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OPINION

Perspective on the interpretation of research and translation to clinical care with therapy-associated metastatic breast cancer progression as an example

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Abstract

This commentary was written as a collaboration between the Board of the Metastasis Research Society and two patients with metastatic breast cancer. It was conceived in response to how preclinical scientific research is sometimes presented to non-scientists in a way that can cause stress and confusion. Translation of preclinical findings to the clinic requires overcoming multiple barriers. This is irrespective of whether the findings relate to exciting responses to new therapies or problematic effects of currently used therapies. It is important that these barriers are understood and acknowledged when research findings are summarized for mainstream reporting. To minimize confusion, patients should continue to rely on their oncology care team to help them interpret whether research findings presented in mainstream media have relevance for their individual care. Researchers, both bench and clinical, should work together where possible to increase options for patients with metastatic disease, which is still in desperate need of effective therapeutic approaches.

Keywords Neoadjuvant chemotherapy · Relapse · Metastatic progression · Survival

Abbreviations

ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
PAM50	Prediction analysis of microarray 50
PR	Progesterone receptor

Introduction

The ethical principle underpinning medicine is '*primum non nocere*'—first, do no harm. As research leads to an improved understanding of disease processes however, it can be difficult for medical practice to keep up with changing knowledge and adhere to that concept. A recent publication from Karagiannis and colleagues has attracted much interest, especially among the patient community, due to its finding that neo-adjuvant chemotherapy appears to cause micro-environmental changes linked to metastatic breast cancer progression [1]. The specific focus of this paper is on a set of tumor cell and stromal alterations that promote the process of breast cancer cell intravasation. It highlighted how the invasion of cancer cells into the lymphatic system or blood stream is altered by chemotherapy. The general concept of therapy-associated metastasis is not new and has been reported previously for taxane therapies [2]. Indeed all standard therapeutic modalities—surgery, radiation, chemotherapy and molecularly targeted agents - have been linked in the research literature to increased markers of metastatic progression in different cancer types (reviewed in [3]) and new studies regularly emerge [4, 5]. Nevertheless, these same therapies are widely used clinically to treat patients at

Members of the Board of the Metastasis Research Society are listed in "Acknowledgments".

Deceased—Beth Caldwell.

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risk of metastatic disease, leading to questions of whether harm is being done. This dichotomy has rightly resulted in some recent confusion, particularly amongst the metastatic patient community. Below, we discuss the patient perspective then offer reasons why research findings, whether positive or negative, should be interpreted cautiously and cannot typically be immediately translated to changes in clinical care. Nevertheless, the purpose of researching how therapies may influence metastasis is to ultimately improve standard of care and benefit to patients. It is thus important for clinicians and basic researchers to work together to design appropriate clinical trials that will provide answers for patients looking for therapies that are safe and effective both short- and long-term. The paper from Karagiannis et al., in fact aims at providing a future solution to this problem.

The patient perspective

When a new scientific article comes out, most patients rely on mainstream journalism (TV news, newspapers, magazines, etc.) to summarize the science and explain the main findings. The majority of scientific articles are not accessible to the patient community directly because they are not published as 'Open Access,' which can cost approximately $3000–$3500 per article. Unfortunately, journalists covering scientific articles generally don't explain the nuances of the science involved. Instead, they write a flashy headline designed to get ratings and page views, a headline that too often is an inaccurate or inadequate description and interpretation of what the data in the article is actually showing.

It is vitally important for patients to discuss mainstream cancer headlines they read with their oncologist, who can accurately explain to them what the article shows, offer an appropriate interpretation, and explain what the findings could mean for an individual patient's treatment. Each patient's cancer is different, and each patient's treatment is individualized for their particular cancer. A patient's oncologist is hands down the most knowledgeable person regarding that patient's cancer, and what the risks and benefits of individual treatments are for that patient. It is risky for a patient to reject their oncologist's treatment suggestions based on what they read in the mainstream news. Patients and their oncologists need to work together to talk about the latest science and the patient's individual needs, with the goal of keeping that patient alive and feeling as well as possible.

Putting research findings into context

Oncologists should be the leading resource for patients trying to interpret translational science results and apply them to their own care. There are also some important limitations of several common basic research and clinical trial attributes and techniques that all can keep in mind to more accurately interpret the potential clinical impact of research findings or trial outcomes in general. There are several differences between bench research, clinical trials and ultimately 'real-world' outcomes. It is incumbent upon researchers, whether basic, translational, epidemiological or clinical, as well as clinical care providers including those disseminating information directly to patients to acknowledge these differences and understand the limitations they impose.

