Editorial Commentary



# Outlook on PRODIGE 7: are we refuting hyperthermic intraperitoneal chemotherapy a bit too early in colorectal peritoneal metastases?

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Ever since introduction of aggressive cytoreduction surgery by Prof. Paul Sugarbaker for peritoneal surface malignancies, the treatment paradigm for stage IV colorectal cancers has changed drastically (1). Cytoreductive surgery (CRS) involves the removal of all macroscopic disease, which may entail multi-visceral resection with total peritonectomy. The efficiency of CRS is measured in terms of various published scales, one of the most popular being the "Completeness of Cytoreduction" (CC) score (2). Role of hyperthemic intra-peritoneal chemotherapy (HIPEC) is supplemental by controlling the minimal residual disease.

Management of colorectal peritoneal metastases (CRPM) involves CRS with an aim of a CC-0 cytoreduction. Verwaal *et al.* showed the superiority of aggressive CRS with HIPEC when compared against palliative surgery and systemic therapy in terms of overall survival (P<0.0001) (3). Morbidity and mortality have been shown to be comparable to other radical surgeries being done for cancer control (4). Ever since CRS establishing a firm ground in the management protocols of CRPM, the additional value of HIPEC has been the matter of research and debate (5).

PRODIGE 7 trial is the first randomised trial evaluating HIPEC after CRS for CRPM (6). With 265 patients randomised and a median follow-up of 63.8 months, the median overall survival was 41.7 months in the CRS plus HIPEC group and 41.2 months in the CRS group (P=0.99). At 60 days, grade 3 or worse adverse events were more commonly observed in the CRS-HIPEC arm [34 (26%) of 131 *vs.* 20 (15%) of 130; P=0.035]. With an overall higher rate of morbidity and no survival benefit, authors have proposed against the use of HIPEC alongside CRS for treatment of CRPM. However, there are several caveats to be considered while drawing conclusions from the trial.

Rovers *et al.* have pointed towards the randomisation of patients with favourable disease biology in the trial (7). The randomised patient cohort does not represent the entire gamut of patients with CRPM. Patients who were heavily pre-treated with intravenous oxaliplatin based chemotherapy and a stable peritoneal disease were preferentially selected for randomisation leading to superior survival rates in either arm.

The value of HIPEC remains untested amongst patients with CRPM who undergo upfront CRS without any preoperative systemic therapy. The role of neoadjuvant chemotherapy in patients with resectable disease will be defined by the CAIRO6 trial (8). Bhatt *et al.* have pointed toward the need of patient stratification with respect to pathological response to the neoadjuvant chemotherapy to help identify patient sub-groups who might potentially benefit from an additional therapy like HIPEC (9).

The heterogeneity in timing of administration of chemotherapy with or without the use of anti-VEGF therapy was a point of contention in the trial (10). The role of single agent, short duration oxaliplatin based intra-peritoneal chemotherapy has been questioned by many, including the authors themselves. Superior combination chemotherapy regimens in the future will add to more meaningful derivation. Parameters reflective of aggressive

of disease namely tumour sidedness, histological sub-type and grade of tumour need to be considered while stratifying patients in future studies.

Till further research on the matter is available, CRS with an aim of CC-0 shall remain the cornerstone of treatment with emphasis on optimisation of surgical quality control and appropriate patient selection. The role of HIPEC certainly cannot be dismissed without further research on the subject after adjusting for the aforesaid caveats.

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