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LETTER TO THE EDITOR

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Colorectal Cancer: Potential use of Perioperative Desmopressin to Reduce Allogenic Blood Transfusion Rates

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Dear Editors,

In the last decade, the correlation between cancer surgery outcome, disease recurrence, and patient survival with perioperative blood transfusion has been a topic of intense debate. In this regard, a large number of studies suggesting a direct link between perioperative blood transfusions and poorer prognosis in colorectal, liver, gastric, esophageal, and pancreatic cancers have been recently published.[1–4] In the August issue of the *Journal of Gastrointestinal Surgery*, Saxena and colleagues conducted an elegant study assessing the impact of massive allogenic blood transfusion (MABT) on perioperative outcomes and overall survival in patients with peritoneal carcinomatosis undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC).[5] After critically reviewing more than 900 cases, the authors demonstrated that MABT is associated with an increased incidence of prolonged hospital stay, in-hospital mortality, and grade III/IV morbidity. Additionally, MABT was found to be an independent risk factor for reduced overall survival in patients with colorectal cancer peritoneal carcinomatosis (CRPC). Given that CRS/HIPEC is a long, complex, and aggressive multimodality surgical approach, nearly 25% of CRPC patients undergoing this procedure require MABT due to high volume blood loss. Besides emphasizing the detrimental impact on cancer surgery outcomes and survival, especially in colorectal cancer, authors highlight the urgent need to manage perioperative care from various aspects to minimize the rates of perioperative blood transfusions in CRS/HIPEC.

The abovementioned remarks are in line with our previous research involving the use of desmopressin (dDAVP) as a surgical adjuvant in oncology.[6] dDAVP is a blood-saving agent with more than 40 years of extensive clinical use in patients undergoing operations characterized by large blood loss and transfusion requirements. With proven hemostatic and antimetastatic properties, dDAVP acts as a selective agonist of vasopressin type 2 receptors present in endothelium and tumor cells.[7,8] Activation of these endothelial receptors causes an abrupt release of hemostatic factors including, but not limited to, factor VIII, P-selectin, and von Willebrand Factor (vWF), from systemic microvasculature.[8] vWF is a blood glycoprotein involved in multiple biological processes such as hemostasis, angiogenesis, inflammation, cancer cell apoptosis, and metastatic resistance.[8–11] On tumor cells, dDAVP triggers antiproliferative signaling pathways involving cAMP/PKA axis and favors the production of angiostatin, a well-known angiostatic endogenous molecule. In preclinical animal studies, administration of clinically relevant doses of dDAVP produced angiostatic and antimetastatic effects in experimental surgical settings.[7,12,13] Interestingly, dDAVP treatment was capable of impairing progression of surgically implanted colorectal cancer cells and inhibiting metastatic disease in liver. Moreover, in an experimental animal model of CRPC, perioperative intravenous dDAVP administration was also associated with a reduction in ascites accumulation and formation of intestinal colorectal cancer tumor nodules in

Letter to the editor in response to "*Allogenic Blood Transfusion Is an Independent Predictor of Poorer Peri-operative Outcomes and Reduced Long-Term Survival after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: a Review of 936 Cases*" by Dr. Saxena and colleagues, published in the August issue of the *Journal of Gastrointestinal Surgery.*

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comparison to control vehicle-treated animals.[7] Taken into account the antitumor activity of dDAVP, as well as its well-characterized effects on hemostasis and safety profile, the compound was recently evaluated in a phase II dose-escalation trial as adjuvant therapy during breast cancer surgical excision (NCT01606072). dDAVP appeared safe when infused slowly before and after surgery at a dose of 1 μg/kg, and treatment was associated with reduced intraoperative bleeding, a raise in vWF plasma levels and rapid post-operative drop in circulating tumor cells.[14] Furthermore, with the aim of assessing safety, tolerability, and symptom control, a phase II clinical trial evaluating the potential benefits of dDAVP in patients with colorectal cancer with rectal bleeding (NCT01623206) is currently ongoing.

To address the need of minimizing the use of blood transfusions in this clinical context, Dr. Saxena and colleagues present two interesting alternative proposals with promising clinical results: early administration of fresh frozen plasma combined with restrictive fluid resuscitation[15] and upfront tranexamic acid treatment in combination with cryoprecipitate.[16] In comparison to fresh frozen plasma or tranexamic acid,[17] dDAVP treatment may potentially result in multiple and additional therapeutic effects by acting on tumor and endothelial cell vasopressin type 2 receptors. dDAVP reduces intraoperative bleeding, minimizing the need of blood transfusions by favoring the release of vWF and other hemostatic factors from microvasculature. Additionally, in cooperation with HIPEC, dDAVP could help to destroy minimal residual disease in resection site and impair tumor cell dissemination by inducing apoptosis and limiting tumor angiogenesis.

In summary, perioperative use of dDAVP could provide several therapeutic benefits aiding CRS/HIPEC in CRPC or other malignancies by improving hemostasis, minimizing surgery-associated risks including the need of MABT, and protecting the patient from local recurrence and metastatic disease. Further prospective investigation is mandatory.

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Compliance with ethical standards Studies NCT01606072 and NCT01623206 were approved by the ethics commitee at each site and by the National Administration of Drugs, Food and Medical Technology (ANMAT) in Argentina.

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