- *Animal models* It is recognized that all pre-clinical models have limitations that can contribute to the failure of novel therapeutic agents in clinical testing [6–9]. These limitations also apply to predicting therapy complications for many of the same reasons. With animal models, researchers generally use a homogenous subject group where the mice are of the same age, genetic background and have been exposed to the same environmental factors. In contrast, human patients are extremely diverse when considering these parameters. Additionally, cancer models in animals are often generated by either injecting a large number of already mutated cancer cells all at once, or by expression of a strong oncogenic gene, which in most cases allows rapid cancer development in a short period of time (weeks to months). These events happen in the setting of an otherwise healthy animal (except perhaps for being immune-compromised in tumor transplantation studies). In people however, cancer can develop from rare mutated cells over many years. Progression is influenced by underlying complex genetic susceptibility traits and can be exacerbated by chronic diseases such as inflammatory conditions or other stresses on general health such as obesity, alcohol-intake or smoking. Thus, findings that are highly significant and consistent in model animals, become much less obvious and more difficult to interpret when there are multiple other variables in human patients. Improvements in tumor modeling in animals can alleviate some of the limitations and ultimately should increase the predictive value of preclinical evaluation. Such improvements include for example using multiple patient-derived xenografts to add heterogeneity, using animals with already established metastatic disease prior to the initiation of therapy and/or using several different types of well-established models—e.g. tumor implant, carcinogen-induced or genetically-engineered models.
- *Use of clinical specimens* A strong component of the study from Karagiannis et al. was their analysis of clinical specimens to show similar changes as observed in the animal studies [1]. Of course, there are limitations regarding the type of questions that can be asked using clinical specimens. Specifically, in such samples it is very difficult to determine cause versus effect directly; instead investigators must look for associations. The strongest

data generally come from longitudinal studies where repeated sampling of the same individual (e.g. from multiple blood draws, biopsies and/or surgical resections) allows determination of when particular changes became apparent. These kinds of studies are challenging to complete partly because repeat biopsies cannot always be justified and partly because patients may drop out of a study before its completion for a variety of reasons. The result is a negative impact on sample size and subsequently the power of the study to draw robust conclusions. Even with longitudinal studies, the endpoint is often relatively short-term constituting measurements that can be made with the samples collected. They often do not extend past the 5 years or longer that may be necessary to see whether there is a long-term impact such as development of overt metastases or even survival.

