Concurrent radiotherapy and capecitabine, followed by high-dose methotrexate consolidation, provided effective palliation in a patient with leptomeningeal metastases from breast cancer

case report
We report the case of a 38-year-old patient, diagnosed with AJCC stage III-A breast cancer (T3N2MO; Estrogen and progesterone receptor negative, her2/neu-negative). She underwent right mastectomy and axillary node dissection. After surgery, she received adjuvant chemotherapy with TAC doxorubicin/docetaxel/cyclophosphamide for six courses.

She was admitted to our hospital while local radiotherapy was being carried out, because of excruciating headache and vomits. Continuous i.v. morphine at a dose of 1000 mg/day was required to achieve pain control. There was not any cranial nerve involvement, and she had an Eastern Cooperative Oncology Group performance status of 1.

Magnetic resonance and cerebrospinal fluid (CSF) cytology revealed leptomeningeal metastases. Twice daily capecitabine (850 m/m²) and whole-brain radiotherapy (30 Gy) were initiated. She also received five doses of twice weekly intrathecal methotrexate and cytarabine, with cytological improvement. During the first 2 weeks, meningeal irritation intensified as a result of intrathecal chemotherapy. From that moment, quality of life (QoL) gradually improved and she could be discharged taking sustained-release morphine.
30 mg every 12 h, with adequately controlled symptoms. One month later, she received four courses of high-dose (HD) methotrexate (8 g/m²) with further recovery and scarce toxicity (NCI-CTC grade 2 nausea).

Progression-free survival was 6 months from the beginning of radiotherapy (3 months from the end of HD methotrexate), but progression affected mainly axial bones, and only scantily the thecal sac. Subsequently, she was treated with weekly paclitaxel (Taxol; Bristol-Myers Squibb Company, NJ) and capecitabine, for 6 months, with partial response and clinical improvement. At that time, the tumour behaved very aggressively and the patient finally died of rapid leptomeningeal progression. Overall, survival since whole-brain radiotherapy was 12 months, toxic effects were amenable and reported QoL was excellent.

discussion

Leptomeningeal carcinomatosis may be present in 2% of cases of breast cancer. A proposed prognostic model stratified patients into four groups on the basis of pretreatment characteristics [1]. According to this system, the survival for this patient should have been 5.5 months, but she finally lived more than twice the expected. This discrepancy is not probably the result of favourable tumour biology, as its short progression-free survival and clinical aggressiveness strongly suggest.

The role of systemic chemotherapy is not unequivocally defined in this condition. A nonrandomized study yielded CSF cytological response in 81% of patients with nonleukemic leptomeningeal cancer, with an overall survival of 13.8 months [2].

Capecitabine has demonstrated activity in metastatic breast cancer, with acceptable toxicity profile. Despite blood-brain-barrier, capecitabine has reported activity in central nervous system metastases [3, 4]. Capecitabine is converted to 5-fluorouracil by the enzyme thymidine phosphorylase (TP). Radiotherapy increases TP activity within tumour cells and is synergistic with capecitabine in human tumour xenografts [5]. A phase I study of capecitabine and concurrent whole-brain radiotherapy informed that combined therapy was safe and well tolerated without unexpected toxic effects.

We believe that opioid reduction and prolonged progression-free survival indicate that induction therapy with capecitabine and concurrent radiotherapy, followed by HD methotrexate, was beneficial for our patient. The main conclusion is that further phase I/II studies evaluating this protocol may contribute to optimize the treatment of this condition.

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references


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