Case Report

Complete Overall Tumor Response to Metronomic Chemotherapy, Anti-Estrogen Tamoxifen, High Dose Vitamin C, and Zoledronic Acid of a Young Adult Woman with Metastatic Bilateral Breast Carcinoma: Case Report and First Statement for Morales-Borges Regimen (MBR)

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Received: 25 June 2020; Accepted: 02 July 2020

ABSTRACT

Breast cancer (BC) is the most prevalent of all cancers in Puerto Rico (PR) and in young women (<40 years of age) is different from BC occurring in older women (>60 years of age). They tend to have an aggressive disease course with increased probability of poor overall survival and disease-free survival. Standard treatment involves systemic chemotherapy and/or immunotherapy plus antiestrogen therapy for positive hormone-receptors, but other modalities less commonly used are metronomic chemotherapy (mCHT) and alternative treatment of high dose intravenous vitamin C therapy (HDIVC). The Di Bella’s Method (DBM) has been used for years by his inventor and it’s a combination modality with MLT (melatonin), retinoids, vitamins E, D₃, and C with differentiating, cytostatic, antiangiogenic, immunomodulating, factorially synergic effects. We are presenting a case of a young adult female patient with mBC treated successfully with a neoadjuvant integrative combined modality using a similar mechanism of DBM which we named Morales-Borges Regimen (MBR).

Keywords: Overall tumor response, Metronomic chemotherapy, Tamoxifen, High dose Vitamin C, Zoledronic acid, Young adult woman, Breast carcinoma, Bone metastases, Liver metastases

Introduction

Cancer is a major public health problem worldwide and is the second leading cause of death in the United States. There will be approximately 276,480 new cases of carcinoma of the...
Breast cancer (BC) is the most prevalent of all cancers in Puerto Rico (PR), accounts for 30.3% of all female cancers, and has the highest mortality of all cancers in this population (Morales et al., 2013). Low DNA repair, late hysterectomy/menopause, family history of cancer, and smoking increases the risk while having multiple children, endometriosis, and being divorced decreases risk (Morales et al., 2013). Even though BC in young women has a relatively small proportion (6%), it does not reduce its significance and impact on public health. Breast carcinoma in young women (<40 years of age) is different from breast carcinoma occurring in older women (>60 years of age). The main differences are negative estrogen receptor status, multicentric position, higher histologic grade, triple-negative tumors, and higher Ki-67 index. These features have been found to be the key attributes for aggressive disease course with increased probability of poor overall survival and disease-free survival (Erić et al., 2018).

Nearly 2,500 young women die annually of the disease (Menen and Hunt, 2016). There are specific issues to caring for the young breast cancer patient including diagnosis, genetic counseling, tumor biology, surgery, and potential for development of contralateral breast cancer. Additionally, there are psychosocial considerations unique to this age group which should be addressed as part of a comprehensive, multi-disciplinary team approach including discussions about fertility, sexual function, behavioral health, and quality of life (Menen and Hunt, 2016). Despite an increased risk of local recurrence, young age alone is not a contraindication to breast conserving therapy given the equivalent survival seen in this population with either mastectomy or breast conservation. However, many young women in recent years are choosing bilateral mastectomy, even without a known hereditary predisposition to the disease (Rosenberg SM and Partridge, 2015). For those who need chemotherapy, multi-agent chemotherapy and biologic therapy targeting the tumor similar to the treatment in older women is the standard approach. Select young women will do well with hormone therapy only (Rosenberg SM and Partridge, 2015).

Metronomic chemotherapy (mCHT) is a form of cytotoxic drug administration that differs from conventional chemotherapy schedules. Conventional therapy is based on the administration of maximum dose therapy with chemotherapeutic regimens, while mCHT consists of the continuous or frequent administration of chemotherapeutic agents at low doses, markedly below the maximum tolerated dose (MTD), without long between-dose intervals (Romiti et al., 2013; Cazzaniga et al., 2016). Oral chemotherapeutic agents such as capecitabine and vinorelbine have demonstrated efficacy in patients with metastatic breast cancer (mBC), with prolonged disease
control and good tolerability. Use of oral chemotherapy reduces the time and cost associated with treatment and is often more acceptable to patients than intravenous drug delivery. Metronomic administration of oral chemotherapy is therefore a promising treatment strategy for some patients with mBC and inhibits tumor progression via multiple mechanisms of action (Cazzaniga et al., 2019). A study was done reviewing few clinical trials using mCHT in mBC and the evaluation of ‘metronomic’ low-dose cyclophosphamide/methotrexate (CTX/MTX) was based on a phase II clinical trial of 64 patients (63 evaluated) which revealed median administration period (MAP) of 75 days, progression-free life/year (PFLY) of 23% (95% CI 17.3–48.5), and overall tumor response (OTR) of 31.7% (95% CI 20.6–44.7) (Bocci et al., 2005). The comparative pharmacoeconomic evaluation they have undertaken was stimulated, to a large extent, by the rapidly growing concern about the hugely escalating costs of recently approved cancer drugs and the treatment protocols involved in using these drugs. They concluded that cyclophosphamide-methotrexate metronomic regimens represent a potentially significant cost-effective palliative treatment for metastatic breast cancer compared with other novel, unapproved chemotherapy strategies (phase II trials) (Bocci et al., 2005). Its use represents good value for money and efficient use of health care resources, at least for those patients with pretreated metastatic breast cancer that are eligible for palliative chemotherapy.

