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Juan Garona & Daniel F. Alonso

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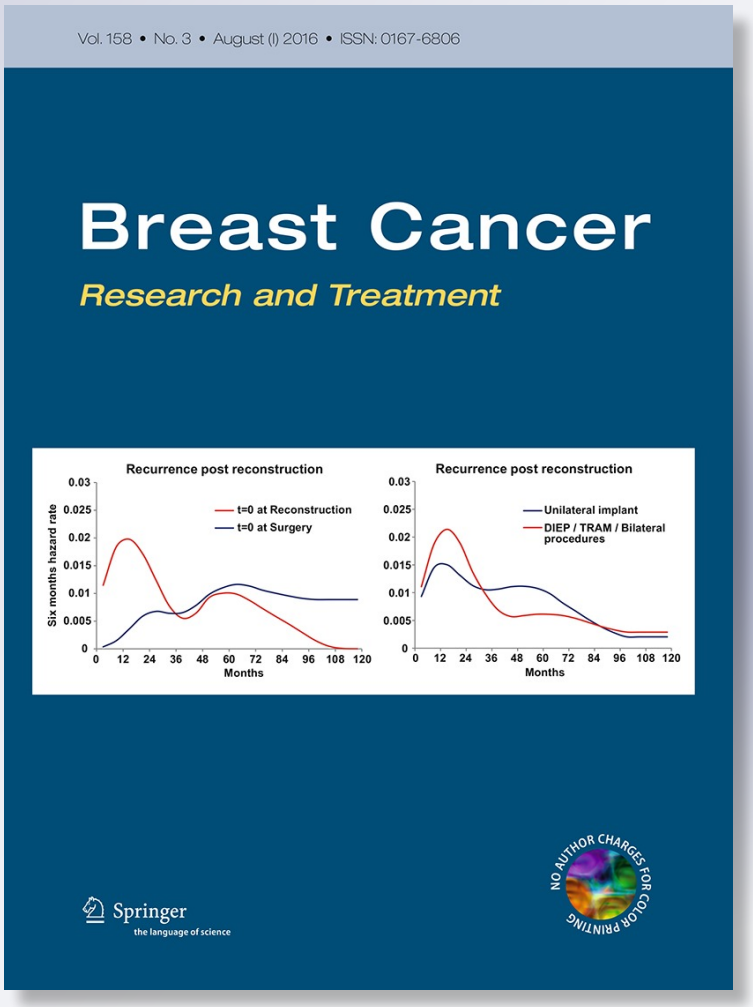

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LETTER TO THE EDITOR

Perioperative biology in primary breast cancer: selective targeting of vasopressin type 2 receptor using desmopressin as a novel therapeutic approach

Juan Garona[1] · Daniel F. Alonso[1,2]

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In breast cancer patients, surgical excision of the primary tumor is commonly the first step toward long-term control of disease progression. However, recent evidence suggests that surgery may also promote metastatic relapse through different deleterious mechanisms, including, but not limited to, tumor cell shedding, immunosuppression, neuroendocrine perturbations, increased production of growth factors, and proangiogenic signaling. In this regard, the perioperative timeframe represents an underexploited window of opportunity that could be targeted in order to modulate tumor-host interactions and minimize the risk of both local and metastatic recurrence.

In the April issue of *Breast Cancer Research and Treatment*, Love and Love meticulously reviewed how different surgical-associated variables could be manipulated in order to improve long-term outcomes in primary breast cancer [1]. After analyzing several preclinical and clinical studies, authors highlight the impact of menstrual cycle timing and sex hormone levels on outcomes following breast tumor resection. As revealed by a Phase III clinical trial, perioperative parenteral administration of progesterone to women with operable breast cancer was associated with better outcomes in axillary node-positive patients. Moreover, premenopausal metastatic breast cancer patients seem to do poorly when adjuvant oophorectomy is conducted during prolonged follicular phases with associated low progesterone levels. Besides emphasizing the importance of hormonal status and progesterone role in breast cancer biology during the surgical setting, these data suggest that further interventional studies are urgently needed in order to evaluate novel therapeutic approaches targeting perioperative tumor-host interactions.

