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Tumor suppressor genes and their interactions and neo-adjuvant therapy in paclitaxel resistance in cancer

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Abstract

Paclitaxel (PTX) is a drug that is often used in the treatment of solid tumours. However, PTX resistance is a significant impediment to cancer therapy. Exploration of drug resistance mechanisms reveals that tumour suppressor genes (TSGs) play a critical role in chemotherapeutic drug responsiveness. TSGs, a group of genes that are frequently inactivated in cancer, have the ability to control a variety of biological processes. A systematic study of paclitaxel and paclitaxel-containing chemotherapy regimens for advanced gastric cancer was conducted. Response rates, median progression-free survivals, and median overall survivals were studied, as well as the treatment regimens and patient numbers in each study. Taxanes, which are suggested in the adjuvant environment, are also taken into account in the neoadjuvant setting. There were twenty studies using nab-paclitaxel in the neoadjuvant context found. In the neoadjuvant treatment of breast cancer, nab-Paclitaxel displayed anticancer efficacy and a tolerable safety profile. Current and upcoming trials will assess preoperative nab-paclitaxel in breast cancer, including in conjunction with a variety of new immune targeted treatments.

Keywords: Paclitaxel resistance; Tumor suppressor genes; Breast cancer; Nab-Paclitaxel; Neoadjuvant; Chemotherapy**.**

1. Introduction

Paclitaxel (PTX) is a kind of cytotoxic drug that is commonly utilised in the first line treatment of lung, ovarian, breast, kidney malignancies, and Kaposi's sarcoma[1-5]. PTX differs from typical anti-cancer medications in that it does not influence tumour cell DNA or RNA synthesis or cause DNA damage, but instead interferes with tubulin to stabilise microtubule composition and normal spindle assembly and cell division, resulting in cancer cell death[6].

The therapeutic use of PTX results in varying reactions in various persons, and the causes of PTX resistance have not been fully understood. Some studies have shown that tumour suppressor genes (TSGs) are major regulators of medication sensitivity[7-9]. Normally, these TSGs prevent aberrant cells from surviving. However, when the genes are inactivated or reduced in expression, the aberrant cells expand uncontrolled, which can lead to cancer development[10].

Breast cancer is still one of the most frequent malignancies in the United States, accounting for 29% of all cancer diagnoses in women each year. More than 200,000 new instances of invasive breast cancer were projected in 2015, with

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an estimated 40,000 fatalities. All stages of breast cancer have a 5-year survival rate of 89%. The major treatment method for reducing recurrence risk and enhancing survival in patients with early-stage breast cancer is surgery with the objective of eliminating the original tumour and obtaining negative tumour margins. Chemotherapy before to surgery, often known as neoadjuvant chemotherapy, aids in the transformation of big, unresectable tumours into resectable tumours[11]. Furthermore, neoadjuvant therapy can decrease operable tumours, allowing breast-conserving surgery rather than mastectomy to be undertaken[12]. Sentinel lymph node biopsy may also reduce regional disease, thereby minimising the requirement for axillary lymph node dissection[13].

Gastric cancer is one of the most prevalent kinds of solid tumour, and it is considered to be the fourth most common cause of morbidity and the second most common cause of cancer mortality worldwide[14]. Gastric cancer is more widespread in Asia, Eastern Europe, and South America, where food is preserved primarily by soaking it in salt and the detection rate of Helicobactor pylori is considered to be high.

2. Cytological and genetic reactions of paclitaxel in cancer cells

Paclitaxel, a taxane, is a novel drug with a distinct chemical structure and mode of action. Paclitaxel was found as part of a Nationwide Cancer Institute (NCI) national initiative in which thousands of plants, microbes, and fungi were evaluated for anticancer activity. A crude extract from the bark of the Pacific yew, Taxus brevifolia, a slow-growing evergreen found in the Pacific Northwest, was discovered to exhibit cytotoxic effect against numerous cancer cells. Paclitaxel was extracted from the plant and used as an anti-cancer agent[15]. Although the development of paclitaxel was first hampered by the scarcity of drug supplies derived from rare natural materials, semisynthetic replacement from other inactive precursor taxanes allowed more plentiful sources.