- *Clinical trial endpoints* The use of chemotherapy as a neoadjuvant therapy (i.e. treatment given prior to the main therapy, usually surgery) in breast cancer patients at high risk for progression was initially tested and showed to be beneficial in relatively small trials [10, 11]. More recently, larger clinical trials have continued to support these findings [12, 13]. The trials showed that in particular populations of high-risk breast cancer patients, treatment with drugs such as paclitaxel prior to surgery was associated with an improvement in surrogate endpoints, for instance 'progression-free survival' or 'pathological complete response'. Other studies in breast cancer have shown improvements in disease-free survival for neoadjuvant use of radiotherapy [14] or hormone therapy [15]. Often, results from these trials report patient outcome at 5–8 year time points by which time disease recurrence is assumed to occur. Yet, when more data over a longer term is available, it seems that there is not always a corresponding increase in overall survival, although this may be dependent on cancer type and aggressiveness [16–20]. A separate study compared 'real-world' outcomes derived from Surveillance and Epidemiology End Results-Medicare data with either overall survival or surrogate survival endpoints from 21 Phase III trials across a range of cancers. This study found agreement when overall survival was the trial endpoint. However, efficacy was reduced when surrogate endpoints were used [21]. Paradoxical findings of improved disease-free survival without affecting overall survival provide rationale for examining untoward effects of neoadjuvant therapy. Nevertheless, it is very important to note that therapy does not appear to lead to a decrease in overall survival either [12, 14]. It is also important to realize that using only the metric of increased overall survival for multiple cancer types could impede rapid availability of new, efficacious drugs that may bring significant benefits to patients, such as improved quality of life. Thus, the balance between using an endpoint that suggests some shorter-term benefit yet no improvement to long-term outcomes, versus only approving agents that increase overall survival significantly is a still-evolving issue [22, 23].
- *Patient stratification—the use of molecular markers* In breast cancer, 'precision oncology' is not an especially new concept given that treatment decisions are already made based on the expression (or lack thereof) of hormone receptors (estrogen and progesterone receptors, ER and PR) and HER2. There is some evidence that breast cancer subtype, based on expression of these receptors, is an important factor in the initial response to neoadjuvant chemotherapy [24, 25]. However, for the longer-term outcome of distant recurrence, tumor size rather than subtype appeared to be a more powerful predictor [26]. More sophisticated stratification of patients may be necessary to determine who is likely to benefit from therapy in both the short and long term [27]. For example, a study examining the molecular profiles of tumor specimens from 861 breast cancer patients on a clinical trial concluded that use of PAM50 and triple-negative genetic subtyping could identify distinct prognostic subsets that had different outcomes compared to overall population [28]. The clinical trial from which these specimens were analyzed (USO 01062) was one testing the efficacy of adding capecitabine to anthracyline/taxane adjuvant chemotherapy in high-risk early stage patients. The conclusion was that in the large, heterogeneous study population, there was no demonstrable benefit of the combined treatment. However, if this trial had instead only included basal-type triple negative cancers there may have been a beneficial outcome. Thus, in trials where stratification is not considered, therapeutic approaches that work well for a small subgroup of patients may not be picked out against the larger pool of patients showing no benefits. Where bench studies have identified factors that may predispose certain subtypes of cancer to a better or worse response to any therapy, it would be valuable to examine which of these factors could be included in subsequent clinical trials of that therapy.

A myriad of other factors can impact reported trial outcomes such as the initial disease burden in patients enrolled in a trial, dose and timing of the administered therapy [29] and even (for progression-free endpoints) bias based on timing of evaluation [30]. Given the complexity involved in determining what therapies should be used when, and with what patients, it is remarkable that the system works as well as it does. However, the continued evaluation by basic and clinical researchers of how drugs behave in more sophisticated animal/cell models as well as in real-world clinical settings provides much-needed feedback to improve the process. Thus, findings such as those reported by Karagiannis

and others offer insights into potential effects that should now be assessed using clinical outcome data to ensure that patients are offered treatments that provide benefit but that also do no harm.

Finally, patients recognize the need to make treatment decisions based on scientific evidence, but it can be frustrating and frightening to realize there is so much about metastatic cancer treatment that is still unknown. While patient choice is an absolute right, treatment decisions should be made with a good understanding of risk and benefit. Patients should continue to rely on their oncologists to help them interpret the relevance of an individual study in the overall context of current evidence. Unfortunately, patients too often hear "we just don't know the answer to that." The Karagiannis study underscores what patients already know—that more research is desperately needed.

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Compliance with ethical standards

Conflict of interest No conflicts of interest to declare.

