Efficacy and Safety of Vinorelbine Plus Cisplatin vs. Gemcitabine Plus Cisplatin for Treatment of Metastatic Triple-Negative Breast Cancer After Failure with Anthracyclines and Taxanes

Junbin Wang, Rongsheng Zheng, Zishu Wang, Yan Yang, Mingxi Wang, Weiyan Zou

Background: This study aimed to compare the efficacy and safety of vinorelbine plus cisplatin (NP regimen) vs. gemcitabine plus cisplatin (GP regimen) for treatment of metastatic TNBC after failure with anthracyclines and taxanes.

Material/Methods: A total of 48 patients with metastatic TNBC that failed in anthracyclines and taxanes treatment were enrolled and randomly grouped. Patients in the NP group (n=22) were given 25 mg/m² vinorelbine on days 1 and 8 and 25 mg/m² cisplatin on days 2–4 of each 21-day cycle, while subjects in the GP group (n=26) were administered 1000 mg/m² gemcitabine on days 1 and 8 and 25 mg/m² cisplatin on days 2–4 of each 21-day cycle. The treatment response and adverse events were compared between the 2 groups every 2 cycles.

Results: The ORR, DCR, and median TTP were 45.5%, 77.3%, and 5 months in the NP group, and 46.2%, 80.8%, and 5.2 months in the GP group, and no significant differences were observed in ORR, DCR, and median TTP between the 2 groups (P>0.05). The major adverse events included grade I–II bone marrow inhibition, gastrointestinal reactions, and phlebitis, and a lower incidence of thrombocytopenia and rash and a higher incidence of phlebitis was found in the NP group than in the GP group (P<0.05).

Conclusions: Either NP or GP regimen is active and tolerated in treatment of metastatic TNBC with anthracyclines and/or taxanes resistance, which may be used as a salvage treatment for metastatic TNBC.

MeSH Keywords: Chemical Safety • Comparative Study • Treatment Outcome • Triple Negative Breast Neoplasms

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/905300
Background

Triple-negative breast cancer (TNBC), an aggressive form of breast cancer that is negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), is characterized by high invasiveness, high metastatic spread, high recurrence, and poor prognosis [1–3]. TNBC, which is relatively highly prevalent in young women, is estimated to account for 10% to 25% of all breast cancers, and the global incidence appears to be increasing [4–6]. In China, a sharp increase is reported in the incidence of both breast cancer and TNBC [7].

To date, there has been no effective therapy for TNBC [8], and the standard treatment still depends on surgery and adjuvant chemotherapy and radiotherapy [9–11]. In general, TNBC exhibits an elevated chemosensitivity relative to other forms of breast cancers [12]. Anthracyclines and taxanes are active against TNBC, and the addition of anthracyclines or taxanes to the chemotherapy regimen has been shown to remarkably improve the clinical outcomes [13–17]. However, there is an increasing number of patients with anthracyclines- and taxanes-resistant TNBC following extensive use of these agents [18–20]. There is still no consensus on the standard therapy of TNBC with resistance to anthracyclines and taxane, and empirical therapy remains the major treatment. Finding effective regimens without cross-resistance to anthracyclines and taxanes is of great importance for the treatment of recurrent and metastatic TNBC.

Vinorelbine, a semi-synthesized vinca alkaloid belonging to the Catharanthus alkaloid group, is a cell cycle-specific agent that exhibits cytotoxicity through binding to tubulin, thereby disrupting microtubule formation during mitosis [21]. Vinorelbine has no cross-resistance to anthracyclines and taxanes, and is an effective agent for the treatment of recurrent and metastatic TNBC [22]. Vinorelbine and cisplatin, which act on various targets, exhibit a synergistic anti-cancer activity and have shown a relatively high efficacy against TNBC [23,24].

