Oncothermia Journal 7:302-304 (2013)

Stabilization of metastatic breast cancer with capacitive hyperthermia plus standard-dose chemotherapy and/or metronomic

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Introduction

Worldwide, breast cancer accounts for 22.9% of all cancers (excluding non-melanoma skin cancer) in women and it is more than 100 times more common in women than in men, although men tend to have poorer outcomes due to delays in diagnosis.

Prognosis and survival rates for breast cancer vary greatly depending on the cancer type, stage, treatment and geographical location of the patient. Survival rates in the western world are high, in developing countries, however they are much poorer.

The size, stage, rate of growth and other characteristics of breast cancer determine the kinds of treatment. Treatment may include surgery, hormonal therapy, chemotherapy (CHT), target therapy, radiotherapy (RT) and thermotherapy (hyperthermia).

Surgical removal of the tumour provides the largest benefit in many cases.

To increase the likelihood of cure, several chemotherapy regimens (Antracycline based or not) and target therapy are commonly given in addition to surgery. Chemotherapy may be standard, which means administered full dosage and scheduled bi-tri-weekly, or metronomic therapy, which refers to repetitive, low doses of drugs, designed to minimize toxicity (Dr. Harold J. Burstein of the Dana-Farber Cancer Institute).

Targeted therapy (TT) is a form of treatment that is designed to specifically inhibit molecules that provide advantageous growth signals to cancer cells.

Current targets: receptor tyrosine kinases, VEGFR inhibitors, EGFR inhibitors, endothelin receptors, KIT, BCR/ABL, PDGFR, growth factors, VEGF, estrogen, androgen, transcription factors.

Radiation is used after breast-conserving surgery and substantially improves local relapse rates and in many circumstances the overall survival too.

Some breast cancers are sensitive to hormones such as estrogen and/or progesterone, which makes it possible to treat them by blocking the effects of these hormones (Tamoxifene or Aromathase Inhibitors or Fulvestrant).

Hyperthermia is a type of cancer treatment in which the body tissue is exposed to high temperatures (40-42°C).

A research has shown that high temperatures can damage and kill cancers cells, usually with minimal injury to normal tissue. Hyperthermia increase blood flow to the warmed area, perhaps doubling the perfusion in tumours, while in the normal tissue the increase might be tenfold or even more. This enhances the delivery of medications.

Thermotherapy also increases oxygen delivery to the area, which may make radiation more likely to damage and kill cells, as well as preventing cells from repairing the damage induced during radiation session.

Numerous clinical trials have studied hyperthermia in combination with radiation therapy and/or chemotherapy. These studies focused on the treatment of many type of cancer, including breast cancer, and shown a significant reduction in tumour size when hyperthermia was combined with other treatments.

Materials and methods

In our long experience in Universitary Hyperthermia treatment of tumours associated with chemotherapy, we have observed that the response to the associated treatment determines the disease stabilization and significant clinical benefit for 24 months in 12 cases of metastatic breast cancer, whereas chemotherapy alone has turned out to be ineffective with disease progression causing bone marrow toxicity G3-4, fatigue G2-3, nausea and vomiting G1-G2, bone pain G3-4 and visceral pain G2-3. (see Table 1).

TOXICITY WITH CHT ALONE	TOXICITY WITH ASSOCIATED THERAPIES (CHT+HT)
Bone pain: G3-4	Bone pain: G1-2
Visceral pain: G2-3	Visceral pain: G1
Fatigue: G2-3	Fatigue: G1-2
Nausea and vomiting: G2	Nausea and vomiting: G1
Bone marrow tox: G3-4	Bone marrow tox: G1-2

Table 1. 2 of 12 patients underwent hormone therapy alone because of their allergy to chemotherapy drugs, other 10 patients underwent to CHT+/- Hormone Therapy according to the protocols seen in Table 2.

ID	Birth Date	Therapy
C. L.	25/08/1969	*Exemestane,*
C. C.	19/02/1947	*CMF, Docetaxel, Nolvadex, Enantone*
D.L.V.	01/05/1956	*Trastuzumab+CBDCA, Myocet+Gemcitabine*
C. P.	22/10/1956	*FEC, Trastuzumab, Vinorelbine, Capecitabine, Fulvestrant*
F. V.	15/03/1946	*Myocet+ Docetaxel, Myocet+Gemcitabine, Zoledronic Acid*
F.D.	20/08/1962	*Fulvestrant+Xeloda, CBDCA+TAX, NVB+GEM*
P.G.	11/12/1957	*Herceptin+NVB, Herceptin,Xeloda*
O.F.	14/09/1959	*Zometa+Tam*
M.D.	19/08/1956	*Xeloda+TXT+BEVA,CBDCA+GEM, TAXOL, NVB, Myocet*
L.G.	28/08/1921	*TXT+Letrozolo*
P.D.A.	24/03/1961	*Herceptin+CBDCA, Myocet+Gemcitabina*
M.C.	19/94/1954	*FEC,CBDCA+GEM, Herceptin+NVB, Lapatinib+Xeloda*

Table 2.

All patients underwent an average 30 cycles of capacitive hyperthermia, each consisting of eight 45-minute sessions every other day, using 300W per session. Heat was applied to a small or large area, site of the tumor or metastases, using radiofrequency (SYCHROTERM RF 13.56 MHz). External applicators two flexible antennas with a diameter of 26 cm) were positioned in area to be treated to raise its temperature.

Results

In these patients the improvement of perfomance status has allowed a return to regular life. This improvement of the quality of life showed a correspondent biochemical response, with a progressive reduction in tumor markers and showed also a diagnostic response with stabilization of disease: in some cases the reduction of size and/or number of metastases and in all cases with absence of metabolic activity disease (TB PET CT scan).

Conclusion

Our data confirms that the association CT-HT is positively viewed by most women treated for MBC perceiving it as helping them to feel healthier and experience a sense of freedom.

The most interesting finding was the observed beneficial effect of HT on pain and an improvement of Quality of Life (QoL).

The use of OT/CHT-HT combination may enhance efficacy vs CHT and OT alone. This surprising result may confer a small, but probably, clinically significant improvement survival and quality of life. However the result of larger collaborative international adjuvant CHT-HT trials will be needed in order to determine the true value of this combination.

According to the studies on P.N.E.I.M (1, 6, 7), the results in the field of Clinical Pharmacology concerning drug abuse and medicines disuse, and the resulting recent studies in anthropology on cancer patients, all of our patients were treated at a preventive, therapeutic and post-treatment level with appropriate behavioural tests and drug treatments to avoid relapse. Clinical Pharmacology, in our opinion, considers every patient, according to the multidimensional approach (biopsychosocial), as a global being (8, 9, 10, 11).

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