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Further Progress for Patients with Breast Cancer Daniel F. Hayes, M.D

ULTIMOS PROGRESOS PARA PACIENTES CON CANCER DE MAMA

Sustanciales progresos se han desarrollado en los últimos 50 años en la evaluación y tratamiento de pacientes con cáncer de mama ,que llevaron a reducir la mortalidad en un 40% y asociado a reducción de las complicaciones..-Este progreso ha ocurrido por el conocimiento de que el cáncer de mama no es una sino diversas enfermedades con distintos subtipos. Cda uno de estos subtipos tiene distintas estategias en el tratamiento del cáncer de mama.

Porejemplo, el tratamiento endocrino en mujeres con receptor estrogenico positivo ,pero no RE Negativo, el cáncer de mama ha mejorado considerablemente la sobrevida mientras que evitaba los efectos toxicos para aquellas que no se beneficiaban.

De la misma manera la identificación de la amplificación del HER 2,identificación de su proteína , factor de crecimiento epidérmico HER 2 , o ambos ha traído buenos resultados.

El anticuerpo monoclonal TRASTUZUMAB ,directamente contra el HER 2 ,es altamente efectivo en pacientes con cancer de mama HER 2 Positivo metastasico .-y ha disminuido la tasa de recurrencia y muerte por casi el 50% de las pacientes en pacientes con cáncer de mama temprano.-

En suma con Trastuzumab con otros agentes incluyendo en la clínica Pertuzumab, Lapatinib, y Neratinib .-

Otro agente, trastuzumab emtansine, designated T-DM1, consists of an antitubulin chemotherapeutic agent, emtansine, el cual es emparentado con Trastuzumab.-

T-DM1 tiene actividad importante contra el cáncer de mama metastasico HER 2 positivo aun en pacientes tratadas anteriormente con terapia Trastuzumab.-

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Resultados de estudios con T-DM1 son alentadores comparados con emtansine, maytansine.-Sin embargo los buenos resultados no vienen sin pagar precio en eventos adversos ocurridos en pacientes que recibieron T-DM1 que en aquellos con Trastuzumab.- Tambien mas pacientes discontinuaron T-DM1 than trastuzumab (18.0% vs. 2.1%)

En conclusion el trial de von Minckwitz and colleagues es un desafio sugiere que con quimioterapia con o sin Trastuzumab es el tratamiento standard especialmente en E II III.-En

pacientes que no tienen respuesta completa la utilización de T-DM1 es una opción valorando costos y beneficios.

No utilizar en pacientes con respuesta patológica completa.-

Further Progress for Patients with Breast Cancer Daniel F. Hayes, M.D. Substantial progress has been made over the past 50 years in the evaluation and treatment of patients with breast cancer, leading to a nearly 40% decrease in mortality from this disease and associated reductions in complications of treatment.¹ This progress has occurred with the understanding that breast cancer is not one but several diseases with biologically driven subtypes.² Each of these subtypes is amenable to different treatment strategies, so that a personalized medicine approach is possible in the treatment of patients with breast cancer. For example, endocrine treatment in women with estrogen-receptor-positive, but not estrogen-receptor-negative, breast cancer has led to considerable improvement in survival while avoiding toxic effects in patients who would not benefit.³ Similarly, identification of amplification of ERBB2, identification of overexpression of its protein product, human epidermal growth factor receptor 2 (HER2), or both has produced remarkable results.⁴ The humanized monoclonal antibody trastuzumab, which is directed against HER2, is highly effective in patients with metastatic HER2-positive breast cancer, and it has decreased the rate of distant recurrence and death by nearly one half among patients with early-stage disease. In addition to trastuzumab, several other anti-HER2 agents, including pertuzumab, lapatinib, and neratinib, have been introduced into the clinic. Yet another agent, trastuzumab emtansine, designated T-DM1, consists of an antitubulin chemotherapeutic agent, emtansine, which is chemically linked to trastuzumab.⁵ T-DM1 has impressive activity against HER2-positive metastatic breast cancer, even in patients with cancer that had previously progressed with trastuzumab-based therapy, and it has serious but mainly reversible toxic effects. Results of studies of T-DM1 suggest that it behaves as a Trojan horse,⁶ delivering emtansine only to HER2-expressing cells and mostly sparing patients from the considerable toxic effects seen with the predecessor of emtansine, maytansine, when used as a single agent.⁷ Successful neoadjuvant treatment of patients with metastatic breast cancer frequently portends even greater benefit in the adjuvant setting. Indeed, tests of most of the new anti-HER2 therapies as preoperative (or neoadjuvant) therapy in patients with early disease have induced substantial tumor shrinkage. However, enigmatically, results of classic trials of adjuvant lapatinib and pertuzumab, either alone or in combination with trastuzumab, have been disappointing with regard to clinically meaningful end points such as a reduction in rates of distant recurrence or death.⁸⁻¹¹ In this issue of the Journal, von Minckwitz et al.¹² report a remarkable benefit in women with stage I to III HER2-positive breast cancer. All patients enrolled in this trial had residual disease after receiving neoadjuvant chemotherapy plus trastuzumab (and, in a minority, after receiving pertuzumab) and were randomly assigned to postoperative T-DM1 or trastuzumab for the succeeding 42 weeks. A significant reduction of nearly one half in the risk of invasive events (invasive breast cancer or death), including the risk of distant recurrence, was observed. Overall, there was an absolute improvement of 11.3 percentage points in the rate of invasive

