Reassessing specificity/selectivity of taxane-based chemotherapy

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ABSTRACT

The paramount prerequisite for effective anti-cancer drugs is their ability to eradicate malignant cells while sparing non-cancer cells. The divergence in properties between malignant and non-cancer cells often establishes a "therapeutic window," a critical consideration for achieving desirable treatment outcomes. Central to this is the imperative of a cancer drug’s "selectivity and specificity." Taxanes, a pivotal class of successful anti-cancer drugs, continue to serve as the linchpin of cancer treatment due to their efficacy across a spectrum of cancer types. Operating as broad-spectrum chemotherapeutic agents, taxanes exert cytotoxic effects on proliferative cancer cells by binding to and stabilizing microtubules, disrupting mitosis, inducing mitotic catastrophe, and resulting in cell death. The distinct proliferative nature of cancer cells, as opposed to less proliferative non-cancer cells, affords taxanes a measure of specificity and selectivity. Nevertheless, sporadic yet recurring evidence suggests that taxanes also operate through non-mitotic mechanisms. Taxanes’ binding and stabilization of microtubules lead to micronucleation and subsequent cell death, impacting both mitotic and non-mitotic cells. Recent discoveries indicate that the flexible nuclear envelope of malignant cells renders them sensitive to taxane-mediated micronucleation and cell death during various phases of the cell cycle. Conversely, non-cancerous cells typically exhibit a more robust nuclear envelope, rendering them more tolerant to taxane-induced nuclear envelope fragmentation and subsequent micronucleation and cell death. The expression levels of nuclear envelope structural proteins, particularly Lamin A/C, emerge as indicators of taxane sensitivity. This evolving understanding underscores that nuclear envelope malleability, in conjunction with a high proliferation rate, is a pivotal determinant of taxane specificity and selectivity against malignant cells. These insights necessitate reconsidering oncological strategies to augment taxane efficacy, overcome resistance, and mitigate side effects.

KEYWORDS

taxanes; Taxol; paclitaxel; microtubules; mitosis; proliferation; nuclear envelope; micronuclei; drug resistance; drug mechanism
1. Introduction

Conceptually, targeted therapy represents a superior strategy compared to the current use of cytotoxic chemotherapy. However, despite some successes, it is unlikely to replace standard chemotherapy, which remains the cornerstone of cancer treatment for the foreseeable future. Key drugs for major solid tumor types, particularly metastatic cancer, include taxanes such as paclitaxel, docetaxel, and cabazitaxel, which have demonstrated impressive efficacy [1-7]. Taxanes are commonly used in combination with other agents, such as carboplatin or cisplatin, and also as standalone treatments in a dosage-dense schedule following the development of resistance to platinum agents [8-11]. Acting as microtubule-stabilizing agents, taxanes bind to beta-tubulins within microtubule filaments, stabilizing microtubules and disrupting the dynamic instability of microtubules, ultimately leading to cell death [12]. Mechanisms downstream of taxanes’ action have been critically analyzed and contemplated [13].

A fundamental requirement of anti-cancer drugs is to eliminate malignant cells while sparing non-cancer cells, a principle known as cancer selectivity and specificity. Selectivity refers to the drug’s preferential binding or interaction with the intended target (typically a protein), while specificity indicates the degree to which the drug impacts the target without causing excessive unintended side effects. The target of chemotherapy drug system administration is shown in the Fig. 1. In theory, targeted therapy is an ideal cancer treatment where the target, such as a mutated gene or protein, is presumed to be present only in cancer cells, not in normal cells. However, in reality, very few targeted therapies have been successfully developed, and those with high selectivity and specificity often become ineffective due to the rapid development of drug resistance. Abundant redundancies and feedback loops enable cancer cells to escape targeted interventions, and a loss of sensitivity to programmed cell death signals in malignant cells further impedes the success of targeted therapy.

**Figure 1.** Challenges to systemic administration of chemotherapeutic agents.

Cytotoxic chemotherapy involves identifying drugs that are somewhat more toxic to malignant cells than...
benign cells, with lower expectations of high selectivity and specificity. The therapeutic window is narrower, and the dosage used may range from lethal toxicity to cancer cells to a level with unacceptable toxicity to host cells. Toxicity and drug resistance are vital issues limiting the use of standard microtubule-targeting chemotherapy[14-17].

