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Aprepitant, When Used with Chemotherapy, Reduces the Risk of Recurrence, Metastasis, And Mortality in Patients with Breast Cancer

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The study included a large number of women (n=13,811) who had been treated with chemotherapy and antiemetics for early-stage breast cancer (2008-2020), with follow-up for metastasis and death until 2021. Compared with any other class of antiemetic, researchers determined that the neurokinin-1 receptor (NK-1R) antagonist aprepitant (125 mg on day 1, 80 mg daily on days 2 and 3) proved to significantly improve survival and decreased the risk of metastasis when used in combination with chemotherapy. Triple-negative breast cancer (TNBC) patients had the highest risk reduction, with a rate reduction of 34% for recurrence and 39% for death [1]. In addition, a cohort study of 654 patients showed that aprepitant improved prognosis in chemosensitizer BC patients. Importantly, treatment with the drug was found to be associated with improved overall survival as well as a longer disease-free interval in all three subtypes, such as triple-negative, HR-positive, and HER2-positive BC [2]. These data support the idea that aprepitant enhances the therapeutic effects of standard chemotherapy drugs, which has been previously suggested for the treatment of TNBC [3]. Hence, in this editorial, aprepitant as an NK-1R antagonist is described in terms of the molecular cascades that result in the heightened cellular chemosensitivity, which leads to better antitumor results in BC [3, 4].

There is a growing body of epidemiological evidence highlighting the therapeutic utility of aprepitant as a chemopreventive drug in the treatment of breast BC [1, 2]. Beyond its well-established role in relieving chemotherapy-induced nausea and vomiting (CINV), aprepitant increases the sensitivity of BC cells to cytotoxic agents, while providing multiorgan protection against chemotherapy-induced toxicities, including cardiotoxicity, neurotoxicity, nephrotoxicity, and hepatotoxicity [4]. Standard regimens for BC typically include anthracyclines, taxanes, and cisplatin, the latter being particularly essential in protocols for TNBC. Despite their clinical efficacy, agents such as doxorubicin and cisplatin often lead to chemoresistance, tumor recurrence, and severe systemic toxicity [3]. However, the co-administration of aprepitant with cisplatin or doxorubicin enhances apoptotic pathways and the generation of reactive oxygen species (ROS) specifically in TNBC cells [3]. Furthermore, this combination inhibits the transcription of genes that drive metastasis, inflammation, cell cycle progression, and drug resistance, while protecting functional tissues—for example, against cisplatin-induced cytotoxicity or cisplatin-induced cardiotoxicity [3]. From a mechanistic perspective, these cellular findings offer a plausible explanation for the survival benefits observed in patients with early-stage BC who receive aprepitant in addition to primary chemotherapy.

The substance P (SP)/NK-1R signaling axis acts as a key factor in BC pathogenesis [5, 6]. NK-1R expression is ubiquitous in all breast cancer subtypes and is vital for BC cell survival [5]. Elevated plasma levels of SP have been found in clinical cohorts of BC patients, but not in healthy subjects. While SP actively stimulates BC cell proliferation, pharmacological inhibition by NK-1R antagonists, such as L-733,060, L-732,138, and aprepitant, inhibits proliferation and triggers time- and dose-dependent breast cancer cell death [5]. In addition, NK-1R antagonists, such as aprepitant, inhibit neovascularization and exhibit anti-metastatic properties by suppressing the invasion and migration of BC cells [6].

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Off-label applications. A clinical trial in HIV-positive patients demonstrated that aprepitant administered at a daily dose of 375 mg for two weeks was safe and well-tolerated. This regimen effectively reduced CD4+ cells expressing PD-1, as well as circulating levels of soluble CD163 and SP [3, 6]. Furthermore, a case study of a lung cancer patient who received palliative radiotherapy combined with compassionate use aprepitant (1140 mg daily for 45 days) showed complete regression of an 8 × 7 cm tumor mass following treatment. Notably, the patient experienced no serious adverse events throughout the course of therapy [3, 6].

In conclusion, epidemiological data indicate that adding aprepitant to chemotherapy regimens for BC—specifically, TNBC—is associated with lower rates of recurrence, distant metastasis, and overall mortality. At the same time, laboratory studies show that combining aprepitant with standard drugs, such as doxorubicin or cisplatin, enhances the elimination of BC cells and offers protection against treatment-related toxicities. Proposed next steps. Phase I: Dose escalation: Evaluate the safety and tolerability of higher doses of aprepitant, beyond standard antiemetic regimens, to achieve therapeutic saturation. Phase II: Clinical evaluation: Evaluate clinical efficacy, overall survival, and recurrence-free survival when administered in combination with systemic chemotherapy in patients with TNBC.

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