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CLINICAL REPORT

Prolonged Survival of a Woman with Breast Cancer Metastatic to Leptomeninges After Treatment with Letrozole and Capecitabine

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Introduction

Leptomeningeal metastasis (LM) occurs in only a small percentage of patients with breast cancer, but it is a significant risk for patients because breast cancer is common. Approximately 2-5% of breast cancers metastasize to the leptomeninges at some point in the course of the disease. It may occur with or without parenchymal brain metastases in the setting of widespread disease or as the only site of spread. As with all metastatic disease in breast cancer, it may occur after a disease free interval of years, and symptom onset may be insidious. MRI scanning may or may not suggest the diagnosis; lumbar puncture with positive cytology is required for diagnosis but may be negative early in the course of the disease. It is thus often not considered until the severity of symptoms makes its presence obvious. At that point, only the most basic palliative interventions may be feasible. The literature associates the diagnosis with a uniformly short survival with reviews reporting approximately 2-8 months[1-3] with few patients living longer.[4] There is no standard therapy for meningeal metastasis as no intervention has demonstrated consistent prolongation of survival and even the optimal approach to palliation is unclear. Our experience of a patient with very prolonged survival argues for attempts to achieve early diagnosis and intervention; as new, effective and well-tolerated treatments may exist.

Case Report

In 1997, a 47-year-old woman was diagnosed with an infiltrating ductal carcinoma of the right breast. She underwent a bilateral mastectomy by her choice in November 1997. The primary tumor was greater than five centimeters, and 14 of 19 lymph nodes were involved by cancer. The primary tumor was grade II, ER and PR positive, and HER2 0 by IHC staining.

She underwent adjuvant chemotherapy with four cycles of standard doses of doxorubicin and cyclophosphamide, followed by autologous stem cell transplant in May 1998. In October 1998, she received radiotherapy to her right chest wall. Tamoxifen was then initiated; however after approximately three months, she found a number of side-effects unacceptable and discontinued tamoxifen. In March 2000, she again accepted tamoxifen and took 20 mg per day until June 2003. At that time, she began having frequent cramps of her lower extremities, questioned if tamoxifen was a cause, and stopped taking it permanently. She also began to have frequent but mild headaches about this time, not greatly out of character with her past history of migraine. These became more bothersome, however, and she was referred for neurological evaluation. CT, MRI, and MRA scans of the head were done at the end of July and were normal. In January 2004, she first reported equilibrium problems. She refused a lumbar puncture at that time. In April 2004, a bone scan and an MRI scan of the head and complete spine were negative for metastatic disease. In June 2004, consent was obtained and lumbar puncture revealed an elevated protein of 738 with negative cytology. A repeat LP two weeks later revealed rare, diagnostic tumor cells with protein of 732, 12 WBC, and 13 RBC. On June 22, 2004, she was begun on letrozole and with only brief interruptions has remained on treatment. She also was begun on capecitabine at a total dose of 1000 mg twice daily for 14 of 21 days as she tolerated it poorly and refused to take a higher dose. Because of a clinical cauda equina syndrome, she received radiation therapy to her lumbar spine. In September, she suffered a catastrophic, apparently unrelated, diverticular bowel perforation and required a temporary colostomy. Recovery from this event was slow. In May 2006, she underwent repeat LP. CSF cytology at that time was positive for rare diagnostic cells**;** protein was 106. She underwent five more cycles of Capecitabine, 1000 mg twice daily 14 of 21 days ending in March 2007. She experienced abdominal cramping at this dose, and thus refused higher doses or the sixth planned cycle. She gradually improved, began to exercise regularly, and was mentally and physically able to carry out most normal activities. Monitoring of her systemic disease led to the discovery of new bone then liver metastases. Because of this, she received a sequence of chemotherapy agents, which gave further control of her disease for another three years.

Therapy became increasingly difficult for her to tolerate, as well as less effective, and she developed increasing bone pain, fatigue, and asthenia. She eventually died from her systemic disease, having survived for six years after the diagnosis of leptomeningeal disease.

Discussion

The patient's length of survival is one of the longest reported in the literature. Her initial therapy involved a traditional approach with involved-field radiotherapy to her lumbar spine, where her pain was most severe, along with initiation of intrathecal methotrexate injections. As she refused these after two injections, it is unlikely that they played a significant role in her recovery. Immediately after cytologic confirmation of the diagnosis of LM, she was begun on letrozole and has continued on it until death. She was also treated with a brief course of capecitabine soon after diagnosis, but it was interrupted by her bowel perforation. She has undergone another course, receiving five cycles at a dose level limited by her tolerance.

