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Current advances in triple-negative breast cancer (TNBC) chemotherapy: A literature review

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ABSTRACT

Triple-negative breast cancer (TNBC) representing 20% of all breast cancer cases, is distinguished by the absence of receptors of estrogen, progesterone, and human epidermal growth factor 2 (HER2). This characteristic results in a restricted range of potential therapeutic options and a generally unfavorable prognosis. This review assesses the efficacy of chemotherapy agents, including vinorelbine, cisplatin, gemcitabine, and pembrolizumab, in the treatment of the TNBC. These agents, frequently combined with other therapies, have exhibited enhanced survival outcomes. However, they are linked with considerable adverse effects, including hematologic toxicity and fatigue. This review underscores the necessity for personalized treatment strategies that consider both therapeutic efficacy and patient safety, while also addressing the economic challenges posed by expensive therapies like pembrolizumab.

ABSTRAK

Kanker payudara triple-negatif (*triple-negative breast cancer*/TNBC) yang mewakili 20% dari seluruh kasus kanker payudara, ditandai dengan tidak adanya reseptor estrogen, progesteron, dan *human epidermal growth factor* 2 *receptor* (HER2). Karakteristik ini mengakibatkan terbatasnya pilihan terapi potensial dan prognosis yang umumnya tidak bagus. Tinjauan pustaka ini menilai kemanjuran agen kemoterapi, termasuk vinorelbine, cisplatin, gemcitabine, dan pembrolizumab, dalam pengobatan TNBC. Agen-agen ini, yang sering digunakan bersama dengan terapi lain, telah menunjukkan peningkatan hasil kelangsungan hidup. Namun, obat ini mempunyai efek samping yang cukup besar, termasuk toksisitas hematologi dan kelelahan. Tinjauan pustaka ini menggarisbawahi perlunya strategi pengobatan yang dipersonalisasi yang mempertimbangkan kemanjuran terapeutik dan keselamatan pasien, sekaligus mengatasi tantangan ekonomi yang ditimbulkan oleh terapi mahal seperti pembrolizumab.

INTRODUCTION

A subtype of breast cancer, triple-negative breast cancer (TNBC) is characterized by the absence of the human epidermal growth factor 2 receptor (HER2), progesterone receptor (ER), and estrogen receptor (PR). It constitutes about 20% of all breast cancer commonly found among woman under 40 y.o. The TNBC can be categorized into various subgroups, such as, claudin low, mesenchymal (MES), luminal androgen receptor, basal-like (BL1 and BL2), and immunomodulatory (IM), with basal like types being the most prevalent of all subtypes (5-70% for BL1 and 20-30% for BL2).[1] TNBC is associated with aggressive behavior, and contributes to death among the patients, which is 40% of total mortalities within the first 5 years after diagnosis is made.[2]

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Treatments of TNBC are often difficult, with its highly invasive nature, which occurs in 46% of the patients associated with TNBC. The median time of survival for TNBC patients is 13.3 mo, with a 25% recurrence rate after surgery. Metastasis occurs mostly in the visceral organ and the brain,[3] with shorter relapse time compared to non-TNBC patients (19-40 mo vs 35-67 mo), and a higher mortality rate than non-TNBC patients (up to 75%).[4,5] Chemotherapy and surgery often are the combination therapy applied to breast cancer patients, including TNBC, with current strategies exploring immunotherapy in combination with chemotherapy to achieve the intended effects.

This review article aimed to inform the reader of the current updates on TNBC chemotherapy in order to use them as a source of information and or consideration for choosing chemotherapeutic agents for TNBC patients.

MATERIAL AND METHODS

In this study, we performed a narrative review of the literature to assess the effectiveness of chemotherapeutic agents on patients with TNBC. The review of this article examined previous research from PubMed as a literature resource. The search strategy used keywords including triple negative breast cancer, TNBC, and chemotherapy. All articles included are from the last 5 yr.

RESULTS

Six articles that met criteria were collected from the PubMed data base to be reviewed (TABLE 1).