Paclitaxel is an alkaloid ester composed of a taxane ring system connected to a four-membered oxetan ring at C-4 and -5**("Fig – 1")**. Paclitaxel stimulates tubulin polymerization, which is essential for the development of the mitotic spindle during cell division. Paclitaxel-induced microtubule formation is firmly stable and dysfunctional, interrupting normal microtubule dynamics essential for cell division and interphase events. Paclitaxel causes apoptosis, or programmed cell death, even at dosages that do not cause tubulin polymerization.Although the specific mechanism of paclitaxel's action has yet to be discovered, cells leave mitosis but do not continue to divide, and subsequently significant DNA fragmentation, suggestive of apoptosis, leads to cell death in 2 to 3 days. TNF-a gene expression is also induced by paclitaxel action, which is independent to its impact on microtubule assembly, increasing the possibility that this cytokine is associated to paclitaxel's anticancer activity[16]. This effect was not found with other taxanes, such as docetaxel, albeit the therapeutic implications of these distinctions are unknown.

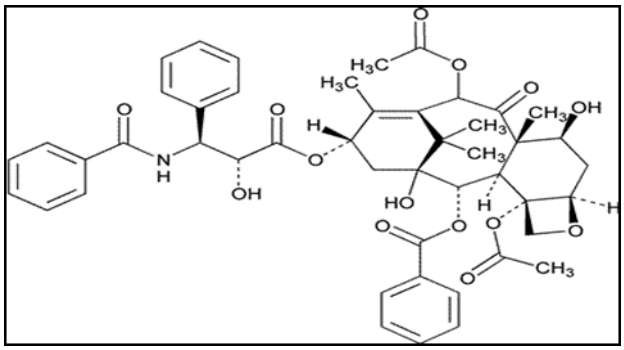

Figure 1 The chemical structure of paclitaxel

Two mechanisms of paclitaxel acquired resistance have been identified. First, it was shown that mutations in tubulin isotype genes are a major predictor of paclitaxel resistance in individuals with non-small cell lung cancer. Resistance to paclitaxel is thought to be linked to changes in tubulin content, expression of tubulin isotype, and polymerization kinetics. The multiplication of membrane phosphor-glycoproteins that operate as drug-efflux pumps is the second mechanism of acquired paclitaxel resistance.Tumor cells with a multidrug-resistant phenotype exhibit varied degrees of cross-resistance to a variety of drugs, including anthracyclines, etoposide, vinca alkaloids, colchicine, and taxanes. Many medications, including calcium channel blockers, tamoxifen, cyclosporin A, anti-arrhythmic therapies, and major components of the vehicles used to synthesise paclitaxel, can reverse paclitaxel resistance (cremophor EL). Several pathways involved in apoptosis throughout development and cancer, as well as essential genes implicated in their

regulation, have recently been found, including bcl-2, bcl-x, p53, and bax[17]. These apoptosis-related genes may also play a role in the control of paclitaxel-induced cytotoxicity and resistance[18].

3. Toxicities of paclitaxel during cancer therapy

3.1. Hypersensitivity reactions

Dyspnea, bronchospasm, urticaria, and hypotension are the most common hypersensitivity responses to paclitaxel. These responses often occur within 2 to 3 minutes of treatment beginning and are virtually always noticed within the first 10 minutes. The majority of them occur with the first or second dose of the medicine. After the paclitaxel infusion is discontinued and therapy with histamine receptor antagonists, fluids, and vasopressors is administered, these hypersensitivity events disappear entirely. Minor hypersensitivity events such flushing and rashes have also been observed in up to 40% of individuals. The incidence of serious hypersensitivity responses is reduced to 1% to 3% when corticosteroids and/or H1, H2 antagonists are used as preventative measures.