It is important to note that the remarks of Love and Love are in line with our previous research involving the use of hormone analog desmopressin (1-deamino-8-D-arginine vasopressin, also known as dDAVP) as adjunctive therapy during breast cancer surgery [2]. dDAVP is a synthetic derivative of the naturally occurring neurohypophysial hormone vasopressin, with hemostatic and antimetastatic properties. dDAVP acts as a selective agonist of vasopressin type 2 receptor (V2r) present in microvascular endothelia and breast cancer cells. Activation of endothelial V2r causes cAMP-mediated release of von Willebrand factor (vWF), a blood glycoprotein involved in hemostasis, cancer cell apoptosis, and metastatic resistance. On tumor cells, dDAVP triggers antiproliferative signaling pathways involving cAMP/PKA axis and favors the production of angiostatin. In preclinical studies, intravenous administration of clinically relevant doses of dDAVP was associated with angiostatic and antimetastatic activities in experimental perioperative settings. Beneficial effects of dDAVP during surgery were confirmed in veterinary clinical trials in dogs with locally advanced mammary cancer. Perioperative infusion of dDAVP at high doses (1–2 μg/kg) significantly prolonged disease-free and overall survival, especially in high-grade carcinomas. Considering the antitumor properties of dDAVP, as well as its well-known hemostatic effect and safety, the compound was recently evaluated in a Phase II

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✉ Daniel F. Alonso
dfalonso@unq.edu.ar

[1] Laboratorio de Oncología Molecular, Universidad Nacional de Quilmes, R. Saenz Peña 352, Bernal, B1876BXD Buenos Aires, Argentina

[2] National Council of Scientific and Technical Research (CONICET), Buenos Aires, Argentina

