Targeted Therapy and Local Control: The Dynamic Duo

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Breast cancer is a heterogeneous entity, comprised of several distinct molecular subtypes with differing genetic profiles and resultant prognostic implications. It has become increasingly evident that tumor biology is the key to understanding not only the pathogenesis of breast cancer but also to tailoring therapies to optimize outcomes. Classically, the hormone receptor-positive subtypes have the most favorable outcomes, whereas the triple-negative (TN) and human epidermal growth factor receptor 2-positive (HER2+) subtypes are ascribed higher rates of locoregional recurrence (LRR) and distant metastases, shown in a number of studies and a large systematic review.^{1–6}

The development of trastuzumab serves as a premier example of targeting tumor biology for therapeutic gain. Trastuzumab is a humanized monoclonal antibody that binds to and interferes with the HER2-mediated signaling cascade, inhibiting proliferation and resulting in cell death. Initially used in the metastatic setting, in the past decade trastuzumab has become a standard component of both neoadjuvant and adjuvant treatment of most HER2+ cancers, resulting in a notable reduction in disease recurrences.^{7–9} The Herceptin Adjuvant (HERA) randomized trial showed a significant reduction in risk of a disease-free survival event (hazard ratio [HR] 0.76) and death (0.74) at 11 years of follow-up with the receipt of 1 year of adjuvant trastuzumab compared with observation among 5,099 patients with HER2+ early breast cancer.⁷ Similar results were seen in a combined analysis of data from the North Central Cancer Treatment Group (NCCTG)

N9831 Intergroup and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trials, with significantly improved disease-free survival (HR 0.52) at 4 years among patients with operable HER2+ disease treated with adjuvant trastuzumab.⁸

In the modern era, rates of LRR after the treatment of early-stage cancers continue to decline steadily, now less than 10% at 10 years.¹⁰ Systemic therapy has been shown to decrease LRR independent of the use of radiotherapy or type of breast surgery.¹¹ However, data are limited on contemporary rates of LRR by subtype since the pivotal incorporation of trastuzumab into adjuvant treatment of HER2+ disease. In this issue of the *Annals of Surgical Oncology*, McGuire et al. have provided LRR outcomes for 11,219 patients treated in the “trastuzumab era.” At a median follow-up of 53 months, the overall LRR rate was 3.4%, lowest among luminal A cancers (1.7%), intermediate among HER2+ cancers (5.7%), and highest among TN cancers (7.4%). Compared with a previous systematic review published by the same group in 2012, there has been a reduction in overall LRR rates, from 7.9 to 3.4%, and this reduction in LRR is seen across all subtypes. The greatest comparative reduction occurred among HER2+ patients, with LRR rates decreasing from 15.7 to 5.7%. The magnitude of this reduction should not come as a surprise and highlights the remarkable impact of targeted trastuzumab therapy among HER2+ patients. The improvement seen among HER2-negative subtypes is likely attributable to concurrent ongoing improvements in imaging, pathologic evaluation, radiotherapy, and other systemic therapies.

Despite an improved understanding of the behaviors of different breast cancer subtypes and an appreciable reduction in LRR as a result of targeted therapy, the nuances of individualizing treatment remain complex. McGuire et al. allude to this intricacy while raising the question of more aggressive local therapy among nonluminal breast cancers based on the yet higher LRR rates in those groups. However,

careful consideration of the available evidence is necessary in making this determination. Multiple prospective, randomized trials have shown equivalent survival outcomes and rates of LRR when comparing breast-conserving therapy (BCT) and mastectomy for early-stage cancers.^{6,10} The Early Breast Cancer Trialists' Collaborative Group meta-analysis of 3100 women in seven randomized trials found no significant difference in survival, even with follow-up through 25 years.^{12,13} While the consistent finding of higher rates of LRR among TN patients has previously prompted the consideration of treating these patients with mastectomy rather than BCT, multiple retrospective studies have demonstrated no difference in rates of LRR among TN cancer patients treated with BCT or mastectomy, even after adjusting for other factors, including young age.^{14–17} Interestingly, McGuire et al. found lower rates of LRR among patients treated with BCT, although interpretation is limited by inconsistent reporting of radiotherapy data across studies and grouped analysis of patients treated with either neoadjuvant or adjuvant therapy. Investigation of the outcomes among these specific subsets may provide further insight.

While adjuvant radiotherapy is a necessary component of BCT and has been shown to reduce risk of both LRR and death, indications for postmastectomy radiotherapy (PMRT) remain controversial.¹⁸ This decision is typically made by consideration of nodal involvement, tumor burden, and other high-risk disease features; yet these may vary in the adjuvant and neoadjuvant systemic therapy treatment settings. The large National Cancer Institute of Canada Clinical Trials Group MA20 trial, which demonstrated improved disease-free survival with comprehensive nodal irradiation among early-stage node-positive and high-risk node-negative cancers treated with upfront surgery, categorized estrogen receptor-negativity as a high-risk feature.¹⁹ Yang et al. found high rates of 5-year LRR, approximating 26%, among TN patients with residual disease after neoadjuvant therapy that were treated with mastectomy and PMRT.²⁰ Conversely, other studies have shown that receptor status does not independently predict LRR in early-stage, node-negative cancers treated with mastectomy and without PMRT.²¹ Further studies are required to assess the bearing of tumor biology on the decision to recommend radiotherapy in specific patient populations. Finally, the interplay of other disease features that have been independently associated with higher risk of LRR, including young age, tumor stage, grade, and lymphovascular invasion, also warrants further investigation.^{4,22,23}

