Old school regimen may turn the tide in metastatic breast cancer

Dear Editor,

Currently, there are a myriad of chemotherapy regimens available for the treatment of metastatic breast cancer. Cyclophosphamide, methotrexate, 5-fluorouracil (CMF) is a regimen commonly used. However, many studies showed superiority of other regimens over CMF, either with regard to efficacy or the number of side effects [1,2]. Emphasizing the biological heterogeneity of breast cancer, we provide a case that sets an example that oral cyclophosphamide plus intravenous (i.v.) methotrexate and 5-fluorouracil (oral CMF) can still remain the choice of treatment in certain cases with metastatic breast cancer.

Our patient was a 29-year-old, premenopausal woman who had left-side modified radical mastectomy and axillary dissection with pathological diagnosis of grade II infiltrating ductal carcinoma, pathological stage T3N3M0, estrogen receptor (ER) (-), progesterone receptor (PR) staining of 10%, and Her2 (-) in March 2008. Adjuvant chemotherapy was initiated with 4 cycles of AC (adriamycin, cyclophosphamide) and 4 cycles of docetaxel, every 21 days, followed by 10 months of adjuvant tamoxifen in addition to adjuvant radiotherapy. During follow up, the patient developed back aches. Radiological imaging showed diffuse bone metastases and mediastinal lymphadenopathy. In view of these findings, capecitabine and zoledronic acid were initiated. During treatment, the regimen was changed to include gemcitabine due to disease progression in both bone and mediastinal lymph nodes and increase in tumor markers CEA and CA 15-3. Our patient kept experiencing bone pain and sternal metastatic findings progressed. Thus, paclitaxel for 8 weeks was administered. However, the patient's condition did not improve and tumor markers continued to increase. Hence, radiotherapy was delivered to the thoracic and lumbar vertebrae for palliation and vinorelbine was initiated. At first, the bone pain decreased and CEA levels lowered while CA 15-3 levels remained high; however, later liver metastases emerged and CEA and CA 15-3 levels were highly increased. Then, CMF (cyclophosphamide 100 mg p.o. every day, and methotrexate 40 mg/m^2 bolus i.v. plus 5-fluorouracil 600 mg/m^2 bolus i.v., every 21 days) was started. CA 15-3 levels markedly declined and the bone pain significantly subsided. After 6 cycles of chemotherapy, the tumor markers reached normal levels, CT scans identified a dramatic regression in liver metastasis and bone scintigraphy revealed osteosclerotic lesions.

In cases of advanced disease cytotoxic single-agent chemotherapy is widely used. Some randomized controlled trials have shown beneficial activity of two-agent regimens but this has not been widely adopted due to increased toxicity and dubious results of the trials. More commonly, chemotherapeutic agents are increasingly being combined with targeted therapy agents. Furthermore, many studies have shown that other available regimens are superior to oral CMF therapy [3]. Interestingly, studies have shown that cyclophosphamide is the most important component of the regimen. Furthermore, oral administration of cyclophosphamide has been found to be more effective than i.v. administration [4]. Thus, as evidenced by our case, oral CMF might make a tight-turn in clinical progression. This benefit may be attributed mostly to the antiangiogenic effects of cyclophosphamide and methotrexate [5].

References

1. Watanabe T, Sano M, Takashima S et al. Oral uracil and tegafur compared with classic cyclophosphamide, methotrexate, fluorouracil as postoperative chemotherapy in patients with node-negative, high-risk breast cancer: National Surgical Adjuvant Study for Breast Cancer 01 Trial. J Clin Oncol 2009; 27: 1368-1374.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687-1717.
3. Oshaughnessy JA, Blum J, Moiseyenko V et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001; 12: 1247-1254.
4. Ejlertsen B, Mouridsen HT, Jensen MB et al. Cyclophosphamide, methotrexate, and fluorouracil; oral cyclophosphamide; levamisole; or no adjuvant therapy for patients with high-risk, premenopausal breast cancer. Cancer 2010; 116: 2081-2089.
5. Colleoni M, Rocca A, Sandri MT et al. Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. Ann Oncol 2002; 13: 73-80.

G. Gezgen, E.C. Roach, M.C. Kizilarslanoglu, K. Altundag

Department of Medical Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey

Correspondence to: Kadri Altundag, MD. E-mail: altundag66@yahoo.com

Castleman disease and adenocarcinoma

Dear Editor,

A male patient presented with massive lymphadenopathy due to Castleman disease (CD). This was successfully treated and while in remission he developed a highly aggressive solid tumor of unknown primary site from which he eventually died.

CD or angiofollicular lymph node hyperplasia is a rare unclassified lymphoproliferative disorder with variable morphology, clinical presentation and prognosis [1]. It may be unicentric or multicentric and has 3 distinct histological types, hyaline-vascular, plasma cell and plasmablastic [2]. It is an entity often presenting elements of chronic inflammation, supporting the hypothesis of a viral stimulus, especially as there is strong association to the HHV-8 virus, mainly in HIV-infected patients [3]. Also, CD is associated with a particular type of non-Hodgkin's lymphoma, recently recognized by the WHO classification and named "large B-cell lymphoma arising in HHV-8 associated multicentric CD". Occasionally, the plasma cell variant is associated with POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, skin changes) [4].

This patient suffered a severe form of erythrodermic psoriasis since the age of 15 for which he had received multiple courses of methotrexate, acitretin, cyclosporine and ultraviolet A (PUVA). Occasionally he presented moderate enlargement of lymph nodes which waxed and waned for more than 30 years. Two previous biopsies showed dermatopathic lymphadenopathy.

At the age of 50 he developed night sweats, weight loss and low grade fever, severe difficulty in walking, slight splenomegaly and massive enlargement of axillary and inguinal lymph nodes. The laboratory work-up revealed normocytic anemia, hyperferritinemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), polyclonal hyperglobulinemia and subclinical diabetes mellitus.

Biopsy of bone marrow and an inguinal lymph node showed