For taxanes, key drugs in treating major cancer types[18-27], the higher proliferative rate of cancer cells compared to most normal cells provides a recognized specificity for targeting malignant cells, given the vital role of microtubules in mitotic cell division[28-37]. However, the molecular mechanisms of taxanes remain mysterious when critically considered. Recent progress and new understanding also suggest that the malleable nuclear envelope found in malignant cells provides another vulnerability for purging by taxanes[38-40]. This article reviews and summarizes the concepts derived from new experimental findings and reasoning and suggests factors determining the specificity/selectivity of taxanes in chemotherapy.

2. Taxanes serve as microtubule-targeting agents with the pivotal ability to stabilize microtubules

The discovery of paclitaxel's capability to promote polymerization and stabilize microtubule bundles spurred interest in the clinical development of taxane drugs[41-47]. Paclitaxel, the initial taxane investigated, extensively studied its binding to beta-tubulin subunits within microtubules, inhibiting their dynamic extension and shortening, thereby stabilizing the microtubule filaments[48-50]. With a near 1:1 ratio binding to beta-tubulin subunits, paclitaxel can be sequestered within cells, reaching concentrations hundreds of times higher than extracellular levels, maintaining microtubule-stabilizing activity long after exposure[51-57]. This sequestration is considered a crucial factor contributing to the clinical success of taxanes as anti-cancer agents[58-67]. Taxanes' consistent targeting of microtubules forms the basis of their cytotoxicity against cancer cells, although downstream events following microtubule stabilization are still under investigation[68].

3. Mechanisms of Taxanes' Specificity/Selectivity for Cancer Cells

Exploring the biological activity of taxanes in microtubule binding reveals several potential mechanisms underlying their anti-cancer specificity. Firstly, the inhibition of mitosis emerges as an apparent mechanism, given the crucial role of microtubules in mitotic processes[69]. Paclitaxel-induced cell growth arrest and mitotic catastrophe confirm this mechanism, aligning with taxanes being recognized mitotic inhibitors[70]. Additionally, taxanes interfere with microtubule spindles, leading to aberrant mitosis and mitotic catastrophe, providing a logical explanation for cancer specificity based on the higher proliferative rate of tumor cells[71]. Considering microtubules' role in cell mobility and endocytic trafficking, interference with these processes by taxanes may serve as another factor distinguishing malignant from non-cancer cells. However, no specific changes attributing to taxanes' specificity/selectivity have been universally defined[72]. A novel explanation suggests that taxane-induced stabilized microtubule bundles cause the tearing of weakened nuclear envelopes in malignant cells, providing another level of specificity/selectivity.

4. Taxanes Targeting Mitotic Cells as a Contributor to Cancer Specificity/Selectivity

Observations of paclitaxel effects on microtubules, leading to growth arrest, mitotic catastrophe, and cell death, formed a unique mechanism supporting taxane's cytotoxic activity against cancer cells, driving early clinical development[73]. Taxanes consistently exhibit mitotic inhibition in cancer cells in culture, aligning with their acknowledged role as mitotic inhibitors with higher toxicity against proliferative cells[74]. The common side effects
of taxanes, myelosuppression, alopecia, and peripheral neuropathy correspond to their targeting of highly proliferative cells, such as hematopoietic progenitor cells and hair follicle matrix cells. Peripheral neuropathy, specifically, is attributed to taxane targeting of axonal microtubules crucial for neuron structure and function. Despite the general consensus on taxanes as mitotic inhibitors, controversies persist. Some argue that targeting mitosis is not the sole or primary mechanism of their anti-cancer activity, citing the taxane mitotic paradox and the sensitivity of non-mitotic fractions of tumor cells to taxanes. This minority perspective underscores the importance of non-mitotic mechanisms in taxane cancer therapy.

5. Taxanes' Induction of Micronucleation in Both Mitotic and Non-Mitotic Cells

Treatment of cancer cells with taxanes consistently results in the appearance of micronucleated cells, characterized by lobulated or fragmented nuclei, considered pivotal in taxane-induced cell death or drug resistance[75, 76]. Micronuclei formation is observed not only in mitotic cells but also in cells in the gap phase of the cell cycle, indicating a broader impact on cellular processes beyond mitosis. A proposed mechanism suggests that taxane-induced stabilized microtubule bundles cause tearing of the nuclear envelope, leading to micronucleation, with the weakened nuclear envelope of malignant cells providing another level of specificity for taxane cytotoxicity. Notably, suppression/deletion of Lamin A/C, nuclear envelope structural proteins, increases taxane-induced micronucleation and sensitivity, further highlighting the role of nuclear envelope malleability in taxane specificity/selectivity [37].

In conclusion, by targeting microtubules, taxanes exhibit a multifaceted approach to cancer cell cytotoxicity, involving mitotic inhibition, interference with cellular processes, and induction of micronucleation. These mechanisms collectively contribute to the specificity/selectivity of taxanes against cancer cells, with the malleability of the nuclear envelope emerging as a novel and crucial factor in their anti-cancer activity.