References

1. Karagiannis GS, Pastoriza JM, Wang Y, Harney AS, Entenberg D, Pignatelli J, Sharma VP, Xue EA, Cheng E, D'Alfonso TM, Jones JG, Anampa J, Rohan TE, Sparano JA, Condeelis JS, Oktay MH (2017) Neoadjuvant chemotherapy induces breast cancer metastasis through a TMEM-mediated mechanism. Sci Transl Med. https://doi.org/10.1126/scitranslmed.aan0026
2. Gingis-Velitski S, Loven D, Benayoun L, Munster M, Bril R, Voloshin T, Alishekevitz D, Bertolini F, Shaked Y (2011) Host response to short-term, single-agent chemotherapy induces matrix metalloproteinase-9 expression and accelerates metastasis in mice. Cancer Res 71(22):6986–6996. https://doi.org/10.1158/0008-5472.CAN-11-0629
3. Ebos JM (2015) Prodding the beast: assessing the impact of treatment-induced metastasis. Cancer Res 75(17):3427–3435. https://doi.org/10.1158/0008-5472.CAN-15-0308
4. Chen WY, Tsai YC, Yeh HL, Suau F, Jiang KC, Shao AN, Huang J, Liu YN (2017) Loss of SPDEF and gain of TGFBI activity after androgen deprivation therapy promote EMT and bone metastasis of prostate cancer. Sci Signal. https://doi.org/10.1126/scisignal.aam6826
5. Dufies M, Giuliano S, Ambrosetti D, Claren A, Ndiaye PD, Mastri M, Moghrabi W, Cooley LS, Ettaiche M, Chamorey E, Parola J, Vial V, Lupu-Plesu M, Bernhard JC, Ravaud A, Borchiellini D, Ferrero JM, Bikfalvi A, Ebos JM, Khabar KS, Grepin R, Pages G (2017) Sunitinib stimulates expression of VEGFC by tumor cells and promotes lymphangiogenesis in clear cell renal cell carcinomas. Cancer Res 77(5):1212–1226. https://doi.org/10.1158/0008-5472.CAN-16-3088
6. Ruggeri BA, Camp F, Miknyoczki S (2014) Animal models of disease: pre-clinical animal models of cancer and their applications and utility in drug discovery. Biochem Pharmacol 87(1):150–161. https://doi.org/10.1016/j.bcp.2013.06.020
7. Kerbel RS (1999) What is the optimal rodent model for antitumor drug-testing? Cancer Metastas Rev 17:301–304
8. Kerbel RS (2003) Human tumor xenografts as predictive preclinical models for anticancer drug activity in humans: better than commonly perceived-but they can be improved. Cancer Biol Ther 2(4 Suppl 1):S134–S139
9. Johnson JI, Decker S, Zaharevitz D, Rubinstein LV, Venditti JM, Schepartz S, Kalyandrug S, Christian M, Arbuck S, Hollingshead M, Sausville EA (2001) Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials. Br J Cancer 84(10):1424–1431. https://doi.org/10.1054/bjoc.2001.1796
10. Swain SM, Sorace RA, Bagley CS, Danforth DN Jr., Bader J, Wesley MN, Steinberg SM, Lippman ME (1987) Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer. Cancer Res 47(14):3889–3894
11. Schwartz GF, Cantor RI, Biermann WA (1987) Neoadjuvant chemotherapy before definitive treatment for stage III carcinoma of the breast. Arch Surg 122(12):1430–1434
12. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, Margolese RG, Hoehn JL, Vogel VG, Dakhil SR, Tamkus D, King KM, Pajon ER, Wright MJ, Robert J, Paik S, Mamounas EP, Wolmark N (2008) Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 26(5):778–785. https://doi.org/10.1200/JCO.2007.15.0235
13. Campbell JI, Yau C, Krass P, Moore D, Carey LA, Au A, Chhieng D, Giri D, Livasy C, Mies C, Rabban J, Sarode VR, Singh B, Esserman L, Chen YY (2017) Comparison of residual cancer burden, American Joint Committee on Cancer staging and pathologic complete response in breast cancer after neoadjuvant chemotherapy: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). Breast Cancer Res Treat 165(1):181–191. https://doi.org/10.1007/s10549-017-4303-8
14. Poleszczuk J, Luddy K, Chen L, Lee JK, Harrison LB, Czerniecki BJ, Soliman H, Enderling H (2017) Neoadjuvant radiotherapy of early-stage breast cancer and long-term disease-free survival.