TABLE 1. Summary of recent advances in TNBC chemotherapies

Author	Study design	Population	Results
Wang *et al.*[6]	Single-center, prospective randomized controlled trial	TNBC patients with clinical stages of T1-4/ N1-3/M0 with prior NAC of anthracycline (8 cycles), and residual tumor in axillary lymph node	Main agent(s): vinorelbine It is the first randomized trial to evaluate vinorelbine as adjuvant intensive therapy in TNBC patients with node-negative disease following standard NAC and showed significantly improved 3-yr DDFS and RFS rates in the intensive arm (90.0 vs. 42.4%; p= 0.022) and a trend toward better OS (90.0 vs. 61.4%; p = 0.149) despite enrollment of only 22 patients (7.2% of the target).
He *et al.*[7]	Multicenter, open label randomized controlled trial	TNBC patients aged 18-70 y.o. after definitive surgery	Main agent(s): gemcitabine and cisplatin into anthracycline/ taxane based therapy. A total of 504 patients, 498 were treated with a median follow-up of 45.1 mo. Patients in arm A (intensive chemotherapy) showed superior 3-yr disease-free survival (90.9 vs. 80.6%; p= 0.03) and relapse-free survival (92.6 vs. 83.2%; p= 0.04) compared with arm B (standard chemotherapy). However, the differences in overall survival were not significant. Arm C, which added further treatment to the arm B regimen, showed superior survival outcomes across all measures, with adverse event rates of 64% (A), 51% (B) and 54% (C) and no treatment-related deaths.
Bardia *et al.*[8]	Multicenter, open label randomized controlled trial	TNBC patients with previous advanced solid cancers treated with therapy intended for metastatic disease	Main agent(s): sacituzumab govitecan-hziy Among 108 patients with TNBC who had received a median of three prior therapies, the response rate was 33.3% (95%CI: 24.6-43.1) with a median response duration of 7.7 mo (95% CI: 4.9-10.8). Clinical benefit was observed in 45.4% of patients. Median progression-free survival was 5.5 mo (95% CI: 4.1-6.3) and overall survival was 13.0 mo (95% CI:11.2-13.7). Adverse events included grade 3-4 anemia and neutropenia, with febrile neutropenia occurring in 9.3% of patients. There were four deaths and 2.8% discontinued treatment due to adverse events.

TABLE 1. Cont.

Author	Study design	Population	Results
Schmid *et al.*[9]	Randomized controlled trial	TNBC patients with untreated stage II or III disease	Main agent(s): pembrolizumab In a randomized trial involving 1,174 patients, 784 received pembrolizumab in combination with chemotherapy, and 390 received placebo in combination with chemotherapy. The median follow-up period was 75.1 mo. At 60 months, the overall survival rate was significantly higher in the pembrolizumab–chemotherapy group (86.6%; 95%CI:84.0–88.8) compared to the placebo–chemotherapy group (81.7%; 95% CI:77.5–85.2; p= 0.002). The adverse events observed were consistent with the known safety profiles of pembrolizumab and chemotherapy.
Dent *et al.*[10]	Double-blind, placebo-controlled trial	TNBC patients eligible for taxane, with no prior chemotherapy for advanced disease	Main agent(s): ipatasertib, paclitaxel A total of 255 patients were randomized between February 2018 and April 2020 to receive either ipatasertib (168) or placebo (87). At the initial analysis, no significant difference was observed in progression-free survival (PFS) between the two arms (median 7.4 vs. 6.1 mo; HR:1.02; 95% CI:0.71–1.45). The final analysis demonstrated no statistically significant difference in overall survival (median 24.4 vs. 24.9 mo; HR: 1.08; 95% CI: 0.73–1.58). However, ipatasertib treatment resulted in a higher incidence of grade ≥3 diarrhea (9 vs. 2%) and dose reductions (39 vs. 14%) compared to the control group. Nevertheless, the rates of grade ≥3 adverse events were similar between the two groups (51 vs. 46%).
Wang *et al.*[11]	Single center, Randomized controlled trial	TNBC patients aged > 18 years, stage pT I-III, previously have been treated with NAC and surgical treatment	Main agent(s): Taxane, lobaplatin, anthracycline In a study of 103 stage I–III TNBC patients, the Arm A (taxane and lobaplatin) regimen demonstrated a significantly higher pCR (pathological complete response) rate compared to the Arm B (taxane-anthracycline-based regimens) regimen (41.2 vs. 21.2%; p= 0.028). Patients with positive lymph nodes and a low neutrophil-to-lymphocyte ratio (NLR) exhibited a greater benefit from Arm A (p= 0.012). However, no significant differences in event-free survival (p= 0.895) or overall survival (p= 0.633) were observed. The incidence of grade 3/4 anemia was higher in Arm A (p= 0.015), while the incidence of grade 3/4 neutropenia was higher in Arm B (p= 0.044).

DISCUSSION

Vinorelbine is a chemotherapeutic agent derived from Vinca rosea (*Catharanthus roseus*), which is used as a primary therapy for cancers such as TNBC. Vinorelbine acts by disrupting microtubule by tubulin binding and preventing the microtubule to polymerize, which is a hallmark of cancer cell with its unstoppable growth. The inhibition causes mitosis to cease, leading to cell cycle arrest and subsequently, apoptosis of tumor cells.[12] Vinorelbine is classified as fourth line of the therapy line for TNBC[13], in combination with trastuzumab. A study conducted by Wang *et al.*[11] reported the overall survival of patients underwent the chemotherapy (90%) is higher than the control group (61.4%; p=0.022).

Adverse events observed during the course of this trial were neutropenia, thrombocytopenia, anemia, vomiting, fatigue, peripheral toxicity and increased aminotransferase. There were only two grade 3/4 neutropenia and febrile neutropenia associated with the treatment group.[6]while TNBC with residual positive axillary lymph node after standard NAC indicates poor prognosis. There is no evidence that

vinorelbine alone can be used as an adjuvant intensive therapy for such patients at present.\nMETHODS: We recruited TNBC patients with clinical stage of T1-4/N1-3/M0, who received NAC with 8 cycles of anthracycline sequential paclitaxel and had residual tumor in axillary lymph node after surgery. The patients were randomly divided into adjuvant intensive treatment group (Group A This study showed that vinorelbine could become a potential neoadjuvant chemotherapy (NACT). However, further study with enough subjects should be conducted to obtain a conclusive result.

