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Pharmacology-Focused Review of Paclitaxel and Gemcitabine for Triple-Negative Breast Cancer, with Perspectives from China

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Abstract. Triple-negative breast cancer (TNBC) lacks expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), known as a relatively aggressive type of breast cancer that is difficult to treat and has a high risk of early recurrence. Systemic therapy for this is generally cytotoxic chemotherapy. Paclitaxel (Taxol) and gemcitabine (GT regimen) have been selected as one of the standard options worldwide. However, the clinical medical community in China has found that the disease affects young premenopausal women more severely and has different mutation spectra. This paper will examine the pharmacology of the GT regimen. First, it will study the molecular structure and physical-chemical properties of paclitaxel and gemcitabine. The clinical delivery strategy will also be discussed. The traditional 21-day intermittent schedule has certain deficiencies, such as dose-limiting toxicity, acquired resistance and suboptimal biodistribution. Last but not the least, given the genetic and clinical differences between Western and Asian TNBC populations, Chinese-specific real-world data are in urgent need. Finally, we put forward three future directions to address the existing bottlenecks: (1) adjunct therapies for synergistic sensitisation and toxicity alleviation, (2) advanced drug delivery systems, (3) genotype-guided patient stratification.

Keywords: Triple-negative breast cancer, Paclitaxel, Gemcitabine, Microtubule stabilization, DNA chain termination, Traditional Chinese medicine adjuncts

1. Introduction

1.1. Diagnostic specificity

Breast cancer, which is considered a heterogeneous disease with several subtypes, remains one of the leading causes of cancer-related mortality among women worldwide. Luminal A, luminal B, normal breast-like, HER2 overexpression and basal-like are considered the main subtypes [1, 2]. Among these subtypes, basal-like patients are generally clinically presented as triple-negative breast cancer (TNBC). It is molecularly defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression [3]. Being devoid of these therapeutic targeting recptors, TNBC paitients may not perform well cured using

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conventional endocrine therapies and anti-HER2 agents. This fact makes cytotoxic chemotherapy the primary systemic treatment modality.

1.2. Impact of TNBC in China and Asia

TNBC accounts for approximately 20% of all breast cancer diagnoses globally. Among all patients, young premenopausal women may be at risk due to a notably higher incidence. In China, compared with Western populations, those individuals under 35 years of age may face more threat of TNBC [4]. Furthermore, the BRCA mutation spectrum observed in Chinese patients exhibits distinct ethnic differences, suggesting unique genetic drivers that warrant region-specific investigation and the development of first-line therapeutic strategies [5].

The epidemiological patterns described above establish the high-risk populations. However, the clinical significance of TNBC is determined by its distinctive recurrence behaviour and the paradoxical survival outcomes that follow treatment.

1.3. Clinical manifestations

While the initial presentation of TNBC, such as a painless and palpable mass, does not differ significantly from that of other breast cancer subtypes. However, TNBC is often reported with a notably more aggressive clinical course. TNBC Patients are frequently diagnosed at an advanced stage according to the primary tumour, lymph node, and metastasis (TNM) classification of the American Joint Commission of Cancer (AJCC) (IIIA or higher, i.e. the tumour may already metastasize), with a pronounced propensity for visceral metastasis, particularly to the lungs, liver, and bones. In addition to these visceral tropisms, positive lymph node involvement and high histological grade (i.e. more undifferentiated cells, being easier to metastasise) further reflect the strong invasive capacity of TNBC [5, 6]. Collectively, these features emphasise that it is critically necessary for first-line chemotherapeutic regimens. The gemcitabine-paclitaxel (GT) combination represents one option of verified therapies, especially in a circumstance of cancer cells metastasising.

