Integrative Cancer Therapies
Volume 19: 1–4

DOI: 10.1177/1534735419890017
journals.sagepub.com/home/ict
SAGE

Breast Cancer With Brain Metastases: Perspective From a Long-Term Survivor

Christopher P. Kofron, PhD[1] and Angela Chapman, PhD[2]

Abstract

The purpose of this essay is to inform others that it is possible to survive breast cancer with brain metastases. The second author is the subject patient and a long-term survivor of systemic metastatic breast cancer with numerous brain metastases (corresponding to 8% survivor group). We credit her survival to a combination of (1) medicine as practiced by an excellent oncologist with whom we developed a partnership to manage the patient's health, (2) our informed exploration of the available scientific knowledge including a review of scientific research articles that go beyond conventional care, and (3) the patient's supplementation with numerous repurposed drugs and other substances reported to have antitumor properties. Alongside her conventional treatment (the medical standard of care), it seems likely that this supplementation has been a key factor in the patient's long-term survival. We also point out that the lack of follow-up magnetic resonance imaging brain scans for early detection of brain metastases poses substantial risks for patients with HER2+ metastatic breast cancer in non–central nervous system locations. Thus, we suggest that research be conducted on such early detection for possible inclusion in the recommendations for the medical standard of care. Finally, medical doctors and also patients with backgrounds in biological science may wish to consider potential options and advantages of repurposed drugs and other substances reported in scientific publications when the medical standard of care has limited options for advanced cancer and other severe chronic health conditions. However, any efforts along this line by patients should be in collaboration with their medical doctors.

Keywords

brain radiotherapy, brain metastases, breast cancer, long-term survival, off-label, standard of care, whole-brain radiation therapy

Submitted May 12, 2019; revised October 17, 2019; accepted October 29, 2019

The purpose of this essay is to inform others that it is possible to survive breast cancer with brain metastases, and the second author is the subject patient to whom we refer. The patient is a survivor of HER2+ metastatic breast cancer in non–central nervous system locations since November 2012 and of brain metastases since June 2014. There has been no evidence of cancer since March 2016; however, the patient is experiencing physical and mental difficulties due to the toxicity of brain radiotherapy. The patient wishes to share the personal details of her medical history in the interests of potentially furthering survival from breast cancer. Accordingly, a signed consent form is on file with the publisher of this journal.

The patient (at age 61 years) was diagnosed with stage IV breast cancer on November 8, 2012. Although the cancer in her breast was small (7.5 × 8 mm), it was HER2+, which is an aggressive type comprising 18% of breast cancer cases in the United States.[1] At the time of diagnosis, the infiltrating ductal carcinoma (estrogen receptor−/progesterone receptor−) had already spread to a nearby lymph node, and from there to the liver, vertebrae, and pelvis. The magnetic resonance imaging (MRI) brain scan showed no evidence of cancer there. Shortly after diagnosis and while awaiting insurance approval and treatment, the patient's liver became so enlarged that it hindered breathing and was almost replaced by tumor. According to the American Cancer Society,[2] the patient had a 23% probability of surviving 5 years.

[1]US Fish and Wildlife Service, Ventura, CA, USA
[2]Biology Program, California State University Channel Islands, Camarillo, CA, USA

Corresponding Author:
Christopher P. Kofron, US Fish and Wildlife Service, 2493 Portola Road, Suite B, Ventura, CA 93003, USA.
Email: chris.kofron@charter.net

The patient received conventional treatment at University of California Los Angeles Health (UCLA Health), specifically, the accepted medical standard of care to which her body responded quickly and completely. The treatment comprised chemotherapy (docetaxel) in combination with monoclonal antibodies (trastuzumab with pertuzumab). The chemotherapy was harsh and caused fatigue, nausea, diarrhea, and loss of hair and nails. However, 6 months later, the cancer was in remission, and the positron emission tomography/computed tomography body scan showed a complete metabolic response to treatment. The liver returned to normal size. By 12 months, the cancer appeared to be in deep remission, as described by the treating oncologist, and our lives returned to normal. In March, April, and May 2014, the patient participated in a clinical trial for HER2+ metastatic breast cancer and received the 3 doses of a trial vaccine.[3] Six days later in May 2014, the patient's speech became garbled. The subsequent MRI brain scan on June 3, 2014, showed >20 tumors, with some in the speech area, the largest measuring 19 mm. Conventional treatments for brain metastases from breast cancer have only minimal success, and overall survival is on the order of months.[4]

Patients with HER2+ metastatic breast cancer in non–central nervous system locations are at increased risk for brain metastases; however, monitoring MRI scans of the brain are not routinely performed.[5] As a consequence, at her diagnosis of cancer recurrence in 2014, the patient had massive metastatic spread to her brain. The current medical standard of care does not include follow-up MRI brain scans,[6-8] even though 30% to 55% of patients with HER2+ metastatic breast cancer in non–central nervous system locations will develop brain metastases too.[9] It seems that patients with HER2+ metastatic breast cancer in non–central nervous system locations should receive follow-up MRI brain scans for early detection of brain metastases. This is supported by a recent study that analyzed the value of MRI brain scans for patients with cancers that frequently metastasize to the brain.[10] We suggest that research be conducted on such early detection for possible inclusion in the recommendations for the medical standard of care.