3.2. Hematological toxicity

Paclitaxel's main haematological adverse effect is neutropenia. The start is generally around days 8-10 following treatment, and recovery takes 2 to 3 weeks. The neutropenia is not cumulative, indicating that paclitaxel does not harm immature hematopoietic cells permanently. When treated every 3 weeks, the highest tolerable dosage of paclitaxel without granulocyte colony-stimulating factor in most individuals is 175-200 mg/m2. Paclitaxel seldom causes thrombocytopenia or anaemia on its own.

3.3. Neurotoxicity

Paclitaxel's primary neurotoxic impact is peripheral neuropathy, which is characterised by sensory complaints such as numbness and paresthesia in a glove-and-stocking-like distribution [16]. Because of the severe neurotoxicity, paclitaxel cannot be used on a long-term basis. The frequency of neurotoxicity has been shown to be especially significant in individuals who receive paclitaxel as a 3-hour infusion, indicating that peak concentration may be a major pharmacological driver. When paclitaxel is combined with cisplatin, neurotoxicity appears to be more common and more severe. There is no clear evidence that any one intervention is beneficial at alleviating current symptoms or avoiding the development or worsening of neurotoxicity. Some individuals may experience optic nerve abnormalities, indicated by scintillating scotomas[19].

3.4. Cardiac toxicity

Transient asymptomatic bradycardia is the most prevalent cardiovascular symptom associated with paclitaxel, occurring in 29% of patients[20]. Paclitaxel treatment should not be stopped because of isolated cardiac bradycardia without hemodynamic consequences. More serious brady-arrhythmias and third-degree heart block have also been observed, but the frequency is less than 0.1%. Except for individuals with ventricular dysfunction, most patients do not require routine cardiac monitoring during paclitaxel treatment.

4. Overall information on the 22 genes related to ptx resistance in cancer

To collect all of the TSGs related to PTX resistance, we searched the PubMed online database and the Google website, followed by an advanced search using the terms "paclitaxel response" or "paclitaxel sensitive" and "drug resistance" or "chemotherapy resistance," and "cancer" or "carcinoma," and "tumour suppressor genes" or "negative regulated protein" or "antioncogene." This search found 22 TSGs, including breast cancer 1 (BRCA1), tumour protein p53 (TP53), phosphatase and tension homolog (PTEN), adenomatous polyposis coli (APC), cyclin-dependent kinase inhibitor 1A (CDKN1A), cyclin-dependent kinase inhibitor 2A (CDKN2A), high in normal-1 (HIN-1), ras association domain containing protein 1((PLK2), 7 f-box and WD repeat domains (FBW7), 10 zinc finger MYND domains (BLU), leucine zipper tumour suppressor 1 (LZTS1), re-1 silencing transcription factor (REST), fas-associated death domain protein (FADD), programmed cell death 4 (PDCD4), transforming growth factor—induced (TGFBI), inhibitor of growth 1 (ING1), bcl-2-associated X protein (Bax), **"Table – 1"** summarises the status, regulatory mode, mechanism, and cancer type implicated in PTX resistance.

4.1. BRCA1

The tumour suppressor BRCA1 is engaged in a variety of physiological processes, including DNA damage repair, cell cycle checkpoint activation, and transcription[21]. Several preclinical investigations have suggested that BRCA1 may be

a major predictor of response to PTX-based chemotherapy. The restoration of exogenous BRCA1 in the BRCA1-mutant HCC1937 breast cancer cell line resulted in increased sensitivity to PTX[22]. Low BRCA1 mRNA expression in ovarian cancer cell lines led in a reduced and enhanced apoptotic response to PTX and platinum, respectively, whereas PTX-sensitive human head and neck squamous cell carcinoma (HNSCC) with acquired cisplatin resistance exhibited high BRCA1 expression. To examine the underlying mechanisms of PTX resistance imparted by BRCA1 loss, Chabalier et al. used small interfering RNA (siRNA) to lower BRCA1 protein levels in MCF7 breast cancer cells, which resulted in PTX resistance via premature inactivation of the spindle checkpoint[23]. Sung et al. discovered that BRCA1 knockdown provided PTX resistance and cisplatin sensitivity in A549 cells via enhancing microtubule dynamics, which reduced the creation of stable microtubules for caspase-8 build-up of PTX-induced apoptosis[24].

