Efficacy of Neoadjuvant Cisplatin and Oral Capecitabine in Triple-Negative Breast Cancers: A Pilot Study
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Abstract: Due to the lack of molecular targets, triple-negative breast cancers (TNBCs) typically represent a worse prognosis compared to their hormone-positive counterparts. While neoadjuvant chemotherapy has been used for breast cancers for a long time, there is no standard chemotherapy regimen for TNBCs. Cisplatin has generally been regarded as an effective chemotherapy agent against TNBCs. However, here we present a pilot study involving the use of cisplatin in combination with oral capecitabine in the neoadjuvant setting in 16 patients with TNBC. Twelve patients were African American and 4 patients were white. Six patients completed all 4 cycles of chemotherapy, 6 patients completed 3 cycles, and 4 patients completed 2 cycles. A complete clinical response was observed in 2 patients, and 10 patients achieved partial clinical response. One patient had progressive disease, and 3 patients were lost to follow-up or taken off study. Following chemotherapy, 12 patients underwent surgery (7 patients had breast conservation, and 5 patients had a mastectomy). Ten of the 12 patients who had surgery achieved a partial pathologic response and the other 2 patients had complete pathologic response. Grade 3 nausea, vomiting, and diarrhea occurred in 7 patients; 1 patient experienced dehydration and renal failure; and 5 patients had grade 1/2 hand-foot syndrome. There were no grade 4 or 5 toxicities. The response to cisplatin-capecitabine combination chemotherapy in the neoadjuvant setting was suboptimal compared to that with single-agent cisplatin in prior studies. The toxicity profile with this combination was also worse than that of cisplatin alone. Based on our findings, we do not recommend this combination regimen in the neoadjuvant setting for TNBCs. However, future studies analyzing the use of cisplatin with other combinations are warranted.
Introduction

Breast cancers lacking gene expression for human epidermal growth factor receptor 2 (HER2), estrogen receptors (ER), and progesterone receptors (PR) are referred to as triple-negative breast cancers (TNBC). In the Western world, the majority of TNBCs are sporadic in nature and represent approximately 15–20% of the total cases of breast cancer. As a whole, TNBCs represent a very heterogeneous group of cancers with distinct subtypes. There are differing opinions regarding the prognosis of TNBC subtypes, but the common consensus is that TNBC is generally more aggressive than its hormone receptor–positive subtype. TNBCs and the BRCA1/BRCA2-associated breast cancers share many features, suggesting a common pathogenesis. While several studies and clinical trials are under way, the data available thus far suggest that, with optimal treatment, patients with TNBC have a 20-year survival rate comparable to that of patients with hormone-positive breast cancers. In an effort to find new ways to counter TNBC, various neoadjuvant chemotherapy agents are being studied. With 4 planned cycles of neoadjuvant cisplatin at 75 mg/m² intravenously every 21 days plus capecitabine 1,000 mg orally twice daily in a 14-days-on, 7-days-off approach. Once patients received neoadjuvant chemotherapy, they underwent planned surgery with standard adjuvant chemotherapy and radiation therapy, per their treating physicians. Clinical and pathologic treatment responses were assessed, and treatment-related toxicities were recorded.

Patients and Methods

This was a single-arm phase II study that involved a total of 16 patients with stage II or III TNBC. Patients were treated with 4 planned cycles of neoadjuvant cisplatin at 75 mg/m² intravenously every 21 days plus capecitabine 1,000 mg orally twice daily in a 14-days-on, 7-days-off approach. Once patients received neoadjuvant chemotherapy, they underwent planned surgery with standard adjuvant chemotherapy and radiation therapy, per their treating physicians. Clinical and pathologic treatment responses were assessed, and treatment-related toxicities were recorded.

