treatment, with HIPEC to be abandoned altogether.¹⁰

These studies highlight a number of salient points. Firstly, given these studies utilised oxaliplatin; it suggests that oxaliplatin is likely suboptimal as a HIPEC agent. Unlike mitomycin C, there is no randomised data supporting the use of CRS with oxaliplatin HIPEC. In the early 2000s, the use of oxaliplatin as a HIPEC agent coincided with its implementation as first line systemic therapy,³ as oncologists were possibly more confident in its efficacy. Additionally, 30 minutes of intraperitoneal exposure with oxaliplatin, compared to 90 minutes with mitomycin C perhaps made it more appealing to surgeons.

While the results of these studies support discontinuation of oxaliplatin as a HIPEC agent, they do not translate to abandoning HIPEC altogether. CRS with mitomycin C based HIPEC should still remain as the recommended treatment for resectable low volume CRPM. It does however bring to light the urgent need for further high quality research in this field. Advances in translational oncology and

collaborative research would allow exploration into identifying other potential intraperitoneal agents, and evaluating other forms of intraperitoneal delivery of drugs to complement high quality cytoreductive surgery.

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