The patient again received the medical standard of care,[6] which comprised whole-brain radiation therapy (2.5 grays × 15 treatments = 37.5 grays), stereotactic radiosurgery twice (one tumor each time, 18 grays per tumor), and combination therapy (capecitabine with lapatinib) along with trastuzumab. Regarding whole-brain radiation therapy, it is used for patients with poor prognoses. For example, in one study of HER2+ patients (n = 270) with breast cancer brain metastases,[5] 49% of the patients survived 1 year after developing brain metastases (estimates from Kaplan-Meier overall survival curve), and 28% survived 2 years after developing brain metastases. It is now December 2019, and the patient corresponds with the 8% survivor group for 5 years or more after developing brain metastases.

In July 2014, the patient started treatment with the combination therapy drugs capecitabine and lapatinib, which was the only option in accordance with the medical standard of care,[6] and she subsequently experienced debilitating side effects from each drug. We are both biologists and, since then, we have extensively reviewed the relevant scientific literature. We learned that the patient actually had other potential options based on scientific research. She discontinued capecitabine in June 2015 and lapatinib in May 2018 because of the intolerable side effects. The patient continued with infusions of trastuzumab with intermittent pertuzumab, which had been ongoing with regular cardiotoxicity screening and breaks since November 2012, or with infusions of off-label ado-trastuzumab emtansine at our request. It appears that these large-molecule drugs can cross damaged blood-brain barriers.[11] In addition, the patient supplemented with numerous other drugs and substances that are reported in scientific publications to have antitumor properties, including artemisinin,[12,13] aspirin,[14,15] cannabidiol,[16] chloroquine,[17-19] doxycycline,[20] flaxseed oil,[21] hydroxychloroquine,[18,19] indole-3-carbinol,[22,23] melatonin,[24,25] nanocurcumin,[22,26] omega-3 fish oil,[27] pterostilbene,[28,29] quercetin,[22,30] resveratrol,[14,22] turkey tail mushroom (*Trametes* [*Coriolus*] *versicolor*),[31,32] and vitamin D_3.[24,33,34] Since March 2013, there has been no evidence of cancer outside the patient's central nervous system. Regarding her brain, there is one lesion persisting since March 2016 that may or may not be cancer—it appears more likely to be a nonhealing radiation injury from stereotactic radiosurgery.

The patient chose to have a break from prescribed cancer drugs beginning September 2018 (last infusion of trastuzumab on August 24, 2018). However, she continues to take aspirin, melatonin, nanocurcumin, omega-3 fish oil, pterostilbene, and vitamin D_3. The cancer has not returned anywhere (most recent MRI brain scan, September 1, 2019; most recent MRI scan chest/abdomen/pelvis, July 7, 2019), and the patient is not experiencing any known adverse effects with the regimen that she uses. However, her estrogen receptor− status combined with her HER2+ status are reported to make her long-term survival unlikely, even with the medical standard of care.[35,36,37] Alongside her conventional treatment, it seems likely that the patient's supplementation with the numerous repurposed drugs and other substances reported to have antitumor properties (starting in June 2014 with turkey tail mushroom) has been a key factor in her long-term survival. The contribution of the trial vaccine is not known at this point in time.

The patient has been adversely affected by the brain radiotherapy with its neural toxicity, and she is experiencing delayed debilitating effects. Her brain has undergone cerebral volume loss resulting in progressive neural decline. The patient now struggles to stand and walk, and her mental abilities are somewhat reduced, in particular technical skills and short-term memory. However, she is mentally fully

competent to coauthor this article and to consent to its publication. Based on recent scientific research and at our request, the patient is receiving off-label pegfilgrastim and metformin, and she is about to commence hyperbaric oxygen therapy. Pegfilgrastim repaired the irradiated brains of laboratory animals,[38] and metformin partially repaired the injured brains (oxygen deprived) of laboratory animals and the irradiated brains of humans.[39,40] Hyperbaric oxygen therapy was reported to be a possible good treatment option for nonhealing, radiation-induced brain lesions, like the patient's.[41] Considering the results of scientific studies such as these may be the patient's only chance for walking again.