Another alternative treatment for mBC is the use of high dose intravenous vitamin C (HDIVC). There are many studies where intravenous Vitamin C has been very effective in treating various types of cancer (Riordan et al., 2000; Jackson et al., 1995; Padayatty et al., 2006; Duconge et al., 2007; Gonzalez et al., 2015; González et al., 2005; Riordan et al., 1990; Gonzalez et al., 2014). Studies have shown that post intravenous vitamin C plasma at a levels of 350 to 400 mg/dL have been very toxic to human cancer cells, especially due to its formation of H2O2 (Chen et al., 2005). Vitamin C also increases collagen production and enhances the immune system activity. It has been demonstrated that high dose intravenous vitamin C has given many cancer patients the opportunity to improve their quality of life (10-12,16). A case report has been published with significant evidence of positive effect of HDVC in mBC (Gonzalez et al., 2017) although combining high-dose intravenous vitamin C with conventional anti-cancer drugs can have therapeutic advantages against breast cancer cells (Lee et al., 1998).

A combination modality has been described and used for years for cancer, particularly in BC, initially in Italy known as Di Bella’s method (Abbasi, 1998; Pellegrini, 1998; Di Bella, 2011). The Di Bella’s Method (DBM) with MLT (melatonin), retinoids, vitamins E, D3, and C has a differentiating, cytostatic, antiangiogenic, immunomodulating, factorially synergic effect, at the
same time reinforcing those functions that physiology considers essential for life. The DBM entails the use of estrogen inhibitors, such as tamoxifen, and minimal apoptotic, non-cytotoxic and non-mutagenic doses of Cyclophosphamide or Oncocarbide, such as mCHT, the tolerability of which is enhanced by MLT and the vitamins in the DBM (Di Bella, 2011).

We are presenting a case of a young adult female patient with mBC treated successfully with a neoadjuvant combined modality using a similar mechanism of DBM which we named Morales-Borges Regimen (MBR).

**Case Report**

This is a case of a 28-years-old Puerto Rican female patient, Jehovah’s witness, with no history of systemic disease, no known drug allergies, and nulliparous, who began complaining pelvic pain and backache by the end of year 2018 with inverted left breast nipple. There is no family history of breast cancer, but paternal grandfather had prostate cancer. BRCA 1 & 2 genetic testings were negative. Computerized tomography of her abdomen and pelvis on December 20th of 2018 revealed multiple vertebral body and skeletal lesions and bilateral breast masses and bilateral digital mammography with breast ultrasound demonstrated bilateral extensive poorly defined masses corresponding with pleomorphic microcalcifications and left breast upper quadrant mass of 5.6 x 4.7 x 2.0 cm’s with bilateral axillary lymphadenopathies. Bilateral ultrasound-guided core biopsies done on January 4 of 2019 and confirmed diagnoses of bilateral invasive and in-situ ductal carcinomas, estrogen receptor positive 90%, progesterone receptor negative, HER-1-neu negative, and Ki-67 focally positive in > 30%. On February of 2019 bilateral breast MRI and body PET-CT scan done and demonstrated she has right breast upper quadrant and retroareolar lesions with nipple retraction, left breast heterogenous enhancement of the entire breast with multifocal multicentric disease with nipple inversion, bilateral axillary adenopathies, few small bilateral pulmonary hilar adenopathies, small left pleural effusion, metastatic lesion at the posterior inferior segment of the right hepatic lobe, and diffuse metastatic bone disease. The serum tumor markers were very high (CA 15-3 of 1020 U/mL and CA 27.29 of 643.65 U/mL).

She visited an oncologic surgeon and a medical oncologist, and they recommended aggressive systemic intravenous chemotherapy followed by surgery. She decided for a second opinion with integrative medicine approach and no surgery. She was evaluated by us on January 22 of 2019 and started on mCHT with CTX/MTX (cyclophosphamide 50 mg po daily days 1-28 & methotrexate 2.5 mg po twice a day days 1 & 4 weekly every 28 days), anti-estrogen therapy with
Tamoxifen (TAM) 20 mg daily, Zoledronic Acid (ZA) 4 mg IVPB every 28 days, and HDVC on February 2019. She had a normal Glucose-6-phosphate dehydrogenase (G6PD) level before HDVC. She received vitamin C 25 gm IVPB weekly since the first week of February 2019 for 2 months then changed dose and frequency to 50 gm every 2 weeks by April 2019. She also was placed on low carbohydrate diet plus oral vitamins and supplements such as retinoids and vitamins E, D3, and C.