Different subtypes show varied recurrence risk curves. Late relapse beyond 10 years is more common in Luminal subtypes, yet a sharp peak characterises TNBC within the first 3 to 5 years following diagnosis. While this feature can be commonly observed in all TNBC patients, younger female patients, who tend to achieve higher pathological complete response (pCR) rates with docetaxel-epirubicin therapy but paradoxically face worse long-term prognosis. These patients have lower 5-year disease-free survival (DFS) and markedly fluctuating 5-year overall survival (OS) [3, 7]. Such circumstances express the dual personality of TNBC.

Reasons for this phenomenon include high cytotoxic responsiveness and relentless recurrence ability of the cancer cells. This duality makes the tumours vulnerable to S-phase and M-phase disruptors, yet equally capable of evading incomplete eradication due to evasion of apoptosis [8]. These biological features, such as rapid turnover and a specific unstable period, are not merely academic descriptors, but direct clues for therapeutic strategy.

The mentioned characteristics of TNBC make this subtype highly threatening. Despite accounting for only ~20% of all breast cancer cases, which was noted by Qiu and colleagues in 2016, TNBC contributes to a disproportionately higher percentage of breast cancer-related mortalities, emphasising its poor prognosis and the high unachieved medical need for more effective interventions [2, 9]. However, clinal evidence is required to determine a optimal application of such regimens. A firm clinical evidence from Chinese TNBC patients, remains insufficiently developed,

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shows a significant importance. As Wu and colleauges noted in 2011, current data on the cure rates for TNBC patients are almost entirely based on Western patients.

1.4. Lack of patient data in China

As Wu and colleagues mentioned in 2011, TNBC clinical presentation could be varied due to differences at the molecular level [7]. In China, the standard first- or second-line regimen for metastatic TNBC often incorporates the combination of gemcitabine and paclitaxel (GT). However, current treatment algorithms are predominantly extrapolated from clinical trials conducted in European and American cohorts. High-quality clinical evidence generated specifically from Asian, and particularly Chinese remain scarce, limiting the precision of therapeutic decision-making in this demographic.

1.5. Origins and historical development of the core drugs

Paclitaxel can be considered a stabiliser of microtubules, which was originally derived from the bark of the Pacific yew tree (*Taxusbrevifolia*) back in the 1960s [10]. Paclitaxel is a complex diterpenoid taxane, modified by a unique microtubule-stabilising mechanism [11]. Contemporary manufacturing predominantly relies on semi-synthesis or plant cell fermentation to ensure sustainable supply. Several clinically important derivatives have subsequently been developed, including docetaxel, which has been applied in first-line regimens [12, 13].

Gemcitabine, designed as an antiviral drug, was first developed by Hertel and colleagues in the 1980s [14]. As a fluorinated deoxycytidine nucleoside analogue, gemcitabine demonstrated potent anticancer activity after its antiviral efficacy proved unsatisfactory [15]. Its key structural innovation enhances metabolic stability and antitumor efficacy. This feature distinguishes it from earlier nucleoside analogues such as cytarabine (Ara-C). Besides, the modification supports two main functions of gemcitabine. A prolonged intracellular retention and unique self-potentiation enable this drug to remain active and effective *invivo*, which will be discussed in subsequent sections.

The distinct origins of these two drugs are reflected in their fundamentally different molecular architectures and physicochemical behaviours, which we now examine in detail in the following section.

2. Chemical structures and physicochemical properties

2.1. Nomenclature and structural classification

2.1.1. Paclitaxel

Paclitaxel, whose molecular structure is shown in Fig.1, can be considered a highly modified skeleton of baccatin III, which is unable to be as active as paclitaxel. Its systematic IUPAC designation ((2α,4α,5β,7β,10β,13α)-4,10-Bis(acetyloxy)-13[(2*R*,3*S*)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl] oxy 1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate) reflects intricate stereochemistry and multiple hydroxylation patterns [10].