In closing, the patient is a long-term survivor of systemic metastatic breast cancer with numerous brain metastases. We credit her survival to a combination of (1) medicine as practiced by an excellent oncologist with whom we developed a partnership to manage the patient's health, (2) our informed exploration of the available scientific knowledge including a review of scientific research articles that go beyond conventional care, and (3) the patient's supplementation with numerous repurposed drugs and other substances reported to have antitumor properties. Of course, there are risks with this approach, but the patient's health is already severely compromised, and conventional care has offered only limited options for improvement. The patient continues with ongoing follow-up cancer care at UCLA Health. Finally, we suggest that medical doctors and also patients with backgrounds in biological science may wish to consider potential options and advantages of repurposed drugs and other substances reported in scientific publications when the medical standard of care offers limited options for advanced cancer and other severe chronic health conditions. However, any effort along this line by patients should be in collaboration with their medical doctors.

Acknowledgments

Dr Catherine Darst, James Kofron, and 2 anonymous reviewers read and commented on the manuscript. We thank Dr Olga Olevsky for discussions regarding cancer biology.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The findings and conclusions in this article are those of the authors and do not represent the views of the US Fish and Wildlife Service.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Christopher P. Kofron https://orcid.org/0000-0002-9028-3512

References

1. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *J Natl Cancer Inst*. 2015;107:1-25.
2. American Cancer Society. *Cancer Facts and Figures*. Atlanta, GA: American Cancer Society; 2012.
3. University of Washington. Vaccine therapy with or without polysaccharide-K in treating patients with stage IV HER2 positive breast cancer receiving HER2-targeted monoclonal antibody therapy. https://clinicaltrials.gov/ct2/show/study/NCT01922921. Accessed August 11, 2019.
4. Kodack DP, Askoxylakis V, Ferraro GB, Fukumura D, Jain RK. Emerging strategies for treating brain metastases from breast cancer. *Cancer Cell*. 2015;27:163-175.
5. Niikura N, Hayashi N, Masuda N, et al. Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer of each subtype: a multicenter retrospective analysis. *Breast Cancer Res Treat*. 2014;147:103-112.
6. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2014;32:2100-2108.
7. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36:2804-2807.
8. Ramakrishna N, Temin S, Lin NU. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: ASCO Clinical Practice Guideline Update Summary. *J Oncol Pract*. 2018;14:505-508.
9. Lin NU, Amiri-Kordestani L, Palmieri D, Liewehr DJ, Steeg PS. CNS metastases in breast cancer: old challenge, new frontiers. *Clin Cancer Res*. 2013;19:6404-6418.
10. Cagney DN, Martin AM, Catalano PJ, et al. Implications of screening for brain metastases in patients with breast cancer and non-small cell lung cancer. *JAMA Oncol*. 2018;4:1001-1003.
11. Keith KC, Lee Y, Ewend MG, Zagar TM, Anders CK. Activity of trastuzumab-emtansine (TDM1) in HER2-positive breast cancer brain metastases: a case series. *Cancer Treat Commun*. 2016;7:43-46.
12. Efferth T. Cancer combination therapies with artemisinin-type drugs. *Biochem Pharmacol*. 2017;139:56-70.
13. Abba ML, Patil N, Leupold JH, Saeed MEM, Efferth T, Allgayer H. Prevention of carcinogenesis and metastasis by artemisinin-type drugs. *Cancer Lett*. 2018;429:11-18.
14. Lissa D, Senovilla L, Rello-Varona S, et al. Resveratrol and aspirin eliminate tetraploid cells for anticancer chemoprevention. *Proc Natl Acad Sci U S A*. 2014;111:3020-3025.
15. Chen WY, Holmes MD. Role of aspirin in breast cancer survival. *Curr Oncol Rep*. 2017;19:48.
16. Elbaz M, Nasser MW, Ravi J, et al. Modulation of the tumor microenvironment and inhibition of EGF/EGFR pathway:

novel anti-tumor mechanisms of cannabidiol in breast cancer. *Mol Oncol*. 2015;9:906-919.
17. Cufi S, Vazquez-Martin A, Oliveras-Ferraros C, et al. The anti-malarial chloroquine overcomes primary resistance and restores sensitivity to trastuzumab in HER2-positive breast cancer. *Sci Rep*. 2013;3(2469):1-13.
18. Manic G, Obrist F, Kroemer G, Vitale I, Galluzzi L. Chloroquine and hydroxychloroquine for cancer therapy. *Mol Cell Oncol*. 2014;1:1-11.
19. Verbaanderd C, Maes H, Schaaf MB, et al. Repurposing drugs in oncology (ReDo)—chloroquine and hydroxychloroquine as anti-cancer agents. *eCancerMedicalScience*. 2017;11(781):1-35.
20. Peiris-Pages M, Sotgia F, Lisanti MP. Doxycycline and therapeutic targeting of the DNA damage response in cancer cells: old drug, new purpose. *Oncoscience*. 2015;2:696-699.
21. Mason JK, Fu M, Chen J, Thompson LU. Flaxseed oil enhances the effectiveness of trastuzumab in reducing the growth of HER2-overexpressing human breast tumors (BT-474). *J Nutr Biochem*. 2015;26:16-23.
22. Ouhtit A, Gaur RL, Abdraboh M, et al. Simultaneous inhibition of cell-cycle, proliferation, survival, metastatic pathways and induction of apoptosis in breast cancer cells by phytochemical super-cocktail: genes that underpin its mode of action. *J Cancer*. 2013;4:703-715.
23. Pfeifer BL, Fahrendorf T. Indole-3-carbinol: a glucosinolate derivative from cruciferous vegetables for prevention and complementary treatment of breast cancer. *Deutsche Zeitschrift für Onkologie*. 2015;47:20-27.
24. Proietti S, Cucina A, D'Anselmi F, et al. Melatonin and vitamin D_3 synergistically down-regulate Akt and MDM2 leading to TGF*B*-1-dependent growth inhibition of breast cancer cells. *J Pineal Res*. 2011;50:150-158.
25. Hill SM, Belancio VP, Dauchy RT, et al. Melatonin: an inhibitor of breast cancer. *Endocr Relat Cancer*. 2015;22:R183-R204.
26. Klinger NV, Mittal S. Therapeutic potential of curcumin for the treatment of brain tumors. *Oxid Med Cell Longev*. 2016;2016(9324085):1-14.
27. Fabian CJ, Kimler BF, Hursting, SD. Omega-3 fatty acids for breast cancer prevention and survivorship. *Breast Cancer Res*. 2015;17(62):1-11.
28. Xing F, Liu Y, Sharma S, et al. Activation of the c-Met pathway mobilizes an inflammatory network in the brain microenvironment to promote brain metastasis of breast cancer. *Cancer Res*. 2016;76:4970-4980.
29. Xing F, Liu Y, Sharma S, et al. Pterostilbene (PTER) suppresses breast cancer brain metastasis by targeting a c-Met mediated inflammation network. *Cancer Res*. 2016;76(14 suppl):abstract 905.
30. Li J, Zhu F, Lubet RA, et al. Quercetin-3-methyl ether inhibits lapatinib-sensitive and -resistant breast cancer cell growth by inducing G_2/M arrest and apoptosis. *Mol Carcinog*. 2013;52:134-143.
31. Torkelson CJ, Sweet E, Martzen MR, et al. Phase 1 clinical trial of *Trametes versicolor* in women with breast cancer. ISRN Oncol. 2012 (251632);1-7.
32. Saleh MH, Rashedi I, Keating A. Immunomodulatory properties of *Coriolus versicolor*: the role of polysaccharopeptide. *Front Immunol*. 2017;8(1087):1-12.
33. Mohr SB, Gorham ED, Kim J, Hofflich H, Garland CF. Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. *Anticancer Res*. 2014;34:1163-1166.
34. Yao S, Kwan ML, Ergas IJ, et al. Association of serum level of vitamin D at diagnosis with breast cancer survival: a case-cohort analysis in the pathways study. *JAMA Oncol*. 2017;3:351-357.
35. Arciero CA, Guo Y, Jiang R, et al. $ER^+/HER2^+$ breast cancer has different metastatic patterns and better survival than $ER^-/HER2^+$ breast cancer. *Clin Breast Cancer*. 2019;19:236-245.
36. Klar N, Rosenzweig M, Diergaarde B, Brufsky A. Features associated with long-term survival in patients with metastatic breast cancer. *Clin Breast Cancer*. 2019;19:304-310.
37. Güth U, Elfgen C, Montagna G, Schmid SM. Long-term survival and cure in distant metastatic breast cancer. *Oncology-Basel*. 2019;97:82-93.
38. Dietrich J, Baryawno N, Nayyar N, et al. Bone marrow drives central nervous system regeneration after radiation injury. *J Clin Invest*. 2018;128:281-293.
39. Dadwal P, Mahmud N, Sinai L, et al. Activating endogenous neural precursor cells using metformin leads to neural repair and functional recovery in a model of childhood brain injury. *Stem Cell Reports*. 2015;5:166-173.
40. Ayoub R. *Placebo Controlled Double Blind Crossover Trial of Metformin for Brain Repair in Children Treated With Cranial Radiation for Brain Tumors* [thesis]. Toronto, Ontario: University of Toronto; 2018.
41. Patel U, Patel A, Cobb C, Benkers T, Vermeulen S. The management of brain necrosis as a result of SRS treatment for intra-cranial tumors. *Transl Cancer Res*. 2014;3:373-382.