Gemcitabine, an antimetabolite, is also a cell cycle-specific agent, which primarily kills cells that are undergoing DNA synthesis (S phase), blocks the cell cycle transition from G1 phase to S phase, and suppresses DNA synthesis, thereby inhibiting cancer cell growth [25,26]. It has been demonstrated that gemcitabine is active for advanced breast cancers, and may serve as an option for the treatment of patients with metastatic breast cancer who failed anthracyclines and/or taxanes treatment [27–29]. Gemcitabine monotherapy was reported to achieve less than 20% response rate (RR) in the treatment of metastatic breast cancer with resistance to anthracyclines and/or taxanes [30,31], and gemcitabine combination chemotherapy has been used for the treatment of many cancers [32,33]. Although multiple chemotherapy regimens have been tested for their efficacies and toxicities against breast cancer, there is still no standard regimen for the treatment of metastatic TNBC.

The purpose of this study was to evaluate and compare the efficacy and safety of vinorelbine plus cisplatin (NP regimen) vs. gemcitabine plus cisplatin (GP regimen) for the treatment of metastatic TNBC after failure with anthracyclines and taxanes.

Material and Methods

Ethics statements

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Bengbu Medical College (permission no. BYFY20110297). Signed informed consent was obtained all participants following a detailed description of the purpose of this study.

Subjects and grouping

The clinical records of 48 female TNBC patients admitted to the Department of Oncology, the First Affiliated Hospital of Bengbu Medical College (Bengbu, China) during the period from July 2011 through June 2014, were retrospectively reviewed. All patients were definitively diagnosed with breast cancer using pathologic examinations, and immunohistochemistry revealed that all breast cancers were negative for ER, PR, and HER2. The patients had a median age of 49 years (range, 33 to 77 years), and the 48 cases included 41 cases with infiltrating duct carcinoma, 5 cases with infiltrating lobular carcinoma, and 2 cases with basal-like breast carcinoma. There were 47 cases undergoing radical or modified radical surgery, and all patients had a history of neoadjuvant therapy, adjuvant therapy, or palliative chemotherapy with anthracyclines and taxanes; however, none of the patients received treatment with gemcitabine or vinorelbine. Physical examinations, imaging examinations, or biopsy revealed TNBC recurrence and metastasis, and CT or MRI scanning displayed at least 1 measurable target tumor focus. All patients were identified with stage IV breast cancer [34], and had Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 to 2 [35]. The subjects had a predicted survival of over 3 months, and did not receive any anti-cancer therapy within the latest month prior to the enrollment. All subjects had nearly normal functions of vital organs, which did not affect chemotherapy.

The patients were assigned into the NP regimen group (n=22) or the GP regimen group (n=26). Patients in the NP regimen group had a median age of 48 years (range, 35 to 74 years), while subjects in the GP regimen group had a median age of 49 years (range, 33 to 77 years).
Treatment protocol

Patients in the NP regimen group were administered an intravenous infusion with vinorelbine at a dose of 25 mg/m² on days 1 and 8 and cisplatin at a dose of 25 mg/m² on days 2–4 of each 21-day cycle, while subjects in the GP regimen group were intravenously infused with gemcitabine at a dose of 1000 mg/m² on days 1 and 8 and cisplatin at a dose of 25 mg/m² on days 2–4 of each 21-day cycle. If patients developed bone metastasis, zoledronic acid was given by intravenous infusion at a single dose of 4 mg administered once every 3 to 4 weeks. All patients underwent 2 to 6 cycles of chemotherapy, and antiemetic therapy with 5-HT3 receptor antagonists during the chemotherapy. Routine blood test, liver and kidney function tests, and electrocardiogram were performed 1 week prior to, during, and 1 week after chemotherapy, and CT and MRI scans were conducted after 2 cycles of chemotherapy. Prophylactic leukocyte-elevated treatment was not given during the chemotherapy, and granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) or IL-11 were administered to enhance leukocyte and platelet levels pre- and post-chemotherapy based on analysis of bone marrow inhibition. If grade III or IV chemotherapy-related toxicity occurred [36], the dose of chemotherapeutic agents was reduced. The response to chemotherapy was assessed once every 2 cycles, and chemotherapy-related toxicity was evaluated once each cycle. The chemotherapy regimen was continued for 6 cycles if the patients had improvements in disease severity or stable disease, and chemotherapy was terminated or the chemotherapy regimen was changed if patients had disease progression or were intolerant to chemotherapy-related toxicity.