6. Increased Nuclear Envelope Malleability: A Crucial Element in Taxane Specificity/Selectivity

In ovarian cancer cell cultures, the expression level of Lamin A/C emerges as a pivotal factor influencing sensitivity to taxanes. Cancer cells with diminished Lamin A/C expression exhibit a more malleable nuclear envelope, making them prone to breaking into multiple micronuclei upon paclitaxel treatment. This insight suggests that cancer cells with a malleable and irregular nuclear envelope are more susceptible to taxanes, which target the nuclear membrane to induce rupture. The main pathways by which chemotherapy agents play a therapeutic role in the treatment of ovarian cancer are shown in Fig. 2.

Non-cancer cells typically possess a robust nuclear envelope, and while taxane-induced microtubule stabilization may cause some deformation, it usually does not result in nuclear envelope breakage. Taxanes interfere with microtubule function in mitotic non-cancer and cancer cells with disassembled nuclear envelopes, leading to mitotic catastrophe and micronucleation. While mitotic cells undergo frequent irreversible rupture of compromised micronuclei, cancer cells, even in non-mitotic states, with a weaker and more malleable nuclear envelope, undergo micronucleation through nuclear budding. The formed micronuclei are defective, undergo rupture, and eventually lead to cell death. Thus, the propensity of the nuclear envelope to tear due to taxane-induced microtubule bundles provides specificity for non-mitotic cells. Lamin A/C proteins notably absent or reduced in various cancer types, including ovarian cancer, are considered potential cancer prognostic markers. The aberrant expression of Lamin A/C in cancer has been actively investigated, with its deletion causing mechanical and shape changes in the nuclear envelope, rendering it more malleable.

Reduced/lost Lamin A/C results in the malleability and deformity of the nuclear envelope in cancer cells, often
characteristic of malignancy in various cancer types. The loss or reduction of Lamin A/C is associated with genomic instability, and aneuploidy generation, and is considered a probable factor rendering aneuploid cancer cells more sensitive to taxanes. Therefore, the expression of Lamin A/C emerges as a potential marker predicting the sensitivity and resistance of cancer cells to taxanes. The loss or reduction of Lamin A/C, or the increased malleability of the nuclear envelope in malignant cells, provides another mechanism for the selectivity of taxanes in killing cancer cells over benign cell.

Figure 2. The main way that chemotherapeutic drugs play a therapeutic role.

7. Conclusions

Three distinct mechanisms contributing to the specificity or selectivity of taxanes against cancer cells are propose. The mechanism of antibody-drug coupling is shown in Fig.3. Firstly, the long-recognized and well-accepted targeting of taxanes to highly proliferative cells. Secondly, alterations in microtubule-mediated endocytic trafficking and cell mobility may contribute to taxane anti-cancer specificity, although specific changes supporting this notion are yet to be identified. Lastly, the recent understanding of taxane mechanisms in breaking nuclei of cancer cells presents a newly recognized specificity or selectivity: the weakened and malleable cancer nuclear envelope. As an irregular nuclear envelope is often a characteristic of malignant cells, it serves as a higher sensitivity indicator to disruption by taxane-induced microtubule bundles.
Figure 3. Antibody-drug conjugate mechanism of action.

Cancer cells sensitive to taxanes, such as ovarian cancer, metastatic breast cancer, hormone-insensitive and metastatic prostate cancer, and metastatic non-small cell lung cancer, often exhibit high nuclear grades and severe nuclear morphological abnormalities, indicating nuclear envelope malleability. There are many types of immune effects of chemotherapy drugs and their related signaling pathways. Fig. 4 showed some of the relevant pathways, hoping to provide corresponding information for immunotherapy. Consequently, the degree of nuclear deformation and the expression of nuclear lamins may serve as predictive markers for sensitivity or resistance of cancer cells to taxanes. Combining agents or methods to perturb nuclear envelope sturdiness may enhance the efficacy of taxanes. In conclusion, the new understanding suggests that nuclear envelope malleability determines sensitivity to taxanes and is another critical factor, alongside a high proliferation rate, contributing to the specificity and selectivity of taxanes toward malignant cells. These revelations prompt a reevaluation of strategies to enhance taxane efficacy, overcome drug resistance, and prevent or reduce taxane side effects.
Figure 4. Immune effects of chemotherapeutic drugs and their related signaling pathways.

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Conflict of interest

The authors declare no competing interests.

Author contributions

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