Pembrolizumab Plus Neoadjuvant Chemotherapy Improves Pathologic Complete Response Rates in Triple-Negative Breast Cancer

Schmid P, Cortes L, Pusztai L, et al; KEYNOTE-522 Investigators. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382:810-821.

Study Overview

Objective. To evaluate the efficacy and safety of pembrolizumab in combination with neoadjuvant chemotherapy followed by adjuvant pembrolizumab in early-stage triple-negative breast cancer.

Design. International, multicenter, randomized, double-blind, phase 3 trial.

Intervention. Patients were randomly assigned in a 2:1 fashion to receive either pembrolizumab or placebo. Patients received 4 cycles of neoadjuvant pembrolizumab or placebo once every 3 weeks, in addition to weekly paclitaxel 80 mg/m^2 plus carboplatin AUC 5 once every 3 weeks. This was followed by 4 cycles of pembrolizumab or placebo plus doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 once every 3 weeks. Patients then underwent definitive surgery 3 to 6 weeks after completion of neoadjuvant therapy. In the adjuvant setting, patients received pembrolizumab or placebo once every 3 weeks for up to 9 cycles. Adjuvant capecitabine was not allowed.

Setting and participants. A total of 1174 patients underwent randomization: 784 patients in the pembrolizumab/chemotherapy group and 390 patients in the placebo/chemotherapy group. Eligible patients had newly diagnosed, centrally confirmed triple-negative breast cancer (nonmetastatic: T1c, N1-2 or T2-4, N0-2). Patients were eligible regardless of PD-L1 status, and those with inflammatory breast cancer and multifocal primaries were eligible.

Main outcome measures. The primary endpoints of this study were pathologic complete response (pCR) rate (defined as ypT0/ypTis, ypN0) at the time of surgery and event-free survival (EFS) in the intention-to-treat population. Secondary endpoints included pCR in all patients, pCR among patients with PD-L1–positive tumors, EFS among patients with PD-L1–positive tumors, and overall survival among all patients and those with PD-L1–positive tumors. PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent, Santa Clara, CA). Expression was characterized according to the combined positive score, with a score of 1% or greater being considered positive.

Outcomes Research in Review Section Editors

Katrina F. Mateo, MPH
CUNY School of Public Health
New York, NY

Daniel Isaac, DO, MS
Michigan State University
East Lansing, MI

Fred Ko, MD, MS
Icahn School of Medicine
at Mount Sinai
New York, NY

Taishi Hirai, MD
University of Missouri
Columbia, MO

William Hung, MD, MPH
Icahn School of Medicine
at Mount Sinai
New York, NY

Gordon Ngai, MD, MPH
Icahn School of Medicine
at Mount Sinai
New York, NY

Results. The baseline characteristics were well balanced between the treatment arms. At the time of the second interim analysis, the median duration of follow-up was 15.5 months. The pCR rate among the first 602 patients who were randomized was 64.8% in the pembrolizumab/chemotherapy group and 51.2% in the placebo group ($P < 0.001$; 95% confidence interval, 5.4-21.8). The pCR rate in the PD-L1–positive population was 68.9% in the pembrolizumab/chemotherapy group, as compared to 54.9% in the placebo group. In the PD-L1–negative population, the pCR rate was 45.3% in the pembrolizumab/chemotherapy group, as compared to 30.3% in the placebo group. At the time of analysis, 104 events had occurred, and the estimated percentage of patients at 18 months who were alive without disease progression was 91% in the pembrolizumab group and 85% in the placebo group. The median was not reached in either group.

Grade 3 or higher adverse events in the neoadjuvant phase were seen in 76.8% and 72.2% of patients in the pembrolizumab and placebo arms, respectively. Serious treatment-related adverse events occurred in 32% of patients in the pembrolizumab group compared to 19% in the placebo group. Febrile neutropenia and anemia were the most common. Discontinuation of the trial drug due to adverse events occurred in 23% of patients in the pembrolizumab arm and in 12% in the placebo arm. The majority of treatment-related adverse events occurred in the neoadjuvant phase. In the adjuvant phase, treatment-related adverse events occurred in 48% and 43% of patients in the pembrolizumab and placebo groups, respectively.