Assessing the response to chemotherapy

The response to the NP and GP regimens was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 [37], including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). RR was calculated as the proportion of patients with CR + PR in all patients, and the disease control rate (DCR) was described as the proportion of patients with CR + PR +SD in all cases. TTP was defined as the length of time from the beginning of chemotherapy to disease progression.

Assessment of chemotherapy-related toxicity

The adverse events caused by chemotherapy were recorded after each cycle of chemotherapy, and the adverse events were classified into grade 0 to IV according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [36].

Statistical analysis

All statistical analyses were performed using the statistical software SPSS version 16.0 (SPSS, Inc.; Chicago, IL, USA). Differences in proportions were tested for statistical significance with the chi-square test or Fisher’s exact test, and survival analysis was performed with the Kaplan-Meier method. A P value <0.05 was considered statistically significant.

Results

Response to the NP and GP regimens

The baseline demographic and clinical characteristics were comparable between the NP and GP regimen groups (P>0.05) (Table 1). All 48 patients were subjected to the evaluation of the response to the chemotherapy. A total of 100 cycles of chemotherapy were administered in the NP regimen group, with a mean of 4.5 cycles given to each subject, and a 45.5% ORR and 77.3% DCR were achieved. In the GP regimen group, a total of 116 cycles of chemotherapy were performed, with a mean of 4.5 cycles given to each patient, and a 46.2% ORR and 80.8% DCR were observed. There were no significant differences detected in the ORR or DCR between the NP and GP regimen groups (P>0.05) (Table 2). A better response to either the NP regimen or the GP regimen was seen in the postmenopausal patients, patients with first-line treatment, patients with local and lymph node metastases, and patients with single metastatic lesion compared to the premenopausal patients, patients with second-line treatment, patients with visceral metastasis, and patients with multiple metastatic lesions (P>0.05) (Table 3).

TTP

Complete follow-up was available for all 48 subjects enrolled in the study. The subjects in the NP regimen group had TTP of 2 to 18 months, with median TTP of 5 months (95% CI: 3.28 to 6.72 months), and patients in the GP regimen group had TTP of 1.8 to 18.5 months, with median TTP of 5.2 months (95% CI: 3.33 to 7.07 months). There was no significant difference in the median TTP between the NP and GP regimen groups (P>0.05) (Figure 1).

Chemotherapy-related toxicity

Bone marrow inhibition, gastrointestinal reactions, and phlebitis were the predominant chemotherapy-induced toxicities, which were mainly identified as grade I and II, and grade III and IV adverse events, mainly leucopenia, thrombopenia, nausea, vomiting, loss of appetite, and phlebitis. A higher incidence of thrombopenia and skin rash was detected in the GP regimen.
Table 1. Comparison of the baseline demographic and clinical characteristics between the NP and GP regimen groups.

| Demographic and clinical feature | NP regimen group (n=22) | GP regimen group (n=26) | P |
|---------------------------------|-------------------------|-------------------------|---|
| Age (years)                     |                         |                         |
| ≤ 45                            | 5                       | 7                       | 0.738 |
| > 45                            | 17                      | 19                      |
| Menses                          |                         |                         |
| Pre-menopause                   | 11                      | 14                      | 0.790 |
| Post-menopause                  | 11                      | 12                      |
| ECOG performance status score   |                         |                         |
| 0–1                             | 15                      | 18                      | 0.938 |
| 2                               | 7                       | 8                       |
| Treatment                       |                         |                         |
| First-line treatment            | 14                      | 17                      | 0.9 |
| Second-line treatment           | 8                       | 9                       |
| Metastatic site                 |                         |                         |
| Lymph node or soft tissues      | 8                       | 10                      | 0.881 |
| Chest wall                      | 3                       | 4                       | 0.864 |
| Lung                            | 12                      | 13                      | 0.753 |
| Liver                           | 5                       | 7                       | 0.738 |
| Bone                            | 8                       | 11                      | 0.675 |
| Brain                           | 1                       | 0                       | 1.000 |
| No. of metastatic foci          |                         |                         |
| Single                          | 8                       | 11                      | 0.675 |
| Multiple                        | 14                      | 15                      |

Table 2. Comparison of the response to the NP and GP regimens in TNBC patients with failure in treatment with anthracyclines and taxanes.

| Group                          | No. patients with CR | No. patients with PR | No. patients with SD | No. patients with PD | ORR (%) | χ² | P |
|--------------------------------|----------------------|----------------------|----------------------|----------------------|---------|----|---|
| NP regimen group (n=22)        | 1                    | 9                    | 7                    | 5                    | 45.5    | 0.305 | 0.959 |
| GP regimen group (n=26)        | 2                    | 10                   | 9                    | 5                    | 46.2    |      |    |

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease, ORR – overall response rate.