Letrozole is an aromatase inhibitor, which works by binding and inhibiting the aromatase enzyme responsible for the production of estrone from androgen precursors. If a breast cancer and its CNS metastases are estrogen receptor positive, it follows pharmacologically that blocking estrone production would have the same effect on CNS sites as metastases elsewhere. A search of the literature reveals two reports of LM from breast cancer achieving longer than usual survival rates with letrozole therapy. Ozdogan et al[3] reported a case of LM from breast cancer treated with letrozole in which progression-free survival of 16 months was achieved, nearly four times as long as current reported median survival rates. The authors reported their search yielded only two other cases of LM from breast cancer that had been treated solely with hormonal manipulation with a positive outcome.[3,5] Madhup et al[6] reported a case of scalp and parenchymal CNS metastases from breast cancer treated with letrozole therapy, which produced survival of at least 19 months. Thus, while letrozole therapy has seldom been reported, evidence suggests aromatase inhibitors may be a form of breast cancer therapy with greater benefits for meningeal disease than has been observed with past hormonal treatments such as tamoxifen.

Capecitabine is among the most frequently used agents in metastatic breast cancer and has demonstrated substantial efficacy as a single agent.[7,8] Monotherapy with this agent has been reported to have a response rate in the range of 15-28%, with these studies often including many heavily pretreated patients.[9-11] A chemotherapeutic agent that is taken orally and well-absorbed through the gastrointestinal tract, capecitabine is a prodrug that is converted to 5-fluorouracil (5-FU) by thymidine phosphorylase, an enzyme that is overexpressed in cancer cells. This overexpression can be advantageous in that it may provide a means of selectively activating the drug while limiting systemic toxicity. Capecitabine may be an especially useful treatment for CNS metastases because of its ability to penetrate the blood-brain barrier. A previous study on CSF penetration after intravenous infusion of 5'-DFUR, a precursor of 5-FU, shows at least 1-6% of the plasma concentration of 5'-DFUR present in CSF.[12,13] Capecitabine penetration of the blood-brain barrier may further be increased if there is disruption of the barrier by mechanical or inflammatory effects of meningeal metastases. Penetration of the BBB is also thought to occur via the human concentrative nucleoside transporter (hCNT) and its two isotypes (hCNT1 and hCNT2). 5-deoxy-5fluorouridine (5-DFUR), a metabolite of capecitabine, is a substrate for hCNT1. This transporter may play a key role in the mechanism of capecitabine penetration across the BBB.[14,15]

Multiple reports suggest benefits from capecitabine treatment for metastatic disease, which has involved the CNS.[14,16] A 2007 study noted significant improvement after capecitabine therapy of multiple manifestations of CNS metastases including parenchymal metastases alone, leptomeningeal disease alone, or a combination of the two. For the 7 patients involved in this report, median overall survival was reported as 13 months and progression-free survival was reported as 8 months.[14] Similarly, a 2004 case study reports a durable 12 month response of a patient with LM from breast cancer to capecitabine monotherapy.[7] Capecitabine administered prior to radiotherapy may be an approach that is superior to radiation therapy alone. Fabi et al[17] report a case of a woman with prolonged survival after 12 cycles of capecitabine followed by radiotherapy. Capecitabine may be useful for CNS metastases even after failure of systemic chemotherapy that includes 5-FU. Wang et al[10] report a case in which brain metastases from breast cancer worsened despite whole-brain irradiation, hormonal therapy, and systemic chemotherapy containing 5-FU. Following 11 months of capecitabine therapy, the patient showed marked improvement of brain lesions on MRI scans as well as in Karnofsky performance status.[10]

These somewhat hopeful reports contrast with years of reports documenting the failure of commonly accepted approaches. Intrathecal therapy has been a standard component of therapy for meningeal metastases for breast cancer for many years. However, as with other forms of treatment, no agent or route of delivery has shown consistent superiority in the therapy of meningeal metastases. Although methotrexate has been the most commonly used, no convincing data have shown that it is more effective than cytosine arabinoside, thiotepa, or DepoCyt.[18,19] Its frequent usage may be due to the fact that it is considered an effective systemic agent against breast cancer and less toxic than other agents. Likewise, superiority has not been shown between either intrathecal or intraventricular delivery of chemotherapy, although demonstration of lumbar CSF flow patency may be necessary for any hope of benefit from lumbar puncture. The only randomized study on the subject suggests that intraventricular chemotherapy does not increase survival and is also associated with increased risk of neurotoxicity.[20]

There is little evidence that any other hormonal therapy has been beneficial in the treatment of CNS disease. Tamoxifen

has been widely used for more than 30 years and thus has been used frequently by patients who develop meningeal disease from breast cancer. There has never been any clear evidence of its efficacy in this setting. The literature suggests that tamoxifen may have some effectiveness in treating parenchymal brain metastases.[21, 22]