Conclusion. The combination of neoadjuvant chemotherapy and pembrolizumab in patients with newly diagnosed, early-stage, triple-negative breast cancer yielded a higher percentage of patients achieving a pCR as compared with chemotherapy plus placebo.

Commentary

The current study adds to the growing body of literature outlining the efficacy of immune checkpoint inhibition in triple-negative breast cancer. The previously published IMpassion130 trial showed that the addition of the PD-L1 antibody atezolizumab to nab-paclitaxel improved progression-free survival in patients with PD-L1–positive (1% or greater), metastatic triple-negative breast cancer.[1] Similarly, in the phase 2 I-SPY2 trial, the addition of pembrolizumab to standard neoadjuvant chemotherapy led to a near tripling of the pCR rates in triple-negative breast cancer.[2] While the current study demonstrated improved pCR rates with pembrolizumab, no difference in EFS has yet been demonstrated; however, longer-term follow-up will be required. There certainly are numerous studies documenting an association between pCR and improved disease-free survival and possibly overall survival. Cortazar and colleagues performed a pooled analysis of 12 international trials, which demonstrated an association between pCR and improved EFS (hazard ratio [HR], 0.24) and overall survival (HR, 0.16) in patients with triple-negative breast cancer.[3] The results of the current study will require longer-term follow-up to confirm such an association.

The current study appears to have demonstrated a benefit with the addition of pembrolizumab across treatment subgroups, particularly in the PD-L1–positive and PD-L1–negative populations. While this differs from the findings of the IMpassion130 trial, it is quite difficult to draw definitive conclusions because the 2 trials studied different antibodies, and thus used a different assay to define PD-L1 positivity. Notable differences exist in determination of PD-L1 status across assays, and it is important for providers to use the appropriate assay for each antibody. These differences highlight the need for more informative biomarkers to predict a benefit from immune checkpoint inhibition.

It is also noteworthy that the control arm in the current trial was a platinum-based regimen. Platinum-based neoadjuvant regimens previously have been shown to induce higher pCR rates in triple-negative breast cancer; however, the incorporation of carboplatin as standard of care remains a topic of debate.[4] Nevertheless, a similar trial evaluating the efficacy of atezolizumab combined with platinum-based neoadjuvant chemotherapy in triple-negative breast cancer, NSABP B-59 (NCT03281954), is underway, with the control arm also incorporating carboplatin. The results of this study will also help validate the role of checkpoint inhibitors in the neoadjuvant setting in triple-negative breast cancer. Of note, this trial did not allow for the use of adjuvant capecitabine, which has been previously shown in the CREATE-X trial to prolong survival in this population.[5]

How the use of adjuvant capecitabine would impact these results is completely unknown.[6] The incidence of grade 3 or higher toxicities in the current trial appeared to be similar in both groups. There did appear to be a higher incidence of infusion reactions and skin reactions in the pembrolizumab groups. Immune-related adverse events were consistent with prior pembrolizumab data.

Applications for Clinical Practice

KEYNOTE-522 adds to the growing evidence suggesting that incorporation of immune checkpoint inhibitors into neoadjuvant therapy in patients with triple-negative breast cancer can improve pCR rates; however, its use as a standard of care will require longer-term follow-up to ensure the noted findings translate into improvement in EFS and, ultimately, overall survival.

–Daniel Isaac, DO, MS

References

1. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med.* 2018;379:2108-2121.
2. Nanda R, Liu MC, Yau C, et al. Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): results from I-SPY 2. *J Clin Oncol.* 2017;35: Suppl:506. Abstract 506.
3. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384:164-172.
4. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant one-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol.* 2015;33:13-21.
5. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med.* 2017;376:2147-2159.
6. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol.* 2014;15:747-756.