Table 3. Response to the NP and GP regimens in TNBC patients with various clinical characteristics.

| Characteristics                  | NP regimen group (n=22) | GP regimen group (n=26) | P value | P value |
|----------------------------------|-------------------------|-------------------------|---------|---------|
|                                  | No. of patients         | CR + PR | ORR (%) |         | No. of patients | CR + PR | ORR (%) |         |
| Menstruation                     |                         |         |         |         |                         |         |         |         |
| Premenopause                     | 11                      | 4       | 36.4    | 0.392   | 14                      | 5       | 35.7    | 0.249 |
| Postmenopause                    | 11                      | 6       | 54.5    |         | 12                      | 7       | 58.3    |         |
| Treatment                        |                         |         |         |         |                         |         |         |         |
| First-line                       | 14                      | 7       | 50.00   | 0.571   | 17                      | 9       | 52.9    | 0.126 |
| Second-line                      | 8                       | 3       | 37.5    |         | 9                       | 3       | 33.3    |         |
| Metastatic site                  |                         |         |         |         |                         |         |         |         |
| Local + lymph node               | 11                      | 5       | 45.5    | 0.337   | 14                      | 7       | 50.00   | 0.133 |
| Viscera                          | 18                      | 5       | 27.8    |         | 20                      | 5       | 25      |         |
| No. of metastatic lesions        |                         |         |         |         |                         |         |         |         |
| Single                           | 8                       | 5       | 62.5    | 0.225   | 11                      | 7       | 63.6    | 0.126 |
| Multiple                         | 14                      | 5       | 35.7    |         | 15                      | 5       | 33.3    |         |
group than in the NP regimen group ($P<0.05$), and a higher incidence of phlebitis was seen in the NP regimen group than in the GP regimen group ($P<0.05$). Other common chemotherapy-induced adverse events included mild constipation, anemia, and hepatorenal dysfunction, which did not affect chemotherapy after active treatment (Table 4).

