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ASO AUTHOR REFLECTIONS

ASO Author Reflections: Is There Still a Role for Intraperitoneal Oxaliplatin for Colorectal Peritoneal Metastases?

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PAST

Since the development of oxaliplatin (Ox) as a potent intravenous (IV) cytotoxic drug for metastatic colorectal cancer in the late 1990s, there were high hopes for its efficacy in the clinical setting of peritoneal metastases (PM). Its benefit was mostly proved in combination with IV fluorouracil (5-FU).[1] Oxaliplatin was rapidly adopted as an intraperitoneal (IP) drug, as the molecule fulfilled at that time all conditions to be an ideal antineoplastic agent for IP therapy, including documented activity against the malignant disease to be treated. During the same period, hyperthermic intraperitoneal chemotherapy (HIPEC) gained popularity for PM of colorectal origin. Several studies suggested increased local absorption of IP oxaliplatin when combined with 5-FU systemically. Thus, high-dose oxaliplatin (Ox) associated with intravenous 5-FU quickly became the regimen of choice after cytoreductive surgery (CRS).[2]

PRESENT

The recently published PRODIGE7 trial randomized patients with colorectal PM after CRS to high-dose Ox-based HIPEC and IV 5-FU versus no HIPEC. The majority of patients received perioperative systemic chemotherapy in addition. Equivalent overall survival results were reported for the two arms (41.7 vs. 41.2 months), but the morbidity rate was significantly higher in the HIPEC group at 60 days (26% vs. 15%).[3] Possible causes of failure of the high-dose Ox-based HIPEC are mainly of a pharmacokinetic nature, namely single-shot administration and short duration. Thus, it cannot be inferred from PRODIGE7 that Ox is the wrong drug for any IP modality.[3] In parallel, pressurized intraperitoneal aerosol chemotherapy (PIPAC) was developed as a new technique for repeatedly delivering cytotoxic agents in the clinical setting of unresectable peritoneal disease. Oxaliplatin-based PIPAC became a valuable option for patients with unresectable PM of colorectal origin who had previously undergone standard lines of treatment.[4] However, in the development of this new modality, the association of oxaliplatin-based PIPAC with IV 5-FU was not thoroughly studied until recently.[4,5]

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FUTURE

While several IP treatment modalities are currently available, they still need to provide response to the main needs in PM of colorectal origin. Potential treatment settings include (1) consolidation of CRS for resectable patients, (2) better response at induction treatment for borderline-resectable patients, and (3) improved quality of life with at least stable disease for unresectable patients. Oxaliplatin still seems to be a valuable cytotoxic agent for IP use, potentially improved by association with IV 5-FU and repeated administrations. Future clinical trials should aim to define and test the best treatment indications and protocols, and to find solutions to overcome acquired resistance to oxaliplatin. Selection of patients for the right IP regimen using chemosensibility assay of primary cultures or organoid is one of the promising pathways for the future, but the key for further development remains a round trip from bedside to bench and from bench to bedside.

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