4.2. TP53

TP53 is one of the first tumour suppressor genes to be discovered and the most often altered gene in cancer. More than half of the TP53 mutations discovered in tumours cause function loss. Cell cycle progression, cell motility, ageing, apoptosis, genetic instability, DNA repair, anti-angiogenesis, and cell metabolism are all influenced by functional p53. The status of TP53 gene mutations has recently been linked to PTX-based treatment and prognosis. It was also shown that increasing the quantity of intracellular p53 protein made three NSCLC cell lines more sensitive to PTX. PUMA (p53 upregulated modulator of apoptosis) is an essential apoptosis regulator that also has a role in drug resistance[25]. It was shown that PUMA was downregulated in the PTX-resistant ovarian cell line SKOV3/PTX, and that p53 administration into SKOV3/PTX could upregulate PUMA expression and restore the apoptotic response to PTX[26]. The TP53 hot spot mutation (TP53-m273) boosted multidrug resistance protein 1 (MDR1, which regulates PTX and doxorubicin efflux) expression and PTX resistance[27,28].

4.3. PTEN

PTEN is a phosphatidylinositol 3-kinase/protein kinase B (PI3k/Akt) signalling pathway inhibitor. Its malfunctioning mutation reduces phosphatidylinositol 3, 4, 5-triphosphate (PIP3) dephosphorylation, boosting cell survival, migration, size, and proliferation. Recently, investigations have focused mostly on the involvement of PTEN in the response of human cancer cells to anti-cancer therapies and in the reversion of multiple drug resistance (MDR)[29-32]. PTEN was implicated with PTX resistance in several studies. Cyclin B1 is essential for the G2/M transition. Through the PTEN/PI3 k pathway, Ou et al. discovered that decreasing the cyclin B1 protein sensitised esophageal squamous cell carcinoma (ESCC) cells to PTX-induced apoptosis[33].

4.4. APC

Gene that suppresses tumour growth APC is often mutated and deleted in colorectal cancer, as well as many other epithelial malignancies such as breast, gastric, and lung cancer. The APC protein's best-known function is to regulate the Wnt signalling cascade by down-regulating -catenin, which can control cell cycle progression; however, APC has multiple Wnt independent activities, such as microtubule dynamics, cytoskeletal architecture, and cell adhesion. Because PTX has been shown to interfere with microtubule protein stability, the interaction between APC and PTX has been studied. Monica et al. discovered that deletion of APC in mouse mammary tumour virus promoter-polyoma middle T-antigen (MMTV-PyMT) breast cancer cells resulted in enhanced expression of MDR1 following cisplatin and PTX therapy[34]. APC expression is controlled by a microRNA 135a (miR-135a)[35].

4.5. CKIs

Loss of cell cycle regulation promotes cancer. Cyclin-dependent kinases are a family of serine/threonine kinases that are essential regulators of the cell cycle (CDKs). CDKs are responsible for the transition from one cell cycle phase to the next and act at distinct periods of the cell cycle. CDKs are negatively regulated by endogenous cyclin-dependent kinase inhibitors (CKIs). CKIs are classified into two groups: the INK4 families, which consist of p16, p15, p18, and p19 and can inhibit the complex of cyclin dependent kinase 4/6 (CDK4/6) and cyclin complex activities; and the CKI families, which consist of p16, p15, p18, and p19. CIP/KIP families, which comprise p21, p27, and p57, control border CDKs. CKIs family members have recently been implicated in PTX resistance in human malignancies, according to research. The degree of p21 expression has been established to play a significant role in determining tumour cell susceptibility to PTX[36], and a notable elevation of p21 in A375P cells following PTX treatment and apoptotic induction after mitotic arrest with PTX. However, PTX only slightly boosted the levels of p21 in A375P/Mdr cells, which were resistant to PTX[37].