Breast Cancer Res 19(1):75. https://doi.org/10.1186/s13058-017-0870-1
15. Ellis MJ (2017) Lessons in precision oncology from neoadjuvant endocrine therapy trials in ER+ breast cancer. Breast. https://doi.org/10.1016/j.breast.2017.06.039
16. Foster NR, Qi Y, Shi Q, Krook JE, Kugler JW, Jett JR, Molina JR, Schild SE, Adjei AA, Mandrekar SJ (2011) Tumor response and progression-free survival as potential surrogate endpoints for overall survival in extensive stage small-cell lung cancer: findings on the basis of North Central Cancer Treatment Group trials. Cancer 117(6):1262–1271. https://doi.org/10.1002/cncr.25526
17. Fiteni F, Westeel V, Bonnetain F (2017) Surrogate endpoints for overall survival in lung cancer trials: a review. Expert Rev Anticancer Ther 17(5):447–454. https://doi.org/10.1080/14737140.2017.1316196
18. Fiteni F, Bonnetain F (2016) Surrogate end points for overall survival in breast cancer trials: a review. Breast 29:44–48. https://doi.org/10.1016/j.breast.2016.06.005
19. Ciani O, Buyse M, Garside R, Peters J, Saad ED, Stein K, Taylor RS (2015) Meta-analyses of randomized controlled trials show suboptimal validity of surrogate outcomes for overall survival in advanced colorectal cancer. J Clin Epidemiol 68(7):833–842. https://doi.org/10.1016/j.jclinepi.2015.02.016
20. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer CE Jr., Pazdur R, Ditsch N, Rastogi P, Eiermann W, von Minckwitz G (2014) Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384(9938):164–172. https://doi.org/10.1016/S0140-6736(13)62422-8
21. Lakdawalla DN, Shafrin J, Hou N, Peneva D, Vine S, Park J, Zhang J, Brookmeyer R, Figlin RA (2017) Predicting real-world effectiveness of cancer therapies using overall survival and progression-free survival from clinical trials: empirical evidence for the ASCO value framework. Value Health 20(7):866–875. https://doi.org/10.1016/j.jval.2017.04.003
22. Mannu GS, Dodwell D (2017) Making progress in early breast cancer: taking time or accepting risk? Eur J Cancer 78:24–27. https://doi.org/10.1016/j.ejca.2017.03.005
23. Carey LA, Winer EP (2014) Defining success in neoadjuvant breast cancer trials. Lancet 384(9938):115–116. https://doi.org/10.1016/S0140-6736(14)60034-9
24. von Minckwitz G, Loibl S, Maisch A, Untch M (2011) Lessons from the neoadjuvant setting on how best to choose adjuvant therapies. Breast 20(Suppl 3):S142–S145. https://doi.org/10.1016/S0960-9776(11)70312-5
25. Gluck S, de Snoo F, Peeters J, Stork-Sloots L, Somlo G (2013) Molecular subtyping of early-stage breast cancer identifies a group of patients who do not benefit from neoadjuvant chemotherapy. Breast Cancer Res Treat 139(3):759–767. https://doi.org/10.1007/s10549-013-2572-4
26. Fei F, Messina C, Slaets L, Chakiba C, Cameron D, Bogaerts J, Bonnefoi H (2015) Tumour size is the only predictive factor of distant recurrence after pathological complete response to neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancers: a sub-study of EORTC 10994/BIG 1-00 phase III trial. Eur J Cancer 51(3):301–309. https://doi.org/10.1016/j.ejca.2014.11.023
27. Esserman LJ, Berry DA, Cheang MC, Yau C, Perou CM, Carey L, DeMichele A, Gray JW, Conway-Dorsey K, Lenburg ME, Buxton MB, Davis SE, van't Veer LJ, Hudis C, Chin K, Wolf D, Krontiras H, Montgomery L, Tripathy D, Lehman C, Liu MC, Olopade OI, Rugo HS, Carpenter JT, Livasy C, Dressler L, Chhieng D, Singh B, Mies C, Rabban J, Chen YY, Giri D, Au A, Hylton N, Investigators IST (2012) Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). Breast Cancer Res Treat 132(3):1049–1062. https://doi.org/10.1007/s10549-011-1895-2
28. Wilson TR, Yu J, Lu X, Spoerke JM, Xiao Y, O'Brien C, Savage HM, Huw LY, Zou W, Koeppen H, Forrest WF, Fridlyand J, Fu L, Tam R, Schleifman EB, Sumiyoshi T, Molinero L, Hampton GM, O'Shaughnessy JA, Lackner MR (2016) The molecular landscape of high-risk early breast cancer: comprehensive biomarker analysis of a phase III adjuvant population. NPJ Breast Cancer 2:16022. https://doi.org/10.1038/npjbcancer.2016.22
29. Vriens B, Vriens IJH, Aarts MJB, van Gastel SM, van den Berkmortel F, Smilde TJ, van Warmerdam LJC, van Spronsen DJ, Peer PGM, de Boer M, Tjan-Heijnen VCG, Breast Cancer Trialists' Group of the Netherlands (BOOG) (2017) Improved survival for sequentially as opposed to concurrently delivered neoadjuvant chemotherapy in non-metastatic breast cancer. Breast Cancer Res Treat. https://doi.org/10.1007/s10549-017-4364-8
30. Michaelis LC, Ratain MJ (2006) Measuring response in a post-RECIST world: from black and white to shades of grey. Nat Rev Cancer 6(5):409–414. https://doi.org/10.1038/nrc1883