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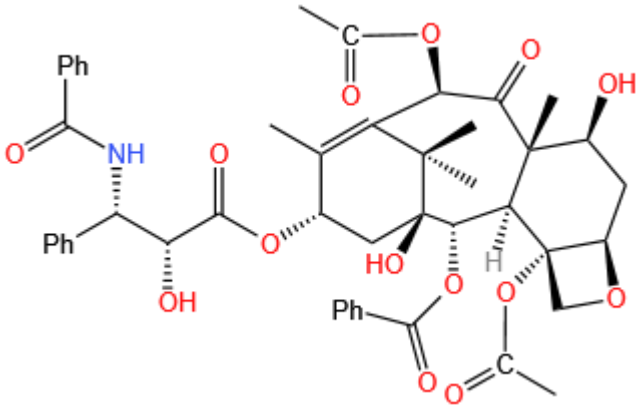

Figure 1. Structure of paclitaxel

2.1.2. Gemcitabine

As a synthetic pyrimidine nucleoside analogue, gemcitabine, systematically named 2 ', 2'-difluoro-2'-deoxycytidine (dFdC), is distinguished from natural endogenous nucleosides via the presence of two fluorine atoms at the 2' position of the sugar moiety, shown in Fig.2 [14]. Gemcitabine exemplifies a classicbioisosteric substitutionstrategy, in which the two hydroxyl groups at the 2' position of natural deoxycytidine are replaced by fluorine atoms. Therefore, the molecule can achieve a masking termination effect when combined with original DNA chains of cells [16].

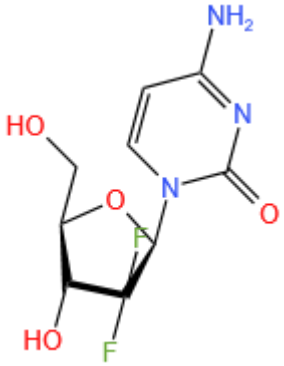

Figure 2. Structure of gemcitabine

2.2. Key physicochemical parametersand structure-activity correlations

Shown in Table1, paclitaxel exhibits a markedly hydrophobic nature, demonstrated by XLogP3 and tPSA values, which are critically determined by its formulation, the N-benzoylphenylisoserine side chain on C-13 and the benzoyl group at C-2 [17]. Thus, paclitaxel requires solubilization with hydrogenated castor oil and ethanol [18]. The high lipophilicity contributes to significant hypersensitivity reactions and necessitates specific intravenous administration protocols.

In contrast, gemcitabine is relatively hydrophilic. The presence of the difluoro substitution imparts resistance to enzymatic deamination by cytidine deaminase, thereby prolonging its plasma half-life and enhancing its intracellular retention compared to natural nucleosides [19].

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Table 1. Hydrophobicity of Paclitaxel and Gemcitabine [20]

	XLogP3	tPSA
Paclitaxel	~2.5	~221 Å²
Gemcitabine	~-1.5	~108 Å²

3. Pharmacological mechanisms and clinical delivery

3.1. Molecular targetsand mechanisms of action

3.1.1. Paclitaxel

Generally, paclitaxel targets the β-tubulin subunit of microtubules. Paclitaxel, as a microtubule-stabilising agent (MSA), rather than inducing depolymerisation, hyper-stabilises microtubule dynamics, preventing their physiological disassembly and normal movement. The hyper-stabilisation (polymerisation), which can be related to the concentration of paclitaxel, demonstrates resistance to the typical enhancement of depolymerisation, such as low temperature or calcium. This function is realised by groups connecting with C-13, C-2 and C-4. The hydrophobic benzoyl groups on C-13 (sensitive to the environment) and C-2 are most essential among these 3 active groups [17]. These researchers proved that analogues of paclitaxel without these 2 groups lost original functions or even performed contrary results. Besides, paclitaxel can also bind to kinetochores and then alter their dynamic behaviour by over-stabilising them. This inhibition effectively arrests actively dividing cells at the G2/M checkpoint, ultimately triggering intrinsic and extrinsic apoptotic pathways, as abnormal kinetochore movement can lead to p55CPC and other checkpoint proteins departing unexpectedly, resulting in multipolar and asymmetric cells [21]. Currently, cancer cells undergo multipolar division, and the chromosomes are unequally distributed among three or more daughter cells. This misallocation directly leads to the acquisition of an incomplete number of chromosomes in the daughter cells, resulting in highly aneuploid cells. These daughter cells often fail to survive due to severe genomic imbalance. However, when the concentration of paclitaxel becomes higher, cells will demonstrate further mitotic slippage at the G2/M checkpoint, as the cells can no longer divide. Therefore, these cells that accidentally exit mitosis will become pseudo-G1 cells, which will experience lysis by PARP.

