

## The Sensitizing Mystery of Taxanes- A Review

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### ABSTRACT

Synchronized use of radiotherapy and chemotherapy has been the gold standard in the treatment of resectable as well as locally advanced head and neck cancer over the past few decades. Radiosensitizers play a key role in sensitizing the tumor cells to radiation, thereby surpassing the normal cells from radiation, thus protecting them. Among the many available radiosensitizers, taxanes being hydrophobic mitotic inhibitors, have indisputably proven effective in the treatment of many malignancies. This review focuses on taxane as a potential radiosensitizer in the treatment of head and neck squamous cell carcinomas.

**Key words:** HNSCC, radiosensitizer, taxane

**H**ead and Neck Squamous cell carcinoma (HNSCC) is the fifth most common cancer worldwide, with a global annual incidence of approximately 500,000 cases [1]. It is an aggressive epithelial malignancy with poor prognosis. As malignancy is linked to abusive habits, many patients present with notable comorbidities linked to lifestyle, a factor that limits the delivery of effective antitumor therapy. Along with the conventional treatment options, several novel therapeutic approaches for HNSCC have emerged over the past decade which include combinations of surgery, radiotherapy and chemotherapy. Concomitant chemoradiation is known to now provide better outcomes in terms of local control and survival in head and neck cancer [2].

There are therapeutic agents which have the potential to sensitize tumor cells to the effects of radiation, thereby improving the therapeutic ratio, taxane is one such agent that is new in HNSCC. Taxane has a significant antitumor activity and are commonly used in treating both locally advanced and distantly metastatic disease. Of late these agents have been tested in the treatment of squamous cell carcinoma of the head and neck in combination with other chemotherapeutic agents, targeted drugs, and radiotherapy

in in-vitro experiments and in the clinic as first-line treatment of patients with metastatic/recurrent and locally advanced HNSCC [3]. This review focuses on the role of taxanes as redaiosensitizer in the management of squamous cell carcinoma of the head and neck.

### PHARMACOLOGY OF TAXANES

Taxanes are being used in the treatment of wide variety of malignancies. The 2 main forms of taxanes are Paclitaxel and Docetaxel. Paclitaxel, discovered in 1971 was one of the first taxane which was used as a chemotherapeutic agent. It is a semisynthetic derivative isolated from the Pacific Yew tree (*Taxus brevifolia*). It has nonlinear kinetics that causes cumulative concentration in the body, thus with changes in doses may lead to unpredictable toxicities. Docetaxel is isolated from needles of European yew tree (*Taxus baccata*), has linear kinetics over the doses. Because of productive effects and noncumulative toxicity, this is preferred over paclitaxel in weekly radiosensitization. Both are made of Tetracycline 17-carbon skeleton, are poorly water soluble, thus require vehicles for IV drug delivery. They are metabolized in the

liver P450 system (cyp2C8 enzyme is responsible for paclitaxel hydroxylation, cyp3A4 for docetaxel hydroxylation) and are cleared through biliary system [4,5].

### MECHANISM OF ACTION

Taxanes inhibit and suppress cell growth, differentiation and proliferation of cancer cells. They act by promoting tubulin polymerization and the formation of stable microtubules affecting the normal mitotic process and leading to cell death. Taxanes bind to  $\beta$  tubulin and stabilize the microtubules and thus induce the mitotic block causing radiosensitization. At the molecular level, with the stabilization of microtubules, cell cycle proteins V12 p34 kinase and cyclin B1 accumulate with increase in the incubation time, inducing the mitotic block. Taxanes also causes the phosphorylation of Bcl- 2 leading to apoptosis. Activation of the caspase-3-dependent pathway leads to DNA fragmentation. All these lead to the G2/M block which is the main mechanism of paclitaxel cytotoxicity and radiosensitization [3,4].

### EFFICACY:

Paclitaxel and Docetaxel have been used as a single agent or in combination with chemotherapy and radiotherapy in the management of locally advanced HNSCC as well as in the recurrent/ metastatic HNSCC. Taxanes have a longer half-life and therefore have a consistent radiosensitization toward the end of the week. The combination docetaxel and cisplatin results in response rates from 40 to 71%, whereas when used as a single agent is the response rate is 20% to 40% [3,4].

### ADVERSE EFFECTS:

Taxanes are poorly soluble in water, therefore solvents are used with taxanes for better absorption contributes to neurotoxicity as well as hypersensitivity reactions requiring pretreatment with antihistamines and corticosteroids to administer them safely [5]. Main side effects are hematologic toxicity, infectious and gastrointestinal complications (nausea, vomiting, and diarrhea), and renal toxicity, significant myelosuppression, grade 3 or 4 leucopenia, neutropenia, grade 3/4 mucositis, acute hypersensitivities and skin reactions, peripheral neuropathies, myalgias, and fatigue are seen at cumulative doses [2,3].

### NOVEL TAXANES:

Recently oral taxanes have emerged as analogues of existing taxanes with a possible broad range of antitumor

activity. When compared to the available taxanes, these oral forms have advantages like ease of administration, better efficacy and lesser toxicity. Novel taxane analogs have been developed that are poor substrates for P-glycoprotein, and are orally bioavailable, eliminating the need for complicated drug vehicles and iv. drug delivery. The novel oral taxanes have the potential advantages over iv. paclitaxel and docetaxel of a better toxicity profile and increased efficacy. Due to the oral route, it is easier to give them in smaller and more frequent doses, which may allow for an increase in the overall dose given, while optimizing toxicity [5].

### CONCLUSION

The use of taxanes has increased in frequency in SCCHN in recent years begging the exploration of novel taxane based clinical regimens in concurrence with radiation therapy in locally advanced HNSCC. Having peaked the pinnacle of enhanced biologic effects, wider applicability, less chances of intrinsic resistance in comparison to other radiosensitizers makes taxanes a promising drug in the field of chemoradiation. However, phase III studies are needed to prove the superiority of these approaches compared to standard treatment.

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