There may soon be other promising new approaches to treating LM disease from breast cancer. Studies using intrathecal trastuzumab,[23] intrathecal injection of the monoclonal Ab I131-8H9,[24] and the oral dual acting inhibitor of HER-2 and EGFR lapatinib[25] have all reported at least some efficacy with mild or minimal toxicity. Temozolomide is another recently studied chemotherapy agent known to cross the blood-brain barrier and has shown efficacy in the treatment of parenchymal brain metastases of different histologies.[26] Although there have been studies showing some efficacy in combination with capecitabine, temozolomide has demonstrated minimal or no activity in breast cancer metastases, including the CNS, as a single agent to date.[27]

Conclusions

The outcome of leptomeningeal disease from breast cancer has been dismal and has not improved significantly in recent years. We believe this case and the literature support early institution of an aromatase inhibitor in receptor positive cancers if the patient has not been previously exposed to this class of agents. Capecitabine should also be considered in patients who are appropriate candidates. If these agents are instituted at the time of diagnosis, there may be sufficient time for a substantial response even in this disease with a reported median survival of only a few months. This more optimistic scenario may encourage clinicians to be aggressive in attempting earlier diagnosis as well, further exploiting this potential benefit.

REFERENCES

1. **Posner JP**. Neurologic complications of cancer. Philadelphia: *Oxford University Press*; 1995.
2. **DeAngelis LM**. Current diagnosis and treatment of leptomeningeal metastasis. *J Neurooncol*. 1998 Jun-Jul;38(2-3):245-52. Review. PubMed PMID: 9696379.
3. **Ozdogan M, Samur M, Bozcuk HS, Sagtas E, Yildiz M, Artac M, Savas B**. Durable remission of leptomeningeal metastasis of breast cancer with letrozole: a case Report and implications of biomarkers on treatment selection. *Jpn J Clin Oncol*. 2003 May;33(5):229-31. PubMed PMID: 12865466.
4. **Chamberlain MC, Kormanik PR**. Carcinomatous meningitis secondary to breast cancer: predictors of response to combined modality therapy. *J Neurooncol*. 1997 Oct;35(1):55-64. PubMed PMID: 9266441.
5. **Chamberlain MC**. Response of leptomeningeal metastases from breast cancer to hormonal therapy. *Neurology*. 2001 Feb 13;56(3):425-6. PubMed PMID: 11171923.
6. **Madhup R, Kirti S, Bhatt ML, Srivastava PK, Srivastava M, Kumar S**. Letrozole for brain and scalp metastases from breast cancer--a case report. *Breast*. 2006 Jun;15(3):440-2. Epub 2005 Sep 16. PubMed PMID: 16169225.
7. **Rogers LR, Remer SE, Tejwani S**. Durable response of breast cancer leptomeningeal metastasis to capecitabine monotherapy. *Neuro Oncol*. 2004 Jan;6(1):63-4. PubMed PMID: 14769142; PubMed Central PMCID: PMC1871963.
8. **Giglio P, Tremont-Lukats IW, Groves MD**. Response of neoplastic meningitis from solid tumors to oral capecitabine. *J Neurooncol*. 2003 Nov;65(2):167-72. Erratum in: J Neurooncol. 2004 Jul;68(3):295. PubMed PMID: 14686737.
9. **Walko CM, Lindley C**. Capecitabine: a review. *Clin Ther*. 2005 Jan;27(1):23-44. Review. PubMed PMID: 15763604.
10. **Wang ML, Yung WK, Royce ME, Schomer DF, Theriault RL**. Capecitabine for 5-fluorouracil-resistant brain metastases from breast cancer. *Am J Clin Oncol*. 2001 Aug;24(4):421-4. PubMed PMID: 11474279.
11. **Seidman AD, O'Shaughnessy J, Misset JL**. Single-agent capecitabine: a reference treatment for taxane-pretreated metastatic breast cancer? *Oncologist*. 2002;7 Suppl 6:20-8. Review. PubMed PMID: 12454316.
12. **Heier MS, Heintz R, Fosså SD**. Passage of 5'-dFUrd and its metabolites 5-FU and 5-FUH2 to CSF in a clinical phase 1 study. *Acta Neurol Scand*. 1986 Sep;74(3):240-4. PubMed PMID: 2947416.
13. **Hikino H, Yamada T, Johbara K, Obayashi N, Ozaki N.** Potential role of chemo-radiation with oral capecitabine in a breast cancer patient with central nervous system relapse. *Breast*. 2006 Feb;15(1):97-9. Epub 2005 Jul 7. PubMed PMID: 16005228.
14. **Ekenel M, Hormigo AM, Peak S, Deangelis LM, Abrey LE**. Capecitabine therapy of central nervous system metastases from breast cancer. *J Neurooncol*. 2007 Nov;85(2):223-7. Epub 2007 Jul 5. PubMed PMID: 17611719.
15. **Mata JF, García-Manteiga JM, Lostao MP, Fernández-Veledo S, Guillén-Gómez E, Larrayoz IM, Lloberas J, Casado FJ, Pastor-Anglada M**. Role of the human concentrative nucleoside transporter (hCNT1) in the cytotoxic action of 5[Prime]-deoxy-5-fluorouridine, an active intermediate metabolite of capecitabine, a novel oral anticancer drug. *Mol Pharmacol*. 2001 Jun;59(6):1542-8. PubMed PMID: 11353816.
16. **Siegelmann-Danieli N, Stein M, Bar-Ziv J**. Complete response of brain metastases originating in breast cancer to capecitabine therapy. *Isr Med Assoc J*. 2003 Nov;5(11):833-4. PubMed PMID: 14650117.