3.1.2. Gemcitabine

Gemcitabine functions as a prodrug. It is a pyrimidine nucleoside analogue with broad-spectrum antitumor activity, structurally distinguished by a 2′,2′-difluoro substitution on the ribose part, which is considered a feature that sets it apart from cytarabine (Ara-C) and other deoxycytidine analogues.

Acting as a prodrug, gemcitabine requires sequential phosphorylation by deoxycytidine kinase (dCK). This process generates monophosphate (dFdCMP), diphosphate (dFdCDP), and ultimately the cytotoxic triphosphate active species (dFdCTP) (Wan & Ruan, 2023). The sequential steps increase the metabolic stability of gemcitabine, largely contributing to a self-potentiation mechanism. The difluoro modification also advances this mechanism. Specifically, gemcitabine inhibits cytidine deaminase (CDA), thereby retarding its own deamination to the inactive metabolite 2′,2′-difluorodeoxyuridine (dFdU) and prolonging its systemic half-life [22].

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Concurrently, its metabolites suppress ribonucleotide reductase (RNR), depleting the intracellular pool of the competitive substrate deoxycytidine triphosphate (dCTP). This process promotes the incorporation of dFdCTP into nascent DNA. Following the incorporation of dFdCTP into DNA chains, an additional nucleotide will be appended. Together with dFdCTP, these two molecules produce a masking chain termination effect. It shields the lesion from DNA repair machinery and leads to irreversible chain termination.

The active metabolites of gemcitabine exhibit prolonged intracellular retention, exceeding 16 hours, versus less than 0.7 hours for its counterpart, Ara-C triphosphate, which ensures sustained and robust antitumor efficacy [23].

3.1.3. Therapeutic synergy

Shown in Table 2, the combined use of paclitaxel and gemcitabine exploits primary targets and cell-cycle phase differentials. While paclitaxel induces mitotic arrest in the G2/M phase, gemcitabine interrupts DNA synthesis in the S-phase, as shown in Fig.3. This complementary blockade effectively prevents tumour cells from bypassing the cytotoxic effects of either single agent. Furthermore, the different uptake pathways also provide the GT therapy with a devious pattern to enhance the effects.

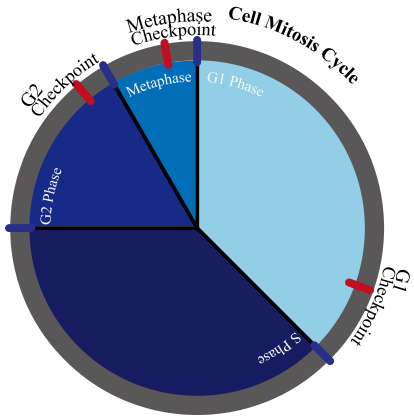

Figure 3. The cell mitosis cycle

Table 2. Comparison of paclitaxel and gemcitabine

	Paclitaxel	Gemcitabine
Cell-cycle target	G2/M (mitotic spindle) phase	S (DNA synthesis) phase
Primary target protein	β-tubulin	Ribonucleotide reductase DNA polymerase
Cellular uptake	Passive diffusion	Active transport

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3.2. Administration routes, pharmacokinetics, and clinical regimens

The delivery of paclitaxel is administered exclusively via intravenous infusion due to the poor oral bioavailability (i.e. first-pass hepatic metabolism) and hydrophobicity [18]. The development of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has circumvented part of the solvent-related toxicities, such as hypersensitivity reactions [24]. Gemcitabine, administered intravenously as well, typically via a 30-minute infusion, follows standard fixed-dose rate infusion protocols to maximise intracellular phosphorylation [25].

