Subcutaneous Treatment vs. IV Infusion for HER2-Positive Breast Cancer

BY CHUCK HOLT

Antoinette R. Tan, MD, MHSc, Chief of Breast Medical Oncology, Co-Director of the Phase I Program, and Full Professor of Medicine at Levine Cancer Institute, Atrium Health, has always felt that it is important for physicians to find ways to optimize the treatment experience for their patients. Her long-felt desire to deliver patient-centric care and provide improved access to it would one day help inspire her to lead a study demonstrating the efficacy and safety of a significantly faster and less-invasive alternative to intravenous infusion of two medicines used to treat HER2-positive breast cancer.

Tan, who led the study, “Subcutaneous administration of the fixed-dose combination of trastuzumab and pertuzumab in combination with chemotherapy in HER2-positive early...”

Safety & Efficacy of Trifluridine/Tipiracil in Metastatic Gastric Cancer

BY BEN GEORGE, MD

Approximately 27,000 patients are diagnosed annually with gastric cancer in the United States, more than half of these patients present with unresectable or metastatic disease (CA Cancer J Clin 2020;70(1):7-30). Patients who receive curative intent treatment for localized gastric cancer undergo either a total or partial gastrectomy based on the location of the primary tumor, and a substantial minority of these patients develop recurrent disease in a metachronous fashion (Ann Surg 1999;230(2):170-178). Thus, patients diagnosed with metastatic gastric cancer (mGC) are comprised of two distinct groups—those with synchronous metastatic disease (and retain an intact stomach) and those with metachronous metastatic disease (after a curative intent gastrectomy—total or subtotal). In fact, patients who have undergone gastrectomy comprise approximately 40 percent of patients with mGC (Lancet Oncol 2014;15(11):1224-1235; Lancet 2017;390(10111):2461-2471; Lancet Oncol 2018;19(11):1437-1448; 2018; Lancet 2018;392(10142):123-133).

Repurposing Classic Chemotherapy Drug to Overcome Therapy Resistance

Drug resistance is a major obstacle in cancer treatment, leading to relapse for many patients. In a new study published online in Nature Cell Biology, researchers from the Stowers Institute for Medical Research, Children’s Mercy Kansas City, and The University of Kansas Cancer Center reported on a promising new strategy to overcome drug resistance in leukemia, using targeted doses of the widely used chemotherapy drug doxorubicin (2020; doi: 10.1038/s41556-020-0507-y).

The study’s researchers found that low doses of the anthracycline antibiotic doxorubicin inhibit the interaction between two molecular pathways that work closely together to promote tumor growth and resistance to therapy. The targeted approach also clears the way for cancer-targeting immune cells to do their work, an unexpected and novel finding, according to the study authors.

“In low doses, doxorubicin actually stimulated the immune system, in contrast with the typical clinical doses, which were immunosuppressive, killing healthy immune cells indiscriminately,” stated John M. Perry, PhD, a researcher with the Children’s Mercy Research Institute at Children’s Mercy. He completed his postdoctoral work at Stowers and is first author of the report.

The findings are the result of a decade-spanning collaborative effort among researchers at the Stowers Institute, Children’s Mercy, The University of Kansas Cancer Center and other institutions, evolving from their studies on how normal, healthy stem cells self-renew.

Continued on page 15
breast cancer: Primary analysis of the phase III, multicenter, randomized, open-label, two-arm FeDeRiCa study,” presented the results in December 2019 at the San Antonio Breast Cancer Symposium.

In this study, Tan and her co-investigators showed that a fixed-dose formulation of pertuzumab and trastuzumab delivered in a single injection over just 5-8 minutes is as safe and as effective as administering the monoclonal antibodies for treatment of HER2-positive breast cancer via IV infusion, which takes up to 2.5 hours for the loading doses and about 60-90 minutes for the maintenance doses.

The clinical implications of having an effective and well-tolerated subcutaneous treatment versus IV administration for patients with HER2-positive breast cancer are many, Tan noted, and include the following:

- reduced infusion chair time and improved capacity in infusion centers;
- shortened drug administration time and more flexible scheduling options for patients;
- reduced drug delivery costs incurred by pharmacy and nursing departments with faster preparation times and administration;
- greater preservation of the veins;
- and less pain and discomfort for patients.

