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INSIDE

Amifostine as a Radioprotector in Head and Neck Cancer: Overview and Management Strategies

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Amifostine was developed during the height of the Cold War by the Walter Reed Army Institute of Research in Washington, DC, as part of a United States Army classified research project to protect the military soldiers and the population against atomic radiation in the event of Nuclear War. Approximately 4,400 compounds were studied as potential radioprotectants and amifostine was 2,721 compound studied by Walter Reed, hence the name WR-2721 (Capizzi, 1999). Amifostine selectively protects a broad range of normal tissues, such as the oral mucosa, salivary glands, lungs, bone marrow, heart, intestines, and kidneys without protecting tumor cells. It reduces radiation-related and selected chemotherapy-related toxicities. It improves long-term functioning and quality of life for the patient and may prevent treatment delays and thus improve survival (Capizzi, 1999).

Pharmacokinetics of Amifostine

Amifostine (WR 2721) is a prodrug, which is dephosphorilated by the membrane-bound enzyme alkaline phosphatase to the free thiol metabolite, WR-1065. WR-1065 is the main metabolite responsible for the radioprotective effects of amifostine and is the metabolite most readily taken up into cells due to higher alkaline phosphatase activity, better vascularization, and higher pH of normal tissue. Once inside the cell, WR-1065 protects against radiotherapy induced damage by scavanging free radicals (Capizzi 1999) (See figures 1 & 2).

Amifostine has a very short half-life. Following intravenous administration, it is rapidly cleared from the plasma (distribution half-life <1 minute). The rapid clearance is due to fast conversion of amifostine to its active metabolite WR-1065. This metabolite is also rapidly removed from plasma due to rapid uptake into cells and conversion into disulfide metabolite (>90% of the drug is cleared from the plasma within 6 minutes) (Capizzi, 1999; Ethyol® Mono-

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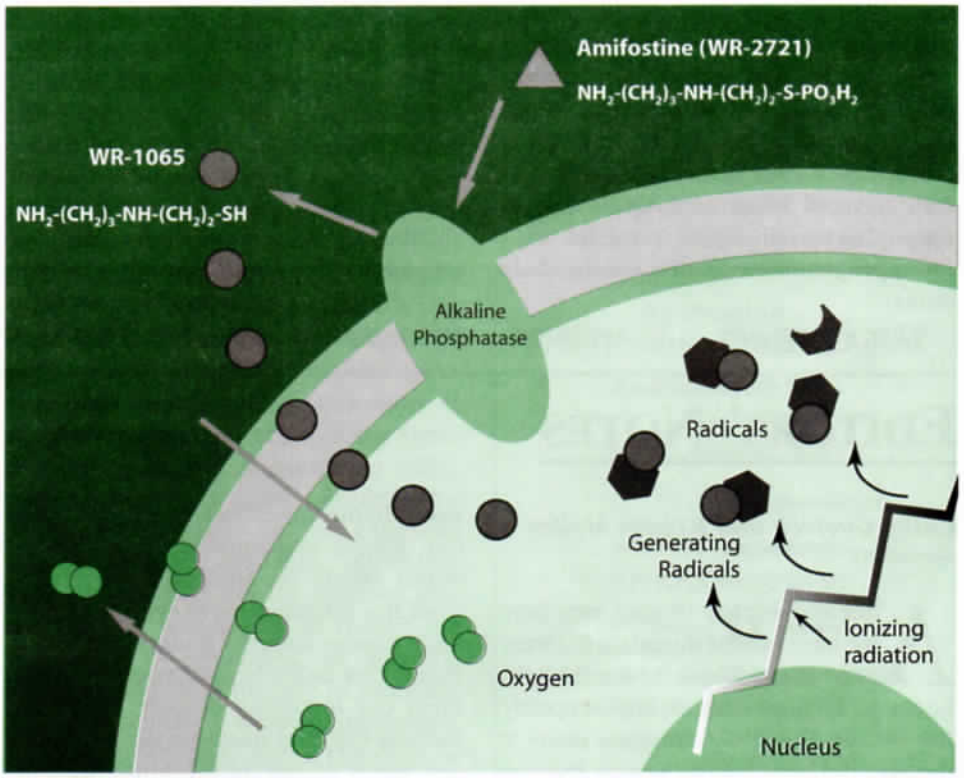

Figure 1: ***Mechanism of action***
Amifostine (WR 2721) is a prodrug, which is converted into free thiol metabolite (WR-1065) in the presence of membrane-bound alkaline phosphatase. Printed with permission from MedImmune Oncology Inc.