Benefit of Metronomic Chemotherapy in Metastatic Triple-Negative Breast Carcinoma: A Case Report

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Introduction:

Breast cancer is the leading cancer among women worldwide, accounting for about a quarter of all incident cancer cases in women[1]. Triple negative (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative) breast cancer (TNBC), a more aggressive subtype of breast cancer, accounts for about 15% of breast cancer diagnoses[2]. Metastatic TNBC (MTNBC) has a median survival of 13 months, compared to 2-3 years with general metastatic breast cancer (MBC)[3]. In addition, MTNBC patients are more likely to see disease recurrence compared to other subtypes of MBC and experience a shorter time to distant recurrence (2.6 years vs 5 years)[4]. There are currently no targeted therapies for MTNBC as there are for hormone receptor-positive or HER2-positive breast cancer. Standard chemotherapy regimens include anthracycline- and taxane-based regimens, while platinum-based regimens have also been shown to be effective[6]. This case report documents the successful use of sequential metronomic chemotherapy in three patients with recurrent MTNBC.

Discussion:

Three female patients (JT, SP, JK) were initially diagnosed with unilateral biopsy-proven invasive ductal breast carcinoma. All patients underwent unilateral or bilateral mastectomies. JT and SP also underwent neoadjuvant or adjuvant chemotherapy treatment, respectively, with standard TAC (docetaxel, doxorubicin, and cyclophosphamide), as well as adjuvant radiation therapy. JK declined neoadjuvant/adjuvant therapy. All patients developed recurrent MTNBC. The median age of diagnosis of MTNBC was 59 years old (range: 30 – 61 years old) (Fig. 1).

Patient	Age at Diagnosis of MTNBC (years)	Metastases	Current Time Out Since Diagnosis of MTNBC (months)	Current Time Out Since Beginning Metronomic Chemotherapy (months)
JT	61	Bone	47	46
SP	30	Lungs, Liver, Bones, Brain*	40	27

JK	59	Lungs, Liver, Bones	152	147

Figure 1: Characteristics of three female patients with MTNBC

The patients pursued metronomic chemotherapy following the development of recurrent MTNBC. Both patients with bone metastases were also put on monthly zoledronic acid. At the time of beginning metronomic chemotherapy, the patients were assessed to be 0-1 by the Eastern Cooperative Oncology Group performance criteria. The patients were started on weekly paclitaxel (60 mg/m²) / carboplatin (AUC 2.25). JT and SP also received 5-fluorouracil (5-FU) (425 mg/m²). Following the completion of approximately (appr) twelve cycles, SP saw good disease response by PET/CT scan. JK saw good disease response as evidenced by tumor shrinkage in the left chest wall and axillary area on physical examination, as well as a drop in CA 27.29 tumor marker level from pretreatment 52.1 to 19.8. JT saw stable metastatic disease in her supraclavicular lymph node and bones by CT scan after twelve cycles.

All patients were switched to a Doxil (liposomal doxorubicin)-based regimen. JT was given appr thirty-two weekly cycles of paclitaxel (60 mg/m^2) / biweekly Doxil (20 mg/m^2) / weekly cisplatin (15 mg/m^2). SP was given the same regimen for twelve cycles. Both patients again saw good disease response by PET/CT scan. JK received weekly Doxil as a single agent (12.5 mg/m^2), although this was discontinued after six cycles due to the development of hand-foot syndrome.

Following the Doxil-based regimen, all patients were switched to a gemcitabine-based regimen. JT and SP were given appr twelve cycles of weekly paclitaxel or Abraxane (nab-paclitaxel) (60 mg/m^2) / gemcitabine (500 - 600 mg/m^2) / cisplatin (10 - 15 mg/m^2), with SP seeing complete resolution of metastatic disease on CT scan upon completion. JK was given seven cycles of gemcitabine (650 mg/m^2) / cisplatin (20 mg/m^2).

JT was then given a weekly regimen of eribulin (1-2 mg/m^2) / cisplatin (15 mg/m^2). After twelve cycles, the regimen was switched to twelve more cycles with weekly eribulin / oxaliplatin (50 mg/m^2). This was followed by eight cycles of weekly vinorelbine (15 mg/m^2) / oxaliplatin (45 mg/m^2), although oxaliplatin was discontinued after four cycles due to severe cytopenia. JT saw stable remaining disease on PET/CT scan in June 2014. Repeat CT scans continue to show no evidence of metastatic disease.

SP was given eight cycles of weekly vinorelbine (20 mg/m^2) / cisplatin (15 mg/m^2) / 5-FU (425 mg/m^2), followed by twelve cycles of weekly eribulin (1 mg/m^2) / oxaliplatin (20 mg/m^2) / 5-FU (425 mg/m^2). However, oxaliplatin was discontinued after four cycles due to an infusion reaction. Repeat PET/CT and CT scans after the completion of the vinorelbine-based regimen confirmed no evidence of metastatic disease.