Geriatric Assessment and Collaborative Medication Review for Older Adults With Polypharmacy

Romskaug R, Skovlund E, Straand J, et al. Effect of clinical geriatric assessments and collaborative medication reviews by geriatrician and family physician for improving health-related quality of life in home-dwelling older patients receiving polypharmacy. A cluster randomized clinical trial. JAMA Intern Med. 2020;180:181-189.

Study Overview

Objective. To examine the effect of clinical geriatric assessments and collaborative medication review by geriatricians and family physicians on quality of life and other patient outcomes in home-dwelling older adults with polypharmacy.

Design. The study was a single-blind, cluster randomized clinical trial enrolling home-dwelling adults aged 70 years and older who were taking 7 or more medications. Family physicians in Norway were recruited to participate in the trial with their patients. Randomization was at the family physician level to avoid contamination between intervention and control groups.

Setting and participants. The study was conducted in Akershus and Oslo, Norway. Family physicians were recruited to participate in the trial with their patients. A total of 84 family physicians were recruited, of which 70 were included in the trial and randomized to intervention versus control; 14 were excluded because they had no eligible patients. The cluster size of each family physician was limited to 5 patients per physician to avoid large variation in cluster sizes. Patients were eligible for enrollment if they were home-dwelling, aged 70 years or older, and were taking 7 or more systemic medications regularly and had medications administered by the home nursing service. Patients were excluded if they were expected to die or be institutionalized within 6 months, or if they were

discouraged from participation by their family physician. A total of 174 patients were recruited, with 87 patients in each group (34 family physicians were in the control group and 36 in the intervention group).

Intervention. The intervention included a geriatric assessment performed by a physician trained in geriatric medicine and supervised by a senior consultant. The geriatric assessment consisted of review of medical history; systematic screening for current problems; clinical examination; supplementary tests, if indicated; and review of each medication being used. The review of medication included the indication for each medication, dosage, adverse effects, and interactions. The geriatric assessment consultation took 1 hour to complete, on average. After the geriatric assessment, the family physician and the geriatrician met to discuss each medication and to establish a collaborative plan for adjustments and follow-up; this meeting was approximately 15 minutes in duration. Lastly, clinical follow-up with the older adult was conducted by the geriatrician or the family physician, as agreed upon in the plan, with most follow-up conducted by the family physician. Participants randomized to the control group received usual care without any intervention.

Main outcome measures. Outcomes were assessed at 16-week and 24-week follow-up. The main study outcome measure was health-related quality of life (HRQoL), as measured by the 15D instrument, at 16 weeks. The quality-of-life measure included the following aspects, each rated on an ordinal scale of 5 levels: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort or symptoms, depression, distress, vitality, and sexual activity. The index scale including all aspects is in the range of 0 to 1, with a higher score indicating better quality of life. A predetermined change of 0.015 or more is considered clinically important, and a positive change of 0.035 indicates much better HRQoL. Other outcomes included: appropriateness of medications measured by the Medication Appropriateness Index and the Assessment of Underutilization; physical function (short Physical Performance battery); gait speed; grip strength; cognitive functioning; physical and cognitive disability (Functional Independence Measure); caregiver burden (Relative Stress Scale); physical measures, including orthostatic blood pressure, falls, and weight; hospital admissions; use of home nursing service; incidence of institutionalization; and mortality.