4.6. Other TSGs

In addition to the TSGs indicated above, abnormalities in ING4, Bax, HIN-1, PLK2, FBW7, LZTS1, BLU, TGFBI, REST, FADD, PDCD4, ING1, and PinX1 have been reported in certain trials to cause PTX resistance. The protein level of ING4

was dramatically reduced in PTX-resistant lung cancer cells. Overexpression of the ING4 protein, on the other hand, might trigger apoptosis and G2/M arrest by reducing the B-cell CLL/lymphoma 2 (Bcl-2)/Bax ratio, which ultimately reversed PTX resistance. Bax is a member of the proapoptotic Bcl-2 family that plays an important role in the production of mitochondrial dependent apoptosis. The Bcl-2/Bax ratio increased in PTX-resistant breast cancer cell lines, and a high ratio inhibited PTX-induced apoptosis in breast cancer and ovarian cancer cells. Hypermethylation reduced HIN-1 expression and impaired PTX sensitivity via the PI3k/Akt pathway. PLK2 hypermethylation lowered the susceptibility of ovarian cancer cells to PTX, as well as G2-M arrest and death. Low LZTS1 protein expression showed little response in patients who received PTX-based chemo-therapy in ovarian carcinoma and breast cancer patients, and it was a worse prognosis patients outcome[38,39]. Previous study by generating LZTS1 knockout mice, detected accelerate mitotic progression resistance to PTX-induced M phase arrest by decreasing CDK1 activity[40], indicating cell cycle distribution may be involved in the above two human cancer.

Table 1 General overview of the 22 TSGs that contribute to PTX-resistance

Sl no.	TSG abbreviation	Full name of the TSGs	Status	Regulation manner	Pathway associated with resistance	Type of cancer
1.	***BRCA1***	Breast cancer 1	Mutation, Protein/mRNA level	Spindle-assembly checkpoint, Microtubule dynamic	Apoptosis, JNK/SAPK and p38/MAPK pathway	Ovarian cancer, HNSCC, Breast cancer, NSCLC
2.	***TP53***	Tumor protein p53	Mutation	G1 phase arrest,Apoptosis	Apoptosis	NSCLC, Ovarian cancer
3.	***PTEN***	Phosphatase and tension homolog	Protein level	Cyclin B1 activity,MiR-22	PI3 K/AKT pathway	ESCC, Colon cancer
4.	***APC***	Adenomatous polyposis coli	Mutation	MDR1, miR-135a	Cell cycle, Cell adhesion	Breast cancer, NSCLC
5.	***p21/CDKN1A***	Cyclin-dependent kinase inhibitor 1A	Protein level	Cell cycle	Cell cycle, Apoptosis	Melanoma
6.	***p16/CDKN2A***	Cyclin-dependent kinase inhibitor 2A	Protein level	Cell cycle	Cell cycle	Triple-negative breastcancer
7.	***FRMD6/hEx***	FERM domain-containing protein 6	Protein level	Cell cycle	Cell cycle	Breast cancer
8.	***RASSF1***	Ras association domain-containing protein 1	Methylation	Cell growth	Cell cycle	Ovarian cancer
9.	***YAP***	Yes-associated protein 1	deletion	Cell cycle	Cell cycle	Breast cancer
10	***ING4***	Inhibitor of growth 4	Protein level	Bcl-2/Bax ratio	Apoptosis, Cell cycle	Lung cancer
11.	***BAX***	BCL2-associated X protein	mRNA level	Bcl-2/Bax ratio	Apoptosis	Breast cancer