In looking to the future, tumor biology is certain to remain a focal point of ongoing research and development. A more recent advance for the HER2+ subtype is pertuzumab, a monoclonal antibody that prevents HER2/HER3 dimerization, and is already used in dual-agent

combination with trastuzumab for the treatment of HER2+ cancers in the metastatic and neoadjuvant settings. The recent phase III APHINITY trial has now demonstrated further reduction in disease recurrence with adjuvant dual-agent treatment of HER2+ patients; yet the magnitude of benefit compared with the costs of treatment, both with respect to patient comorbidity and financial burden require careful consideration.²⁴ Weighing potential adverse effects and patient selection will be of key importance. We anticipate continued appreciation and optimization of the interplay between effective systemic therapy and local regional control in hormone receptor positive disease as we await results of recent and ongoing adjuvant trials employing CDK4 and CDK6 inhibitors. This includes the PALLAS trial, which is comparing the use of palbociclib along with standard adjuvant endocrine therapy to endocrine therapy alone. Ongoing studies of targeted therapies for TN cancers, such as platinum-based chemotherapy and immunotherapy agents, are also critical to improve both local regional and survival outcomes for these higher-risk patient populations.

REFERENCES

- Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat*. 2012;133:831–41.
- Wu X, Baig A, Kasymjanova G, et al. Pattern of local recurrence and distant metastasis in breast cancer by molecular subtype. *Cureus*. 2016;8:e924.
- Gabos Z, Thoms J, Ghosh S, et al. The association between biological subtype and locoregional recurrence in newly diagnosed breast cancer. *Breast Cancer Res Treat*. 2010;124:187–94.
- Truong PT, Sadek BT, Lesperance MF, et al. Is biological subtype prognostic of locoregional recurrence risk in women with pT1-2N0 breast cancer treated with mastectomy? *Int J Radiat Oncol Biol Phys*. 2014;88:57–64.
- Steward L, Conant L, Gao F, Margenthaler JA. Predictive factors and patterns of recurrence in patients with triple negative breast cancer. *Ann Surg Oncol*. 2014;21:2165–71.
- Braunstein LZ, Taghian AG, Niemierko A, et al. Breast-cancer subtype, age, and lymph node status as predictors of local recurrence following breast-conserving therapy. *Breast Cancer Res Treat*. 2017;161:173–9.
- Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017;389:1195–205.
- Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol*. 2011;29:3366–73.
- Kiess AP, McArthur HL, Mahoney K, et al. Adjuvant trastuzumab reduces locoregional recurrence in women who receive breast-conservation therapy for lymph node-negative, human epidermal growth factor receptor 2-positive breast cancer. *Cancer*. 2012;118:1982–8.

10. Anderson SJ, Wapnir I, Dignam JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. *J Clin Oncol*. 2009;27:2466–73.
11. Bouganim N, Tsvetkova E, Clemons M, Amir E. Evolution of sites of recurrence after early breast cancer over the last 20 years: implications for patient care and future research. *Breast Cancer Res Treat*. 2013;139:603–6.
12. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Engl J Med*. 1995;333:1444–55.
13. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233–41.
14. Zumsteg ZS, Morrow M, Arnold B, et al. Breast-conserving therapy achieves locoregional outcomes comparable to mastectomy in women with T1-2N0 triple-negative breast cancer. *Ann Surg Oncol*. 2013;20:3469–76.
15. Adkins FC, Gonzalez-Angulo AM, Lei X, et al. Triple-negative breast cancer is not a contraindication for breast conservation. *Ann Surg Oncol*. 2011;18:3164–73.
16. Radosa JC, Eaton A, Stempel M, et al. Evaluation of local and distant recurrence patterns in patients with triple-negative breast cancer according to age. *Ann Surg Oncol*. 2017;24:698–704.
17. Kim EK, Noh WC, Han W, Noh DY. Prognostic significance of young age (<35 years) by subtype based on ER, PR, and HER2 status in breast cancer: a nationwide registry-based study. *World J Surg*. 2011;35:1244–53.
18. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378:1707–16.
19. Whelan TJ, Olivetto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med*. 2015;373:307–16.
20. Yang TJ, Morrow M, Modi S, et al. The effect of molecular subtype and residual disease on locoregional recurrence in breast cancer patients treated with neoadjuvant chemotherapy and postmastectomy radiation. *Ann Surg Oncol*. 2015;22(Suppl 3):S495–501.
21. Mamtani A, Patil S, Stempel M, Morrow M. Are there patients with T1-T2, node-negative breast cancer who are “high-risk” for locoregional recurrence? *Cancer*. 2017;123(14):2626–633.
22. Sharma R, Bedrosian I, Lucci A, et al. Present-day locoregional control in patients with t1 or t2 breast cancer with 0 and 1 to 3 positive lymph nodes after mastectomy without radiotherapy. *Ann Surg Oncol*. 2010;17:2899–908.
23. Abi-Raad R, Boutrus R, Wang R, et al. Patterns and risk factors of locoregional recurrence in T1-T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy. *Int J Radiat Oncol Biol Phys*. 2011;81:e151–7.
24. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377:122–31.