### Table 4. Adverse events caused by the chemotherapy with NP and GP regimens.

| Adverse events       | NP regimen group (n=22) | GP regimen group (n=26) | Incidence of grade III and IV adverse events (%) | $p$ value |
|----------------------|------------------------|------------------------|-------------------------------------------------|-----------|
| Leucopenia           | Grade 0: 1, Grade I: 6, Grade II: 9, Grade III: 4, Grade IV: 2 | Grade 0: 27.3, Grade I: 0, Grade II: 8, Grade III: 11, Grade IV: 5, Grade V: 2 | 26.9 | 0.866 |
| Thrombopenia         | Grade 0: 11, Grade I: 6, Grade II: 4, Grade III: 1, Grade IV: 0 | Grade 0: 4.5, Grade I: 3, Grade II: 9, Grade III: 8, Grade IV: 4, Grade V: 2 | 23.1 | 0.04 |
| Anemia               | Grade 0: 13, Grade I: 6, Grade II: 3, Grade III: 0, Grade IV: 0 | Grade 0: 0, Grade I: 15, Grade II: 7, Grade III: 4, Grade IV: 0, Grade V: 0 | 0.965 |
| Nausea and vomiting  | Grade 0: 12, Grade I: 5, Grade II: 3, Grade III: 2, Grade IV: 0 | Grade 0: 9.1, Grade I: 13, Grade II: 6, Grade III: 5, Grade IV: 2, Grade V: 0 | 7.7 | 0.96 |
| Loss of appetite     | Grade 0: 3, Grade I: 4, Grade II: 8, Grade III: 5, Grade IV: 2 | Grade 0: 31.8, Grade I: 2, Grade II: 6, Grade III: 9, Grade IV: 6, Grade V: 3 | 34.6 | 0.961 |
| Constipation         | Grade 0: 14, Grade I: 5, Grade II: 3, Grade III: 0, Grade IV: 0 | Grade 0: 0, Grade I: 15, Grade II: 6, Grade III: 5, Grade IV: 0, Grade V: 0 | 0.863 |
| Skin rash            | Grade 0: 22, Grade I: 0, Grade II: 0, Grade III: 0, Grade IV: 0 | Grade 0: 19, Grade II: 5, Grade III: 2, Grade IV: 0, Grade V: 0 | 0 | 0.031 |
| Phlebitis            | Grade 0: 13, Grade I: 5, Grade II: 3, Grade III: 1, Grade IV: 0 | Grade 0: 4.5, Grade I: 24, Grade II: 2, Grade III: 0, Grade IV: 0, Grade V: 0 | 0 | 0.041 |
| Neurotoxicity        | Grade 0: 15, Grade I: 4, Grade II: 3, Grade III: 0, Grade IV: 0 | Grade 0: 23, Grade II: 3, Grade III: 0, Grade IV: 0, Grade V: 0 | 0 | 0.104 |
| Hair loss            | Grade 0: 17, Grade I: 4, Grade II: 1, Grade III: 0, Grade IV: 0 | Grade 0: 18, Grade II: 6, Grade III: 2, Grade IV: 0, Grade V: 0 | 0 | 0.806 |
| Hepatic dysfunction  | Grade 0: 16, Grade I: 4, Grade II: 2, Grade III: 0, Grade IV: 0 | Grade 0: 19, Grade I: 5, Grade II: 2, Grade III: 0, Grade IV: 0, Grade V: 0 | 0 | 0.975 |
| Renal dysfunction    | Grade 0: 18, Grade I: 3, Grade II: 1, Grade III: 0, Grade IV: 0 | Grade 0: 19, Grade I: 6, Grade II: 1, Grade III: 0, Grade IV: 0, Grade V: 0 | 0 | 0.705 |

**Discussion**

Breast cancer is a highly heterogeneous malignancy [38–41], and TNBC is a specific heterogeneous subgroup of breast cancer [2]. The clinico-pathological characteristics and biological behaviors of TNBC are characterized by high invasiveness, poor prognosis, early onset of disease, high recurrence, and early metastasis [2]. Currently, the standard therapy for TNBC is surgery with adjuvant chemotherapy and radiotherapy [9–11]. However, it is reported that most of the TNBC patients develop recurrence and metastasis 2 to 3 years after surgery [42]; adjuvant therapy is thus necessary for TNBC patients, which may improve patient survival and prognosis [43]. Since TNBC has no specific targets and is negative for hormone receptors, the TNBC patients are not susceptible to endocrine therapy or targeted therapy [44–46]. Chemotherapy remains the major approach for the systemic treatment of recurrent and metastatic TNBC [47]; however, to date there is no consensus on the chemotherapy regimens for the treatment of recurrent and metastatic TNBC [20].

To date, anthracyclines and taxanes remain important agents for TNBC [13–17], and adding an anthracycline or taxane to the chemotherapy has been found to substantially improve the treatment outcomes [15]. However, anthracyclines- and
In the present study, a 45.5% ORR and 77.3% DCR were achieved in the NP regimen group undergoing vinorelbine 25 mg/m² on days 1 and 8 plus cisplatin 25 mg/m² on days 2–4, and a 46.2% ORR and 80.8% DCR were observed in the GP regimen group receiving gemcitabine 1000 mg/m² on days 1 and 8 plus cisplatin 25 mg/m² on days 2–4, which was similar to previous findings [59,61–63]. Subgroup analyses showed a better response to either the NP regimen or the GP regimen in the postmenopausal patients, patients with first-line treatment, patients with local and lymph node metastases, and patients with single metastatic lesion than in the premenopausal patients, patients with second-line treatment, patients with visceral metastasis, and patients with multiple metastatic lesions; however, no significant differences were seen between the 2 groups (P>0.05). In addition, there were no significant differences detected in the ORR, DCR, or TTP between the NP and GP regimen groups (P>0.05).