Main results. The study included 174 patients with an average age of 83.3 years (SD, 7.3); 67.8% were women. Of those who were randomized to the intervention and control groups, 158 (90.8%) completed the trial. The average number of regularly used medications was 10.1 (SD, 2.7) in the intervention group and 9.5 (SD, 2.6) in the control group. At week 16 of follow-up, patients in the intervention group had an improved HRQoL score measured by the 15D instrument; the difference between the intervention group and control groups was 0.045 (95% confidence interval [CI], 0.004 -0.086; $P = 0.03$). Medication appropriateness was better in the intervention group, as compared with the control group at both 16 weeks and 24 weeks. Nearly all (99%) patients in the intervention group experienced medication changes, which included withdrawal of medications, dosage adjustment, or new drug regimens. There was a trend towards a higher rate of hospitalization during follow-up in the intervention group (adjusted risk ratio, 2.03; 95% CI, 0.98-4.24; $P = 0.06$). Other secondary outcomes were not substantially different between the intervention and control groups.

Conclusion. The study demonstrated that a clinical geriatric assessment and collaborative medication review by geriatrician and family physician led to improved HRQoL and improved medication use.

Commentary

The use of multiple medications in older adults is common, with almost 20% of older adults over age 65 taking 10 or more medications.[1] Polypharmacy in older adults is associated with lower adherence rates and increases the potential for interactions between medications.[2] Age-related changes, such as changes in absorption, metabolism, and excretion, affect pharmacokinetics of medications and potentiate adverse drug reactions, requiring adjustments in use and dosing to optimize safety and outcomes. Recognizing the potential effects of

medications in older adults, evidence-based guidelines, such as the Beers criteria[3] and START/STOPP criteria,[4] have been developed to identify potentially inappropriate medications in older adults and to improve prescribing. Randomized trials using the START/STOPP criteria have demonstrated improved medication appropriateness, reduced polypharmacy, and reduced adverse drug reactions.[5] Although this study did not use a criteria-based approach for improving medication use, it demonstrated that in a population of older adults with polypharmacy, medication review with geriatricians can lead to improved HRQoL while improving medication appropriateness. The collaborative approach between the family physician and geriatrician, rather than a consultative approach with recommendations from a geriatrician, may have contributed to increased uptake of medication changes. Such an approach may be a reasonable strategy to improve medication use in older adults.

A limitation of the study is that the improvement in HRQoL could have been the result of medication changes, but could also have been due to other changes in the plan of care that resulted from the geriatric assessment. As noted by the authors, the increase in hospital admissions, though not statistically significant, could have resulted from the medication modifications; however, it was also noted that the geriatric assessments could have identified severe illnesses that required hospitalization, as the timeline from geriatric assessment to hospitalization suggested was the case. Thus, the increase in hospitalization resulting from timely identification of severe illness was more likely a benefit than an adverse effect; however, further studies should be done to elucidate this.

Applications for Clinical Practice

Older adults with multiple chronic conditions and complex medication regimens are at risk for poor health outcomes, and a purposeful medication review to improve medication use, leading to the removal of unnecessary and potentially harmful medications, adjustment of dosages, and initiation of appropriate medications, may yield health benefits, such as improved HRQoL. The present study utilized an approach that could be scalable, which is important given the limited number of clinicians with geriatrics expertise. For health systems with geriatrics clinical expertise, it may be reasonable to consider adopting a similar collaborative approach in order to improve care for older adults most at risk. Further reports on how patients and family physicians perceive this intervention will enhance our understanding of whether it could be implemented widely.

–William W. Hung, MD, MPH

References

1. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "There's got to be a happy medium". *JAMA.* 2010; 304:1592-1601.
2. Vik SA, Maxwell CJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. *Ann Pharmacother.* 2004;38:303-312.
3. American Geriatrics Society 2015 Updated Beers criteria for potentially inappropriate medication use in older Adults. *J Am Geriatr Soc.* 2015;63:2227-2246.
4. Hill-Taylor B, Sketris I, Hayden J, et al. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther.* 2013;38:360-372.
5. O'Mahony D. STOPP/START criteria for potentially inappropriate medications/ potential prescribing omissions in older people: origin and progress. *Expert Rev Clin Pharmacol.* 2020;13:15-22.