Meanwhile, the results of the FeDeRiCa study, led by Tan and colleagues, is being used to support a recent filing for a Biologic License Application with the FDA for the fixed-dose combination of pertuzumab and trastuzumab administered by subcutaneous injection in combination with intravenous chemotherapy for the treatment of patients with HER2-positive breast cancer.

What’s more, the potentially practice-transforming, patient-centric, non-inferiority study has earned Tan and colleagues First Place in the 2020 Excellence in Oncology Award presented by Oncology Times.

“ar to achieve patient-centric care, one can start to evaluate ways in which patients can spend less time in a treatment chair getting an infusion, and look at models of care where there is a shift to administering anticancer therapy outside of the infusion center to home-based cancer care,” Tan explained. “One way to accomplish this is through product optimization, which can be achieved in several ways, including the development of subcutaneous formulations or oral administration of drugs, as well as self-injectable devices.”

Proving Non-Inferiority

The randomized FeDeRiCa non-inferiority study was conducted at 106 sites in the neoadjuvant-adjuvant setting and enrolled 500 patients aged 18 years and older, with an ECOG PS of 0 or 1, and HER2-positive, operable, locally advanced or inflammatory stage II-stage IIIIC breast cancer (Abstract PD4-07).

The patients were randomly assigned (1:1) to receive chemotherapy with pertuzumab IV (840 mg loading dose, 420 mg maintenance dose) plus trastuzumab IV (8 mg/kg loading dose, 6 mg/kg maintenance dose) or the new fixed-dose combination (1,200 mg/600 mg loading dose, 600 mg/600 mg maintenance dose) every 3 weeks.

The dose of the subcutaneously delivered trastuzumab was confirmed in the phase III HannaH trial (NCT00950300). The dose of subcutaneous pertuzumab was established in a phase I study (NCT02738970).

Chemotherapy was the “investigator’s choice” of either 4 cycles of dose-dense doxorubicin plus cyclophosphamide q2w followed by weekly paclitaxel for a total of 12 weeks, or 4 cycles of doxorubicin plus cyclophosphamide q3w followed by 4 cycles of docetaxel q3w.

A total of 476 patients completed the neoadjuvant treatment phase by July 2019, including 242 patients (96%) who received an IV infusion and 234 (94.4%) treated subcutaneously. Following surgery to remove any remaining cancer, the patients continued their anti-HER2 treatment, per randomization, for 18 cycles.

The study met its primary endpoint of comparable pre-dose cycle 8 serum C<sub>trough</sub> with the pertuzumab component of the fixed-dose subcutaneous formulation, with a mean value of 93.7 compared to 78.5 µg/mL with IV pertuzumab. Geometric means were 88.7 and 72.4 µg/mL, respectively (geometric mean ratio [GMR] 1.22; 90% CI, 1.14-1.31).

Non-inferiority was also observed in the pre-dose cycle 8 serum C<sub>trough</sub> for the trastuzumab component with corresponding mean values of 62.9 versus 48.1 µg/mL and geometric means of 58.7 and 44.1 (GMR 1.33; 90% CI, 1.24-1.43) for subcutaneous fixed-dose combination versus IV formulation.

Total pathological complete response (pCR) in the breast and axilla (defined as ypT0/Tis ypN0) and safety endpoints were similar between the two arms as well. Ultimately, pCR was achieved by 150 of 252 patients treated intravenously (59.5%, 95% CI 53·2-65·6) and 148 of 248 patients in the subcutaneous arm (59.7%, 95% CI 53·3-65·8).

Safety data, including cardiac data, was comparable between the IV versus subcutaneous delivery arms in the study, which is significant because both HER2 monoclonal antibodies can cause heart problems, such as reduced heart function or congestive heart failure, the researchers noted.

The most common side effects were similar in type and rate of occurrence, the study showed. They included neutropenia/fibrile neutropenia, IV group (52.8%) versus subcutaneous group (48%); nausea, IV group (60.3%) versus subcutaneous group (58.9%); and diarrhea, IV group (55.2%) versus subcutaneous group (58.5%). About 18 percent of the IV group had serious side effects, as did 16 percent of the subcutaneous group.

Evaluating the Pharmacokinetics

When evaluating the outcomes of the study, Tan said it is important to highlight the fact that the trial “was designed to evaluate the pharmacokinetics of the fixed-dose subcutaneous formulation of trastuzumab and pertuzumab compared with trastuzumab IV and pertuzumab IV formulations.”