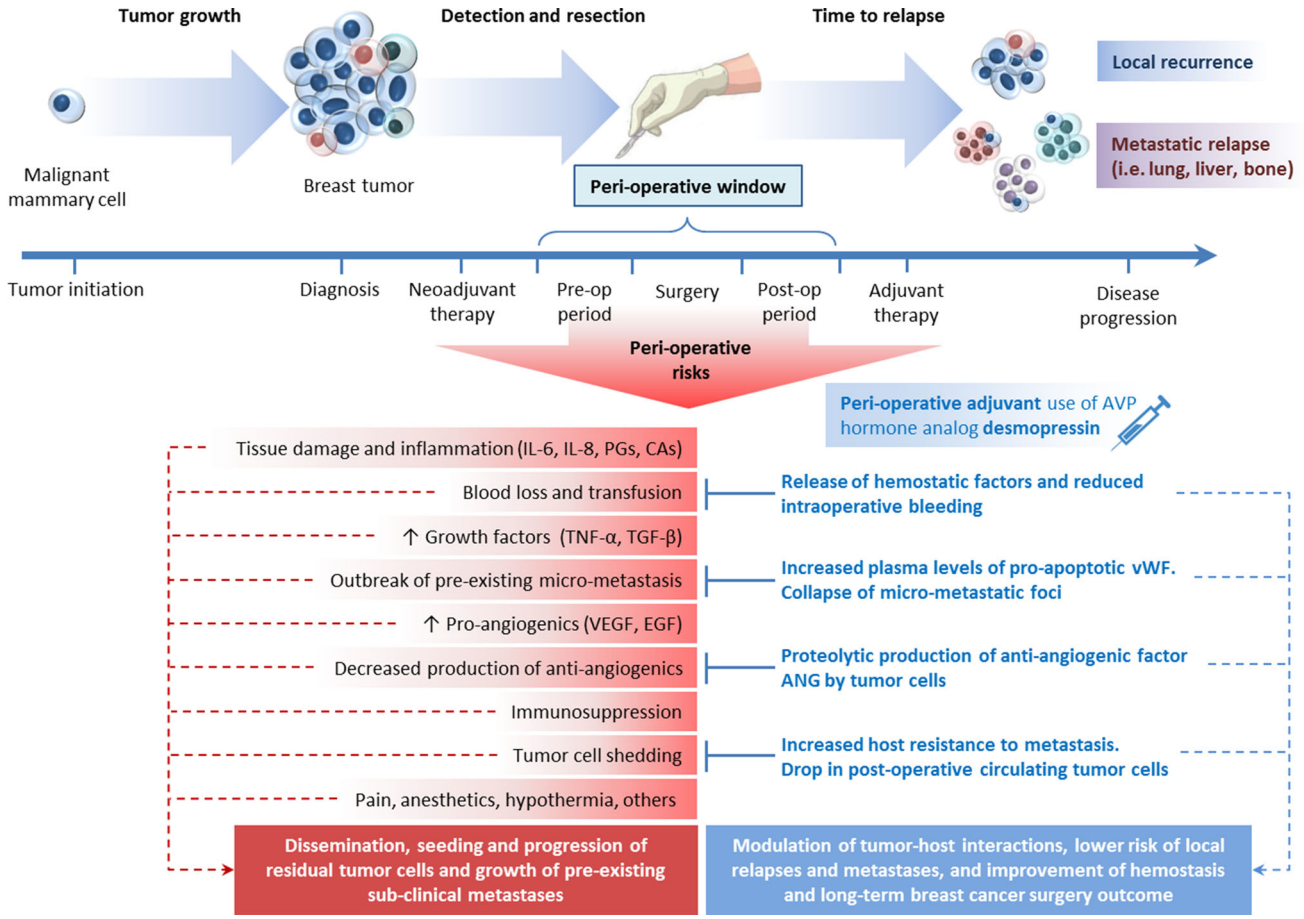

Fig. 1 Breast cancer surgery-associated risks and potential therapeutic benefits of perioperative adjuvant use of desmopressin. *AVP* arginine vasopressin hormone, *PGs* prostaglandins, *CAs* catecholamines, *TNF-α* tumor necrosis factor alpha, *TGF-β* transforming growth factor beta, *vWF* von Willebrand factor, *VEGF* vascular endothelial growth factor, *EGF* epidermal growth factor, *ANG* angiostatin

dose-escalation trial in women as adjuvant therapy during breast cancer surgical excision. dDAVP appeared safe when infused slowly before and after surgery at a dose of 1 μg/kg. Treatment was associated with reduced intraoperative bleeding, higher vWF levels, and an early postoperative drop in circulating tumor cells. Taking all these data into account, selective V2r agonists such as dDAVP seem to aid surgical management of primary breast cancer by minimizing perioperative risks, improving hemostasis, and protecting the patient from local and metastatic recurrence (Fig. 1).

Interestingly, given recent economic pressures on healthcare budgets by biologic therapies, Love and Love also emphasize the urgent need of developing low-cost, practical, and effective therapeutic interventions, especially for newly diagnosed breast cancer patients which comes from low- and middle-income regions [1]. Despite its novel perioperative use in oncology, dDAVP has been employed as a hemostatic drug for nearly 40 years with a history of good tolerability and high clinical effectiveness. As reviewed by Bertolini et al., repurposing of already-approved drugs with a nononcology primary purpose stands as an interesting strategy to offer highly effective therapeutic options to cancer patients, allowing faster development, reducing costs, and safety concerns [3]. Moreover, synthetic peptide compounds like dDAVP show unique features such as high biological activity, specificity and stability, and low toxicity and production costs, fitting the needs of the medical industry and financially overwhelmed healthcare systems.

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Compliance with ethical standards

Conflicts of interest D.F. Alonso has served as a consultant for Elea Laboratories (Argentina) and currently conducts an R&D program on antitumor peptide compounds at the National University of Quilmes sponsored by Chemo-Romikin SA (Argentina).

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