17. **Fabi A, Vidiri A, Ferretti G, Felici A, Papaldo P, Carlini P, Mirri A, Nuzzo C, Cognetti F**. Dramatic regression of multiple brain metastases from breast cancer with Capecitabine: another arrow at the bow? *Cancer Invest*. 2006 Jun-Jul;24(4):466-8. PubMed PMID: 16777702.
18. **Glantz MJ, Jaeckle KA, Chamberlain MC, Phuphanich S, Recht L, Swinnen LJ, Maria B, LaFollette S, Schumann GB, Cole BF, Howell SB**. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res*. 1999 Nov;5(11):3394-402. PubMed PMID: 10589750.
19. **Jaeckle KA, Phuphanich S, Bent MJ, Aiken R, Batchelor T, Campbell T, Fulton D, Gilbert M, Heros D, Rogers L, O'Day SJ, Akerley W, Allen J, Baidas S, Gertler SZ, Greenberg HS, LaFollette S, Lesser G, Mason W, Recht L, Wong E, Chamberlain MC, Cohn A, Glantz MJ, Gutheil JC, Maria B, Moots P, New P, Russell C, Shapiro W, Swinnen L, Howell SB**. Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine. *Br J Cancer*. 2001 Jan;84(2):157-63. PubMed PMID: 11161370; PubMed Central PMCID: PMC2363714.
20. **Boogerd W, van den Bent MJ, Koehler PJ, Heimans JJ, van der Sande JJ, Aaronson NK, Hart AA, Benraadt J, Vecht ChJ**. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study. *Eur J Cancer*. 2004 Dec;40(18):2726-33. PubMed PMID: 15571954.
21. **Pors H, von Eyben FE, Sørensen OS, Larsen M**. Longterm remission of multiple brain metastases with tamoxifen. *J Neurooncol*. 1991 Apr;10(2):173-7. PubMed PMID: 1716670.
22. **Salvati M, Cervoni L, Innocenzi G, Bardella L**. Prolonged stabilization of multiple and single brain metastases from breast cancer with tamoxifen. Report of three cases. *Tumori*. 1993 Oct 31;79(5):359-62. PubMed PMID: 8116083.
23. **Stemmler HJ, Schmitt M, Harbeck N, Willems A, Bernhard H, Lässig D, Schoenberg S, Heinemann V**. Application of intrathecal trastuzumab (Herceptintrade mark) for treatment of meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer. *Oncol Rep*. 2006 May;15(5):1373-7. PubMed PMID: 16596213.
24. **American Association of Cancer Research**. Abstract LB-4. Oncology News International. 2007; 16(6):12.
25. **Christodoulou C, Bafaloukos D, Kosmidis P, Samantas E, Bamias A, Papakostas P, Karabelis A, Bacoyiannis C, Skarlos DV; Hellenic Cooperative Oncology Group**. Phase II study of temozolomide in heavily pretreated cancer patients with brain metastases. *Ann Oncol*. 2001 Feb;12(2):249-54. PubMed PMID: 11300333.
26. **Trudeau ME, Crump M, Charpentier D, Yelle L, Bordeleau L, Matthews S, Eisenhauer E**. Temozolomide in metastatic breast cancer (MBC): a phase II trial of the National Cancer Institute of Canada - Clinical Trials Group (NCIC-CTG). *Ann Oncol*. 2006 Jun;17(6):952-6. Epub 2006 Mar 24. PubMed PMID: 16565212.
27. **Rivera E, Meyers C, Groves M, Valero V, Francis D, Arun B, Broglio K, Yin G, Hortobagyi GN, Buchholz T**. Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. *Cancer*. 2006 Sep 15;107(6):1348-54. PubMed PMID: 16909414.

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