12.	***HIN-1/SCGB3A1***	High in normal-1	Methylation	Apoptosis	PI3K/AKT pathway	Ovarian cancer
13.	***PLK2***	Polo-like kinase 2	Methylation	G2/M phase checkpoint	Cell cycle, apoptosis	Ovarian cancer
14.	***LZTS1/FEZ1***	Leucine zipper tumor suppressor 1	Protein/mRNA level	Cell cycle	Cell cycle	Ovarian cancer, Breast cancer
15.	***FBXW7/FBW7***	F-box and WD repeat domain containing 7	Mutation	Ubiquitination	Ubiquitination	Ovarian cancer
16.	***ZMYND10/BLU***	zinc finger MYND type containing 10	Methylation	Bcl-2/Bax ratio	Apoptosis, PI3 K/Akt pathway	Ovarian cancer
17.	***TGFBI***	Transforming growth factor-β-induced	mRNA/protein level	β3 integrin	Apoptosis	NSCLC, Ovarian cancer
18.	***REST***	RE-1 silencing transcription factor	Protein level	TUBB3	PI3K/AKT pathway	Ovarian cancer
19.	***FADD***	Fas-associated death domain protein	Phosphorylation	Apoptosis Cell cycle	JNK/SAPK pathway	Cervical carcinoma, Prostate cancer
20.	***PDCD4***	Programmed cell death 4	Protein/mRNA level	Mir-182	Cell growth, Cell cycle	Ovarian cancer, Cervical carcinoma
21.	***ING1***	Inhibitor of growth 1	Protein level	Apoptosis	p53-dependent path- way	Osteosarcoma
22.	***PinX1***	PIN2/TRF1 interacting telomerase inhibitor 1	Protein level	Spindle-assembly checkpoint	Cell cycle	Cervical carcinoma

5. Paclitaxel chemotherapy for advanced gastric cancer

5.1. Administration of paclitaxel every 3 weeks (3-weekly)

Because a comprehensive treatment for advanced stomach cancer has yet to be established, the therapeutic aims are to limit disease progression, relieve symptoms, enhance quality of life, and extend survival. Paclitaxel has showed promising results in the treatment of advanced gastric cancer patients. Paclitaxel has traditionally been given as a bolus infusion every three weeks. Paclitaxel monotherapy in the first-line and second-line treatment of advanced illness has achieved response rates of roughly 17%-28%[41-42] and much longer survival durations (median survival time [MST] around 8 months) than other drugs with comparable response rates.Researchers are considering further development of the taxanes in combination with existing fluoropyrimidine-platinum regimens in advanced gastric cancer due to the significant activity seen in these early phase II studies, as well as the lack of cross-resistance to other drugs and the lack of overlapping toxicities.

Various combination medicines have been tested in clinical trials in try to enhance the outcomes. Paclitaxel, in particular, appears to have a schedule-dependent synergy with platinum drugs, as demonstrated in established human

gastric cancer cell lines[43]. This synergy has resulted in the creation of paclitaxel-platinum combination regimens in a variety of solid malignancies, including gastric cancer. Phase II studies using 3-weekly paclitaxel-containing combinations in the treatment of individuals with advanced gastric cancer[44].In a first-line therapy context, combination regimens of paclitaxel plus platinum, paclitaxel plus 5-FU, or both produced response rates of 32%-65% with MSTs of roughly 11 months (range, 6-14 months). Response rates for patients receiving more than second-line therapy varied from 22% to 28%, with median survival ranging from 6 to 10 months. Although the treatment regimens and demographics studied in these research varied, the regimens were usually well tolerated, with myelosuppression being the most prevalent hazard. Alopecia, myalgia, mucositis, and neurotoxicity were also documented as side effects of these combination therapy.

When the regimens were used in first-line, the effect of paclitaxel in these combination regimens was clear in terms of response rates and MST when compared to paclitaxel monotherapy. However, as compared to paclitaxel alone, combination chemotherapies did not provide significant survival advantages in the second-line situation.

5.2. Weekly administration of paclitaxel

Weekly paclitaxel may be more successful and less harmful than every three weeks, according to phase II research. In a phase III trial, the Cancer and Leukemia Group B protocol 9840 was launched to examine this subject. The final results were published in 2008, and it was confirmed that weekly paclitaxel administration was superior to every three weeks (3-weekly) paclitaxel administration for metastatic breast cancer, with a significant increase in response rate and an important advantage in time to progression[45]. Based on the findings of these investigations, studies with weekly paclitaxel, as well as different paclitaxel-containing combinations with other chemotherapeutic drugs, have been conducted for the treatment of advanced gastric cancer.