Results

There were a total of 16 patients with stage II or III breast cancer who were enrolled in the study; 12 patients (75%) were African American and 4 patients (25%) were white (Figure 1). Six patients (37.5%) completed all 4 cycles of chemotherapy, 6 patients (37.5%) completed 3 cycles, and 4 patients (25%) completed 2 cycles (Figure 2). Two patients (12.5%) had complete clinical responses and 10 patients (62.5%) achieved partial clinical response (Figure 3). Three patients (18.7%) were lost to follow-up or taken off study.
and 1 patient (6.25%) had progressive disease. A total of 12 (75%) patients underwent surgery after chemotherapy, 7 patients (43.75%) had breast conservation, and 5 patients (31.25%) had a mastectomy (Figure 4). Ten of the 12 patients (83.3%) who had surgery had partial pathologic response and the other 2 patients (16.6%) had complete pathologic response (Figure 5). A total of 7 patients (43.8%) experienced grade 3 nausea, vomiting, and diarrhea; 1 patient (6.25%) experienced dehydration and renal failure; and 5 patients (31%) had grade 1/2 hand-foot syndrome (Figure 6). There were no grade 4 or 5 toxicities.

Discussion

Unlike their hormone-positive subtypes, TNBCs lack clinically validated targets, thus limiting the use of therapeutic regimens to cytotoxic agents. However, a growing body of evidence has emerged regarding the use of inhibitors of vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), poly ADP-ribose polymerase (PARP), and mammalian rapamycin (mTOR) as molecular targets for TNBC.

It is important to note that treatment guidelines have yet to be established for these promising markers. Furthermore, in which stage of disease these treatment modalities are most efficacious remains undetermined. Pooled data from several studies have shown that the vast majority of breast cancers (as high as 70% in some instances) in individuals with a BRCA1 mutation are triple-negative. TNBC is also associated with a high tumor grade, an increased preference for visceral and cerebral metastasis, and a relatively poor prognosis after recurrence.

Both BRCA1-associated breast cancers and the sporadic subtypes of breast cancers share similar vulnerabilities in their genetic code, which are characterized by allelic loss. These discoveries have led to an increased interest in using therapies that target the DNA repair mechanism. Cross-linking chemotherapy agents, like cisplatin, are effective in BRCA1-deficient cells, and research with animal-models shows very promising results. The response rate to cisplatin, as it relates to...
increased dose, intensity, or duration of therapy, is not well-understood.2 The use of cisplatin as a neoadjuvant increased dose, intensity, or duration of therapy, is not response to treatment.

Figure 5. The majority of patients achieved a partial pathologic response to treatment.

In this study, 75% of the patients were African American while 25% were white. Data collected from several epidemiologic studies have revealed that the incidence of TNBCs is more common in African American women20 and carries a poorer prognosis.21 Compared to single-agent cisplatin, which resulted in a pCR of 22%, only 2 (12.5%) of our 16 patients treated with combination cisplatin-capecitabine achieved complete remission. Overall, 75% of patients had at least a partial response to the regimen.

The results from this pilot study, which demonstrated a relatively low pCR rate with combination cisplatin-capecitabine, argue against the administration of this regimen for TNBCs. In our experience, the addition of oral capecitabine to the neoadjuvant regimen did not significantly improve the response rate, and there was an increased occurrence of toxicities. However, in recent studies, the use of capecitabine in combination with ixabepilone (Ixempra, Bristol-Myers Squibb) has been shown to be efficacious in metastatic breast cancers.22 Keeping these findings in mind, we believe that future trials of cisplatin in combination with taxanes, PARP inhibitors, or ixabepilone are warranted.

Conclusion

There were several limitations to our study, including, but not limited to, a very small sample size and poor patient compliance. Based on data, the response to cisplatin-capecitabine combination chemotherapy in the neoadjuvant setting was suboptimal compared to that seen with single-agent cisplatin demonstrated in prior studies. However, the toxicity profile with this combination neoadjuvant chemotherapy was also worse than that of cisplatin alone. Based on these findings, we do not recommend this combination regimen in the neoadjuvant setting for TNBCs. In our experience, the addition of oral capecitabine to the neoadjuvant regimen did not significantly improve the response rate, and there was an increased occurrence of toxicities. However, in recent studies, the use of capecitabine in combination with ixabepilone (Ixempra, Bristol-Myers Squibb) has been shown to be efficacious in metastatic breast cancers. Keeping these findings in mind, we believe that future trials of cisplatin in combination with taxanes, PARP inhibitors, or ixabepilone are warranted.

References

Figure 6. Grade 3 nausea, vomiting, and diarrhea were the most common treatment-related toxicities.