disease-free survival. Even though the trial was underpowered to detect a significant reduction in mortality, the hazard ratio for death was similar to the hazard ratio for distant recurrence (0.7 and 0.6, respectively). These results are impressive and clinically meaningful. However, success does not come without a price. More serious adverse events occurred in patients who received T-DM1 than in those who received trastuzumab (12.7% vs. The New England Journal of Medicine Downloaded from nejm.org at HINARI-Syrian Arab Republic on February 14, 2019. For personal use only. No other uses without permission. Copyright © 2019 Massachusetts Medical Society. All rights reserved. Editorials n engl j med 380;7 nejm.org February 14, 2019 677 8.1%), and more patients discontinued T-DM1 than trastuzumab (18.0% vs. 2.1%) before the completion of the anticipated 14 postsurgical cycles. One of the five deaths among patients who did not have disease recurrence occurred in a patient who had an intracranial hemorrhage after a fall associated with T-DM1-induced thrombocytopenia (Table S2 in the Supplementary Appendix of the article, available at NEJM.org). Like any well-designed and well-conducted trial, this one also raises many questions. Could single-agent T-DM1 be used as the sole therapy instead of combination chemotherapy with trastuzumab for many patients with HER2-positive disease? At least two trials have suggested that rates of pathological complete response, and even disease-free survival, are similar with neoadjuvant T-DM1 and trastuzumab.^{10,13} Could the use of adjuvant anthracyclines be reduced? Although most patients in the current trial received anthracyclines, the availability of yet another active agent in early-stage breast cancer could lead to less use of anthracyclines, which would avoid the small but real risk of congestive heart failure and hematologic cancers. What are the implications of the results of this trial for antiHER2 agents other than trastuzumab? Postoperative T-DM1 might eliminate the use of neratinib, which has produced a significant but very modest absolute reduction in benefits as compared with placebo after 12 months of trastuzumab.¹⁴ These questions all warrant careful consideration and need to be addressed in subsequent trials. In conclusion, the trial by von Minckwitz and colleagues is a game changer. It suggests that neoadjuvant chemotherapy with trastuzumab, with or without pertuzumab, is the standard of care for patients with newly diagnosed HER2-positive breast cancer, especially those with stage II or III disease. This approach has the ability to reduce the extent of local treatment. More important, it will guide postoperative systemic therapy. If patients do not have a pathological complete response with such a regimen, postoperative treatment with T-DM1 offers a major opportunity to improve long-term outcomes. Caveat emptor: doctors and patients need to be aware that the side effects of this regimen are more common than with trastuzumab alone, and occasional severe toxic effects need to be considered. Therefore, T-DM1 should not be used in patients with a pathological complete response or in those with stage I disease; these patients have a very favorable outcome with adjuvant paclitaxel and trastuzumab alone.¹⁵ Nonetheless, this trial is one more step toward personalized medicine and reduced mortality among patients with early-stage breast cancer. Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org. From the University of Michigan Rogel Cancer Center, Ann Arbor. 1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7-30. 2. Perou CM, Jeffrey SS, van de Rijn M, et al. Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. *Proc Natl Acad Sci U S A* 1999;96:9212-7. 3. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998;351:1451-67. 4. Hurvitz SA, Gelmon KA, Tolaney SM. Optimal management of early and

advanced HER2 breast cancer. Am Soc Clin Oncol Educ Book 2017;37:76-92. 5. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367:1783-91