Weekly paclitaxel monotherapy in the first- and second-line treatment of advanced illness generated response rates of roughly 16%-18% and MSTs of around 8 months [46, 47] that were nearly equal to the findings of 3-week administration. However, patients' quality of life and adherence to the trial regimens appeared to be greater with weekly administration than with 3-weekly administration.

Three trials investigated 5-FU+leucovorin or 5-FU combination treatments. The addition of either a bolus 5-FU (2400-2600 mg/m2) or a 5-day continuous infusion of 600 mg/m2 5-FU to monthly paclitaxel at 80 mg/m2 was shown to have no effect on patient safety. All of these trials had response rates ranging from 39% to 41%, and the median progression-free survival time was greater than 3.5 months. The MST increased from 8.8 to 11.0 months, indicating that the combination of weekly paclitaxel and 5-FU is better to weekly paclitaxel monotherapy in terms of response rate and prognosis. Weekly paclitaxel with cisplatin has also been studied. Weekly paclitaxel 80 mg/m2 plus weekly cisplatin 25 mg/m2 showed no increased toxicity when compared to weekly paclitaxel monotherapy[48]. Although the response rates of these regimens ranged from 18% to 41%, the combination of weekly or biweekly paclitaxel with cisplatin resulted in an improved prognosis of around 11 months.

Paclitaxel, 5-FU, and cisplatin triplet treatment was also investigated. Although this regimen had a high response rate of roughly 50%, the median survival was around 11 months and was not significantly improved over doublet paclitaxel-5-FU regimens or paclitaxel-cisplatin regimens. A new phase II experiment is presently underway, based on the recommended dose of weekly paclitaxel 80 mg/m2, cisplatin 25 mg/m2, and 5-FU 600 mg/m2 suggested by an 83% response rate in a phase I trial[49].

In terms of oral chemotherapeutic drugs, weekly paclitaxel combination with oral UFT (uracil, tegafur) and leucovorin demonstrated a 50% response rate and a mean survival time of 9.8 months. There have also been studies of combinations with oral S-1 (tegafur, gimeracil, oteracil). Response rates varied from 40% to 65% in these studies, while MSTs ranged from 8.9 to 15.5 months. Weekly treatment of 40-60 mg/m2 paclitaxel coupled with 80 mg/m2 S-1 for 14 days in a 4-week cycle[50] appeared to provide a better prognosis (median, 13.85 months) than biweekly administration of paclitaxel plus S-1.Because the background of patients who are eligible for paclitaxel plus oral agents is assumed to be better due to their ability to take oral agents, it is not surprising that paclitaxel plus S-1 showed the most significant improvement in prognosis in patients with advanced and metastatic gastric cancer.

6. Neoadjuvant therapy

Neoadjuvant chemotherapy offers the benefit of transforming unresectable breast cancers to resectable tumours, allowing for more conservative surgery in some mastectomy candidates. There are several advantages to using neoadjuvant chemotherapy. It provides a one-of-a-kind chance to assess therapy response, with full pathologic response

serving as a surrogate measure of survival, as well as a more fast assessment of the efficacy of novel therapeutic drugs and early discontinuation of unsuccessful treatment. Furthermore, in the event of therapeutic resistance, modifying the dose and/or switching to a different medicine relieves patients of the burden of toxicity and side effects. Furthermore, neoadjuvant chemotherapy enables for personalised treatment and the collection of tumour samples before, during, and after treatment for translational research[51-52]. This evaluation of tumour behaviour in situ during neoadjuvant treatment and its relationship to clinical outcome is an effective model for determining tumour features' predictive value. The ultimate objective of neoadjuvant chemotherapy translational research is the implementation of individually individualised treatment regimens based on an individual risk profile.

In addition to the benefits of therapy, neoadjuvant investigations give excellent tissue samples for biomarker screening. Because locoregional responses to neoadjuvant therapy correspond with long-term outcomes, neoadjuvant therapies provide unique potential for early response prediction and treatment individualization.