Standard Regimen. The classic 21-day cycle (with gemcitabine on Days 1 and 8, and paclitaxel on Day 1) is employed worldwide. This intermittent schedule is strategically designed to balance anti-tumour activity with manageable myelosuppression. It has been demonstrated that the two drugs would not interfere with each other, in pharmacokinetic perspective [26]. Moreover, paclitaxel has been noted that able to increase the concentration of dFdCTP and reduce the systemic clearance of gemcitabine [25]

3.3. Current clinical limitations

Despite its established efficacy, the current synergistic regimen is confronted with significant obstacles, including dose-limiting toxicities (e.g., neurotoxicity and bone marrow suppression) and sequence-dependent adverse effects [27]. Besides, acquired chemoresistance and suboptimal tumour drug delivery are also considered challenges in the application of paclitaxel and gemcitabine.

4. Future perspectives of GT-based therapy for TNBC

4.1. Adjunct therapies for synergistic sensitisation and toxicity alleviation

Given the substantial systemic toxicity associated with the GT regimen, there is growing interest in natural bioactive compounds to serve as adjunct therapies. Traditional Chinese medicine (TCM) has shown a dual effect of enhancing efficacy and reducing toxicity. Niu and colleagues (2025) mentioned that various cure status indicators of patients accepting TCM-GT regimen were significantly superior to those receiving only the original therapy [28]. Meanwhile, agents such as curcumin, resveratrol, and quercetin can downregulate multiple abnormal pathways, including PI3K, Akt, and mTOR, thereby reducing the effective chemotherapy dose and minimising side effects [29]. This aligns with the integrated traditional Chinese and Western medicine approach prevalent in Chinese clinical practice.

4.2. Advanced drug delivery systems

Novel nano-formulations capable of co-encapsulating paclitaxel and gemcitabine (P/G NPs) are being developed to achieve synchronised pharmacokinetics and synergistic tumour accumulation [30]. Recently, natural carriers such as plant-derived extracellular vesicles have also proved to be more effective than ordinary artificial delivery systems [31].

4.3. Genotype-guided patient stratification

Future clinical application should also prioritise the identification of predictive biomarkers (e.g., hENT1, RRM1, or BRCAness) to define the subpopulation of TNBC patients. Some patients may be most likely to derive durable benefit from the GT regimen [32]. This measure can be able in shifting

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current treatment plans from one-size-fits-all to precision chemotherapies. Furthermore, many studies have also established effective precise treatments, as shown in Table 3.

Table 3. Advanced synergistic strategies and curative effects of TNBC [33, 34]

Genotypes	Synergistic Strategy	Curative Effect
BRCA1/2 Mutation	PARP inhibitor (Olaparib) + Chemotherapies	Increased TNBC inhibition
PD-L1 (Programmed death ligand 1) Positive	Immune checkpoint inhibitors + Nab-Paclitaxel	Increased overall survival
AR (Androgen receptor) Positive	AR pathway inhibitor	Increased effects on LAR subtype
Notch Mutation	Synergistic immune pathway inhibitor	Increased effects on specific mutation groups

5. Conclusion

The GT regimen remains an indispensable pillar in the management of TNBC, particularly in the Chinese context where targeted endocrine and anti-HER2 options are not applicable. However, its value extends beyond being a major choice of cytotoxic therapy. To fully unlock its potential, future research should aim at three perspectives. Immune-targeted agents can be integrated with former chemical therapies. The adoption of novel delivery vehicles and the development of predictive algorithms based on the unique genomic landscape of Asian patients are also considered promising. Only through this multi-dimensional optimisation can the therapeutic efficacy of the GT regimen be maximised while minimising its off-target impact.

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