She is tolerating the regimen well and has been compliance with it. She is asymptomatic, pain-free, and enjoying her life. Her only side effect was leukopenia grade 1. By September 2019 her tumor markers were as following: CA 15-3 of 95.10 U/mL and CA 27.29 of 144.69 U/mL. By January 2020 they were 50.8 U/mL and 98.28 u/mL respectively. On June 2020 the CA 15-3 was 39.10 U/mL. PET/CT scan was repeated on June 2020 and there is partial metabolic response with interval decrease activity of a left breast mass and interval complete resolution of right axillary and bilateral hilar lymphadenopathy, liver metastases, left pleural effusion and most of the skeletal lesions, except for right intertrochanteric proximal femur lesion. She has an excellent performance status with more than 75% response rate and almost 15 months survival without surgery nor radiotherapy.

Discussion

The case illustrates a young adult woman with stage IV mBC to lymph nodes, pleura, bones and liver who underwent neoadjuvant integrative oncology approach who was asymptomatic with excellent performance status. The regimen was well tolerated with minimal or none toxic profile, cost-effective, and provided an excellent overall tumor response and survival rate at this point (so far 15 months).

We combined mCHT with CTX/MTX, anti-estrogen TAM, ZA plus HDVC and there are no previous cases reported in the medical literature using this regimen. As per Munzone and Colleoni (Munzone and Colleoni, 2015), mCHT induces disease control in patients with advance-stage BC with an adverse events profiles less when compared with conventional maximum tolerated dose chemotherapy. Most drugs are orally and generics which makes them inexpensive and have well-tolerated cumulative toxicity. Several clinical trials are ongoing, and they should whether this will be an accepted regimen and future combination with molecularly targeted therapy and immunotherapy (Cazzaniga et al., 2019; Munzone and Colleoni, 2015).
In respect to HDIVC, Riordan et al (Riordan et al., 2004) reported a case of end-stage mBC with generalized bone pain not controlled with narcotics, cellulitis and deep vein thrombosis treated with HDIVC with an excellent response improving her pain as well as her performance status, although six-months after starting the HDVC she fell, sustained a fracture and died. It demonstrated that HDIVC is not toxic for cancer patients, has no interference with the effect of conventional therapy and inclusive decreases toxicity of chemotherapy. Regarding the combination of HDIVC plus TAM, Vitamin C is a water-soluble chain-breaking reduction molecule that has beneficial effects on lipid-metabolizing enzymes. In a study by Muralikrishnan et al (Muralikrishnan et al., 2010), the level of thiobarbituric acid (TBA) substances and antioxidant enzymes such as catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione-S-transferase were assayed in 60 postmenopausal women with breast cancer. The data obtained from the study revealed that the levels of TBA and the antioxidant enzymes catalase, SOD, glutathione peroxidase and glutathione-S-transferase were significantly normalized by vitamin C treatment in the RBC hemolysate. The results compared vitamin C-treated breast cancer patients with normal individuals and showed that co-administration of vitamin C is more beneficial in breast cancer patients treated with tamoxifen.

Finally, the DBM has demonstrated complete objective response of plurifocal BC (Di Bella, 2008). He treated a woman with bilateral axillary adenopathies with his regimen and she achieved 50% OTR at seven months and got totally cured after 14 months. It was done without toxicity, no needs for hospitalization, even with minimally reducing the patient’s daily work routine.

Regarding bone metastasis, zoledronic acid (ZA) is an imidazole-containing bisphosphonate that has been extensively studied as an osteoclast inhibitor. ZA blocks protein isoprenylation, a key step in many survival and proliferation pathways (Steinman et al., 2012). In patients, it has been effective against both lytic and blastic bone disease, reducing bone symptoms and skeletal-related events in bone-metastatic disease. In the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial, premenopausal women with either ER-positive or ER-negative tumors responded less well to ZA than did postmenopausal women (Coleman et al., 2011). They enrolled 2,259 premenopausal or perimenopausal women and 1,101 postmenopausal women and found that ZA did not improve the overall survival or disease-free survival (DFS) of the entire cohort, but a prespecified subgroup analysis in the AZURE study indicated that postmenopausal women - but not premenopausal women - treated with ZA showed an increased DFS of a magnitude comparable with that observed in the Austrian Breast & Colorectal Cancer Study Group 12 (ABGCS12) trial (29). ZA was effective in preventing new secondary primary tumors and
locoregional and non-skeletal distant recurrences in postmenopausal women in the AZURE trial. In our patient who is premenopausal, ZA worked very well with improvement in bone disease and so far preventing skeletal bone events such as pathologic fractures contrary to AZURE result.

So, as we can see in our case, the new Morales-Borges Regimen (MBR) is an excellent option for young adult women with mBC. Further cases and clinical trials should be done.

**Conclusion**

In our case and review, mCHT with CTX/MTX, anti-estrogen TAM, ZA plus HDIVC have been shown to be effective in the mBC with better profile than standard pharmacologic therapies available. Now we are playing a significant role with the use of MBR in those patients. Its cost-effective, accessible, and well tolerated with excellent clinical results. We encouraged the physicians to incorporate these agents within their armamentaria against mBC as neoadjuvant therapy. More clinical studies are also welcome.

**References**