In this study, we observed bone marrow inhibition, gastrointestinal reactions, and phlebitis as the predominant chemotherapy-induced toxicities, which may have been caused by peripherally inserted central venous catheterization [64].

Conclusions

In summary, the results of the present study demonstrate that either vinorelbine plus cisplatin or gemcitabine plus cisplatin is active and tolerated in metastatic TNBC with resistance to anthracyclines and/or taxanes, which may be used a salvage treatment for metastatic TNBC.

Statements

The funders had no role in the study design, data collection and analysis, or preparation of the manuscript.

Conflict of interests

None.
References:

1. Cetin I, Topcul M: Triple negative breast cancer. Asian Pac J Cancer Prev, 2014; 15: 2427–31
2. Foulkes WD, Smith IE, Reis-Filho JS: Triple-negative breast cancer. N Engl J Med, 2010; 363: 1938–48
3. Chacón RD, Costanzo MV: Triple-negative breast cancer. Breast Cancer Res, 2010; 12: 53
4. Boyle P: Triple-negative breast cancer: Epidemiological considerations and recommendations. Ann Oncol, 2012; 23: v7–12
5. Gierach GL, Burke A, Anderson WF: Epidemiology of triple negative breast cancers. Breast Dis, 2010; 32: 5–24
6. Brewster AM, Chavez-MacGregor M, Brown P: Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. Lancet Oncol, 2014; 15: e625–34
7. Fan L, Strasser-Weippl K, Li J J et al: Breast cancer in China. Lancet Oncol, 2014; 15: e279–89
8. Marmé F, Schneeweiss A: Targeted therapies in triple-negative breast cancer. Breast Care (Basel), 2015; 10: 159–66
9. Andreopoulou E, Schweber SJ, Sperano JA, McDaid HM: Therapies for triple-negative breast cancer. Expert Opin Pharmacother, 2015; 16: 983–98
10. Carbo D, Lurlinetto I, Vicentini C et al: Neoadjuvant strategies for triple negative breast cancer: ‘State-of-the-art’ and future perspectives. Anticancer Agents Med Chem, 2015; 15: 15–25
11. Shastry M, Yardley DA: Updates in the treatment of basal/triple-negative breast cancer. Curr Opin Obstet Gynecol, 2015; 27: 40–48
12. Sethi N, Mundhe NA, Kumar P et al: Therapeutic targets of triple-negative breast cancer. A review. Br J Pharmacol, 2015; 172: 4227–37
13. Mustacchi G, De Laurentis M: The role of taxanes in triple-negative breast cancer: literature review. Drug Des Devel Ther, 2015; 9: 4033–18
14. Teshome M, Hunt KK: Neoadjuvant therapy in the treatment of breast cancer. Surg Oncol Clin N Am, 2014; 23: 505–23
15. Huidis CA, Gianni L: Triple-negative breast cancer: An unmet medical need. Oncologist, 2011; 16: 1–11
16. Li Q, Li Q, Zhang P et al: A phase II study of capcitabine plus cisplatin in metastatic triple-negative breast cancer patients pretreated with anthracyclines and taxanes. Cancer Biol Ther, 2015; 16: 1746–53
17. Carey LA: Directed therapy of subtypes of triple-negative breast cancer. Oncologist, 2011; 16: 71–78
18. Yin Y, Zhang P, Xu BH et al: Unfavorable pathological complete response rate of neoadjuvant chemotherapy epirubicin plus taxanes for locally advanced triple-negative breast cancer. J Huazhong Univ Sci Technol Med Sci, 2013; 32: 262–65
19. Palma G, Frasci G, Chirico A et al: Triple negative breast cancer: Looking for the missing link between biology and treatments. Oncotarget, 2015; 6: 26550–74
20. Kumar P, Aggarwal R: An overview of triple-negative breast cancer. Arch Gynecol Obstet, 2016; 293: 247–69
21. Soa KL, Faulds D: Vinorelbine. A review of its pharmacological properties and clinical use in cancer chemotherapy. Drugs Aging, 1994; 5: 200–34