Cisplatin is a chemotherapeutic agent belonging to the class of alkylating agent. It is commonly used in the therapy of solid tumors and hematologic malignancies. Cisplatin acts by binding covalently to the purine bases of guanine and adenine, causing subsequent strand break.[14] The administration of cisplatin alone, or in combination with taxane and transtuzumab, in women diagnosed with TNBC resulted in a notable rise in the number of complete responses in those who received NACT. However, this treatment approach was also linked to higher rates of systemic problems, including neutropenia, anemia, and diarrhea.[15]and that synergy may exist for the combination of a taxane, trastuzumab, and a platinum salt for HER2-positive breast cancer. We therefore aimed to assess the efficacy of the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive breast cancer.\nMETHODS: Patients with previously untreated, non-metastatic, stage II-III, triple-negative breast cancer and HER2-positive breast cancer were enrolled. Patients were treated for 18 weeks with paclitaxel (80 mg/m(2

Gemcitabine, on the other hand, directly affects DNA by inhibiting its replication. Myelosuppression is a common adverse event experienced by patients taking gemcitabine.[12] A study by He *et al.*[7] evaluated the use of gemcitabine and cisplatin into anthracycline or taxane based adjuvant therapy. Patients underwent intensive chemotherapy (90.9%) showed better 3-years disease free survival (DFS) compared to the standard chemotherapy regimen (80.6%; p=0.04), although overall survival of patients was not significant statistically. Hematological adverse events including neutropenia, anemia, thrombocytopenia, and febrile neutropenia were observed.

Although the combination between gemcitabine and cisplatin did not increase the incidence of serious ADR, proper management should be added in order to increase patient compliance with the endpoint of higher success rate for chemotherapy. Both gemcitabine and cisplatin/carboplatin is listed as category 1 or preferred first line therapy for TNBC, alongside pembrolizumab.[13]

Cyclophosphamide, epirubicin and 5-fluorouracil prescribed to TNBC patients along with the addition of docetaxel for tumors more than 2 cm in size leads to a positive response in 20% of patients.[16] Complete pathomorphological response to NACT, mainly consisting of anthracyclines and taxanes (23%) was higher than other types of BC such as luminal subtypes, and associated with decreased recurrence rates.[17] Another study discovered that the rate of complete pathomorphological response to NACT was 36% out of 72 observations.[18]local surgery (breast conservation or mastectomy The utilization of NACT in patients with TNBC also decreases the requirement for total removal of lymph nodes in the armpit due to the transformation of cancer that had spread to the lymph nodes (N1) to cancer that had not spread to the lymph nodes (N0).[19]

Pembrolizumab is listed as the preferred first line therapy for TNBC, combined with several chemotherapeutic agents such as paclitaxel, gemcitabine, and carboplatin.[13] The mechanism of action of pembrolizumab is by binding to programmed death receptor 1 (PD-1) on lymphocytes, targeting tumor cells which express high level of programmed

death receptor ligand-1 (PD-L1). This engagement causes the function of t-cell to be inhibited, allowing improved t-cell mediated killings on specified tumor cells.[20]

A randomized controlled trial of Keynote-522 in its third phase explored the use of pembrolizumab in a platinum-containing chemotherapy regimen, with an OS at 60 mo of 86.6% (95%CI: 84-88.8) vs placebo with 81.7% (95%CI: 77.5-85.2). Median follow up was 75.1 mo with a range of 65.9 vs 84.0. Pembrolizumab is associated with adverse effects such as rash, hypothyroidism, hyperthyroidism, pneumonitis, adrenal insufficiency, diarrhea and skin toxicity. Utmost care is warranted in patients with preexisting autoimmune disorders following the use of pembrolizumab.[15]and that synergy may exist for the combination of a taxane, trastuzumab, and a platinum salt for HER2-positive breast cancer. We therefore aimed to assess the efficacy of the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive breast cancer.\ nMETHODS: Patients with previously untreated, non-metastatic, stage II-III, triple-negative breast cancer and HER2-positive breast cancer were enrolled. Patients were treated for 18 weeks with paclitaxel (80 mg/m(2 Besides, the use of pembrolizumab, although with good efficacy, is still hardly reachable for lower income patients due to its price of 11.773 US $ per 28-d cycle.[21] Alternative treatments of TNBC should be considered if the patients and or healthcare system is not capable of handling such prices in treatment.

CONCLUSION

Triple-negative breast cancer is distinguished by its assertive characteristics, along with increased chances in metastasis, leading to difficulties in diagnosis and encouraging radical surgical treatment. The use of newer immunotherapy in conjunction with proven chemotherapy agents increases the overall survival, and disease free or progression free survival in patients with TNBC, alongside the increase of potential ADR. Healthcare provider must consider socioeconomic in choosing chemotherapeutic agents, in order to increase patient compliance with the endpoint of improving their quality of life.

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