**SP developed metastatic ER+/PR+/HER-2- breast carcinoma to the brain, three months after a PET/CT scan of the skull base to mid-thigh showed continued remission of metastatic disease in the body. A craniotomy / resection of two cerebellar masses and*

stereotactic Edge radiosurgery to the cerebellar masses were performed. This was followed by chemotherapy treatment with eight cycles of weekly paclitaxel (60 mg/m^2) / irinotecan (100 mg/m^2) / 5-FU (425 mg/m^2), then four cycles of weekly vinblastine (2 mg/m^2), and then four cycles of weekly temsirolimus (25 mg) / cisplatin (15 mg/m^2). Following the final dose of temsirolimus / cisplatin, an MRI scan of the brain showed resolution of intracranial metastases. A PET/CT scan at the time of the brain MRI showed continued remission of osseous and visceral metastases.

JK was given weekly vinorelbine (25 mg/m^2) as a single agent following the gemcitabine-based regimen. This was discontinued after eight cycles due to leukopenia. Repeat scans following completion of vinorelbine confirmed no evidence of metastatic disease.

Conclusion:

There are no preferred chemotherapy options for patients with MTNBC. Taxanes are among the most effective effect agents in MBC and have shown good efficacy in MTNBC[5,6]. Other regimens include anthracyclines and platinum agents[6]. However, these regimens carry a high-risk of chemotoxicity and adverse effects. Additionally, there remains a high risk of disease recurrence in this patient demographic. Given that there are currently no targeted molecular therapies for MTNBC as there are for hormone receptor-positive and HER-2-positive breast cancers, developing new chemotherapy treatment regimens with lessened cytotoxicity is imperative.

The dosing and schedule of metronomic chemotherapy has been shown to provide equal, and even improved, treatment efficacy in a number of cancers[7,8]. When administered metronomically, certain chemotherapy agents, including paclitaxel, cyclophosphamide, and vinblastine, have also been shown to have an increased specificity against tumor endothelial cells and disrupt the process of angiogenesis[9,10,11]. This anti-angiogenic effect of metronomic chemotherapy may contribute to more effective chemotherapy delivery to the tumor bed, thus increasing treatment efficacy[12, 13]. Dosing between metronomic and standard chemotherapy was for the most part equitable: for example, the dose of weekly paclitaxel at 60 mg/m^2 is equal to the standard dose of paclitaxel given every three weeks at 175 mg/m^2 (i.e. 58.3 mg/m^2 every week). The increased administration frequency in metronomic chemotherapy, however, increases dose density, which has been shown to improve overall survival in randomized phase III trials[14,15,16].

Chemotherapy has traditionally been used at the maximum tolerated dose (MTD), ideally to maximize the killing of the cancer cells. However, chemotherapy used at MTD can cause serious, and even life-threatening, side effects including myelosuppression, immunosuppression, cardiotoxicity, nephrotoxicity, nausea, vomiting, diarrhea, and peripheral neuropathy, to name a few[14]. Due to these side effects, dose reduction or long breaks (2-3 weeks per cycle) are required to allow patients to recover; some patients may even choose to forgo further treatment depending on the severity of their adverse events. Because the metronomic dosing in these patients' regimens was significantly lower than the MTD, adverse events and side effects were greatly reduced. Chief complaints were

Grade 1-2 neuropathy secondary to paclitaxel/Abraxane, Grade 1-4 cytopenia, diarrhea, and nausea secondary to oxaliplatin, and Grade 2 hand-foot syndrome secondary to Doxil. Sargramostim (GM-CSF) was administered for the treatment and prevention of chemotherapy-induced leukopenia.

Current chemotherapy protocol involves maintaining a treatment regimen until there is noticeable disease progression due to the cancer developing chemotherapy-resistance. Coldman and Goldie developed a mathematical model that demonstrated that tumors have a nonzero chance of gaining a mutation and that the chance of having one tumor cell with resistance to a chemotherapy agent increases rapidly[17]. The goal of sequential switch therapy in these patients' treatment was to keep the rate of spontaneous mutations in cancer cells at a low level, minimize the development of resistance to chemotherapy and accumulation of chemotoxicity to any single chemotherapy regimen, and maximize treatment efficacy. Sequential TAC has been shown to reduce mortality compared to doxorubicin/docetaxel combination or concurrent TAC in locally metastatic breast cancer[18]. Switching regimens before obvious disease resistance/progression occurs also allows for the reuse of chemotherapy agents that had demonstrated efficacy in the past.

Our use of metronomic chemotherapy in three patients with recurrent MTNBC has been very successful. Overall, median survival for these patients at this time since beginning metronomic chemotherapy treatment is 46 months (range: 27 – 147 months), far superior to the the overall median survival of 13 months. Their survival is expected to continue, since all of the patients are living a good quality of life and their latest scans have shown no evidence of recurrent disease. Our treatment results suggest strong efficacy of metronomic chemotherapy in MTNBC.

Consent

Written informed consent was obtained from the patient for publication of this case report.

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