22. Gregory RK, Smith IE: Vinorelbine – clinical review. Br J Cancer, 2000; 82: 1907–13
23. Mustacchi G, Muggia M, Milani S et al: A phase II study of cisplatin and vinorelbine in patients with metastatic breast cancer. Ann Oncol, 2002; 13: 1730–36
24. Peng LV: Clinical research of vinorelbine combined with cisplatin in the treatment for triple negative breast cancer. Pract Pharm Clin Remedies, 2012; 15: 792–94
25. Plunkett W, Huang P, Xu YZ et al: Gemcitabine: Metabolism, mechanisms of action, and self-potentiation. Semin Oncol, 1995; 22: 3–10
26. Plunkett W, Huang P, Sealy CA, Gandhi V: Gemcitabine: Preclinical pharmacology and mechanisms of action. Semin Oncol, 1996; 23: 13–15
27. Carmichael J, Walling J: Advanced breast cancer: Investigational role of gemcitabine. Eur J Cancer, 1997; 33: 527–30
28. Possinger K: Gemcitabine in advanced breast cancer. Anticancer Drugs, 1995; 6: 55–59
29. Carmichael J, Possinger K, Phillip P et al: Advanced breast cancer: A phase II trial with gemcitabine. J Clin Oncol, 1995; 13: 2731–36
30. Ferrazzi E, Stivelano L: Gemcitabine: Monoclonal chemotherapy of breast cancer. Ann Oncol, 2006; 17: 169–72
31. van Moorsel CI, Veerman G, Bergman AM et al: Combination chemotherapy studies with gemcitabine. Semin Oncol, 1997; 24: 57–23
32. Heinemann V, Boeck S, Hinke A et al: Meta-analysis of randomized trials: Evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer, 2008; 8: 82
33. Mutsch DG: Gemcitabine combination chemotherapy of ovarian cancer. Gynecol Oncol, 2003; 90: 516–20
34. Zhang MH, Zhang QY, Zhao S et al: Gemcitabine and cisplatin combination chemotherapy for triple-negative metastatic breast cancer patients with anthracycline resistance. Chin Clin Oncol, 2011; 16: 46–49
35. Berndt H, Titze U: TNM clinical stage classification of breast cancer. Int J Cancer, 1969; 4: 837–44
36. Young J, Badgery-Parker T, Dobbins T et al: Comparison of ECOG/WHO performance status and ASA score as a measure of functional status. J Pain Symptom Manage, 2015; 49: 258–64
37. Liu Y, Zhu GP, Guan XY: Comparison of the NCI-CTCAE version 4.0 and version 3.0 in assessing chemoradiation-induced oral mucositis for locally advanced nasopharyngeal carcinoma. Oral Oncol, 2012; 48: 554–59
38. Aras M, Erdil TY, Dan F et al: Comparison of WHO, REICST 1.1, EORTC, and PERCIST criteria in the evaluation of treatment response in malignant solid tumors. Nucl Med Commun, 2016; 37: 9-15
39. Polvak K: Heterogeneity in breast cancer. J Clin Invest, 2011; 121: 3786–88
40. Zhang Y, Lu Y, Niu Y et al: Role of circulating tumor cell (CTC) monitoring in evaluating prognosis of triple-negative breast cancer patients in China. Med Sci Monit, 2017; 23: 3071–79
41. Wang J, Chen H, Chen X, Lin H: Expression of tumor-related macrophages and cytokines after surgery of triple-negative breast cancer patients and its implications. Med Sci Monit, 2016; 22: 115–20
42. Zhong Z, Shan M, Wang J et al: Decreased Wnt5a expression is a poor prognostic factor in triple-negative breast cancer. Med Sci Monit, 2016; 22: 1–7
43. Yagata H, Kajura Y, Yamauchi H: Current strategy for triple-negative breast cancer: Appropriate combination of surgery, radiation, and chemotherapy. Breast Cancer, 2011; 18: 165–73
44. Perez EA, Moreno-Apitia A, Aubrey Thompson E, Andorfer CA: Adjuvant therapy of triple negative breast cancer. Breast Cancer Res Treat, 2010; 120: 285–91