7. Role of neoadjuvant paclitaxel in breast cancer

Paclitaxel has been shown in several clinical trials to be effective in the neoadjuvant treatment of breast cancer. After neoadjuvant AT followed by CMF, ECTO achieved a 23% in-breast PCR and a 20% breast-plus-node PCR. The NOAH study found a 17% in-breast PCR and a 16% breast-plus-node PCR in HER2-negative patients treated with neoadjuvant AT followed by paclitaxel and CMF. PCR rates in patients with HER2-positive disease treated with neoadjuvant chemotherapy plus neoadjuvant and adjuvant trastuzumab were 43% in the breast and 38% in the breast-plus-axilla.

SWOG 0012 compared 21-day AC followed by paclitaxel to weekly AC with granulocyte colony-stimulating factor (G-CSF) support followed by paclitaxel. Although PCR was somewhat higher following weekly AC with paclitaxel (24.3 vs 20.7%; P = 0.45), PCR was considerably higher in individuals with stage IIIB disease who received weekly AC versus 21-day AC (25.8 vs 9.3%; P = 0.0057). Following that, phase III Neo-tAnGo discovered that paclitaxel followed by anthracyclines significantly improved PCR compared to anthracyclines followed by paclitaxel (20 vs 15%; P = 0.03).

In CALGB 40603, triple-negative breast cancer patients were given neoadjuvant weekly paclitaxel followed by dose-dense AC bevacizumab and/or carboplatin (TNBC). Carboplatin substantially raised both breast and breast-plus-axilla PCR (60 vs 46%; P = 0.0018), but bevacizumab significantly increased just breast PCR (59 vs 48%; P = 0.0089).

Neoadjuvant lapatinib plus trastuzumab, followed by neoadjuvant lapatinib plus trastuzumab plus paclitaxel, significantly improved PCR against neoadjuvant trastuzumab alone, followed by neoadjuvant trastuzumab plus paclitaxel (51.3 vs 29.5%; P = 0.0001) in patients with HER2? Similarly, when neoadjuvant AC followed by trastuzumab plus lapatinib plus paclitaxel was compared to AC followed by trastuzumab plus paclitaxel, NSABP B-41 had greater PCR (62 vs 52.5%; P = 0.095). CALGB 40601 also had numerically higher PCR following weekly paclitaxel plus trastuzumab plus lapatinib compared weekly paclitaxel plus trastuzumab (51 vs 40%; P = 0.11).

These trials show that neoadjuvant paclitaxel is effective in all subtypes of breast cancer. As a result, taxanes are currently included in many neoadjuvant regimens recommended by the National Comprehensive Cancer Network.

8. Conclusion

Paclitaxel's introduction throughout the last two decades has extended therapy choices for various types of cancer patients. This was especially noticeable in breast, ovarian, and lung malignancies. Many phase I and phase II studies for gastric malignancies have been implemented and published, indicating the potential efficacy of paclitaxel in either advanced disease or curatively resected stomach tumours in an adjuvant context. The main source of worry is the scarcity of randomised clinical studies of paclitaxel for gastric cancer.

In terms of adjuvant chemotherapy, following a feasibility study to confirm the regimen's safety in an adjuvant setting, one large trial, the Stomach Cancer Adjuvant Multi-institutional Trial Group (SAMIT) trial, is currently enrolling over 1300 patients; the trial will further define the benefits of paclitaxel and oral fluorinated pyrimidines in the treatment of curatively resected gastric cancers.

In conclusion, nab-paclitaxel appears to be a safe and effective neoadjuvant treatment for breast cancer. Ongoing and future trials will look at nab-efficacy paclitaxel's in all subtypes of breast cancer, including TNBC, which has a high sensitivity to this therapeutic method. Future trials should include molecular or biological/immunological analysis to

help uncover predictive indicators of response that may be utilised to guide patient selection and, eventually, increase response rates to neoadjuvant nab-paclitaxel-based regimens.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript.

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