45. Gu G, Dustin D, Fuqua SA: Targeted therapy for breast cancer and molecular mechanisms of resistance to treatment. Curr Opin Pharmacol, 2016; 31: 97–103
46. Rossi L, Pagani O: Adjuvant endocrine therapy in breast cancer: Evolving paradigms in premenopausal women. Curr Treat Options Oncol, 2017; 18: 28
47. Ribnikar D, Sousa B, Cufer T, Cardoso F: Extended adjuvant endocrine therapy – A standard to all or some? Breast, 2017; 32: 112–18
48. Gluz O, Liedtke C, Gottschalk N et al: Triple-negative breast cancer – current status and future directions. Ann Oncol, 2009; 20: 1913–27
49. Moreno-Apitia A, Perez EA: Anthracycline- and/or taxane-resistant breast cancer: Results of a literature review to determine the clinical challenges and current treatment trends. Clin Ther, 2009; 31: 1619–40
50. Petrelli F, Colina A, Borgonovo K et al: The value of platinum agents as neo-adjuvant chemotherapy in triple-negative breast cancers: A systematic review and meta-analysis. Breast Cancer Res Treat, 2014; 144: 223–32
51. Liedtke C, Rody A, Untch M: Clinical evaluation of platinum agents for the treatment of triple negative breast cancer. Curr Breast Cancer Rep, 2014; 6: 289
52. Guan X, Ma F, Fan Y et al: Platinum-based chemotherapy in triple-negative breast cancer: A systematic review and meta-analysis of randomized-controlled trials. Anticancer Drugs, 2015; 26: 894–901
53. Greenup R, Buchanan A, Lorizio W et al: Prevalence of BRCA mutations among women with triple-negative breast cancer (TNBC) in a genetic counseling cohort. Ann Surg Oncol, 2013; 20: 3254–58
54. Boulkais T, Vougiouka M: Cisplatin and platinum drugs at the molecular level (Review). Oncol Rep, 2003; 10: 1663–82
55. Chong L, Tian HJ, Yang KH: Systematic review of GP regimen vs. NP regimen to treat metastatic breast cancer. J Pract Oncol, 2013; 28: 36–40
56. Shen G, Bian G, Yu H et al: Comparison between cisplatin plus vinorelbine and cisplatin plus docetaxel in the treatment of advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials. Mol Clin Oncol, 2014; 2: 146–50
57. Shamseddine A, El-Saghir N, Chehal A et al: Cisplatin and vinorelbine (PVn) for the treatment of advanced breast cancer: 10 years of experience. J Med Liban, 2004; 52: 126–30
58. Shamseddine A, Khalifeh M, Chehal A et al: A clinical phase II study of cisplatinum and vinorelbine (PVn) in advanced breast carcinoma (ABC). Am J Clin Oncol, 2005; 28: 393–98
59. Vassilomanolakis M, Koumakis G, Demiri M et al: Vinorelbine and cisplatin for metastatic breast cancer: A salvage regimen in patients progressing after docetaxel and anthracycline treatment. Cancer Invest, 2003; 21: 497–504
60. van Moorsel CJ, Veerman G, Bergman AM et al: Combination chemotherapy studies with gemcitabine. Semin Oncol, 1997; 24: S7–23
61. Stemmler HJ, diGioia D, Freier W et al: Randomised phase II trial of gemcitabine versus cisplatin vs. gemcitabine plus capecitabine in patients with pretreated metastatic breast cancer. Br J Cancer, 2011; 104: 1071–78
62. Zhang MH, Zhang QY, Zhao S et al: Gemcitabine and cisplatin combination chemotherapy for triple-negative metastatic breast cancer patients with anthracycline resistance. Chin Clin Oncol, 2011; 16: 46–49
63. Peng LY: Clinical research of vinorelbine combined with cisplatin in the treatment for triple negative breast cancer. Pract Pharm Clin Remedies, 2012; 15: 792–94
64. Frasca D, Dahyot-Fizelier C, Mimoz O: Prevention of central venous catheter-related infection in the intensive care unit. Crit Care, 2010; 14: 212