While there were no unexpected findings or surprising outcomes within the study results, the investigators were pleased to discover that efficacy in terms of total pCR (i.e., no tumor in the breast or lymph nodes) were nearly identical in each arm of the study, she said.

Continued on page 13

Antoinette R. Tan, MD, MHSc

Excellence in Oncology

Oncology Times announces winners of the 2020 Excellence in Oncology award contest designed to recognize the wonderful research, dedication, and dramatic impact on patients (and their families) that occur every day in oncology. This initiative garnered submissions from all areas of the cancer field, highlighting research and clinical programs in a variety of specialties and cancer centers. In this issue, honorees will be announced and then highlighted in stories throughout the year. Congratulations to the winners!

1st Runner-up

Regression of Glioblastoma After Chimeric Antigen Receptor T-Cell Therapy

Lead author: Christine E. Brown, PhD, City of Hope

2nd Runner-up

Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma

Lead author: Maria Gavriatopoulou, MD, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Honorable Mentions

Primary Results from SAUL, A Multinational Single-arm Safety Study of Atezolizumab Therapy for Locally Advanced or Metastatic Urothelial or Nonurothelial Carcinoma of the Urinary Tract

Lead researcher: Cora Sternberg, MD, Weill Cornell Medicine and NewYork-Presbyterian

Unilateral unifocal advanced intraocular retinoblastoma: Is reasonable to adopt intra-arterial chemotherapy as single therapeutic choice?

Lead researcher: Sonia De Francesco, MD, University of Sienna, Italy

NonY ork-Presbyterian

Myeloma

Urothelial or Nonurothelial Carcinoma of the Urinary Tract

NewY ork-Presbyterian

Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma

Lead author: Maria Gavriatopoulou, MD, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Honorable Mentions

Primary Results from SAUL, A Multinational Single-arm Safety Study of Atezolizumab Therapy for Locally Advanced or Metastatic Urothelial or Nonurothelial Carcinoma of the Urinary Tract

Lead researcher: Cora Sternberg, MD, Weill Cornell Medicine and NewYork-Presbyterian

Unilateral unifocal advanced intraocular retinoblastoma: Is reasonable to adopt intra-arterial chemotherapy as single therapeutic choice?

Lead researcher: Sonia De Francesco, MD, University of Sienna, Italy

Oncology Times

May 20, 2020

12
The study by Tan, et al, “demonstrated that non-inferior levels of pertuzumab and trastuzumab were achieved in the blood compared to standard IV infusion of pertuzumab and trastuzumab in combination with chemotherapy in patients with early-stage HER2-positive breast cancer,” she emphasized.

The research also highlighted marked differences in giving the agent as a subcutaneous formulation compared to intravenous that may not be apparent to some observers, Tan noted. First, unlike the IV formulation of trastuzumab, dosing of the subcutaneous fixed-dose formulation is not dependent on the patient’s body weight and is administered in the thigh over 5-8 minutes as opposed to the 2-2.5 hours it takes for an IV infusion of the loading dose of the two medicines, and roughly 60-90 minutes for maintenance doses. Additionally, the incidence of subcutaneous injection site reactions is low.

Also significant is that the combination of pertuzumab and trastuzumab delivered subcutaneously is co-formulated with recombinant human hyaluronidase, which is a permeation enhancer that allows subcutaneous delivery of co-administered therapeutics at higher drug volumes, Tan noted.

She explained the way it works: “rHuPH20 is an enzyme that transiently hydrolyzes hyaluronan, a component of the subcutaneous matrix, leading to reduced viscosity of the extracellular matrix of the hypodermis and, thus, to an improved delivery of subcutaneously administered drugs to the systemic circulation,” she said. “To me, this is an interesting novel drug delivery technology.”

Looking Ahead
Going forward, the researchers highlight the need to follow up on the long-term results of the FeDeRiCa trial in terms of efficacy and safety, which are expected to be available in June 2023.

Ongoing and future research should remain centered on improving the patient experience, Tan believes. There is a recently completed phase II study called PHranceSCa that addresses a patient’s preference and satisfaction with subcutaneous compared to IV treatment of pertuzumab and trastuzumab (NCT03674112).

In previous studies of other subcutaneous formulations, subcutaneous delivery of trastuzumab has been shown to be strongly preferred by the majority of patients compared to IV administration of the same medicine, with the most common reason being that administration required less time in the clinic, as shown in the PrefHER trial (NCT01401166).

Looking into the near future, Tan would like to see a trial that evaluates the safety and tolerability of the new fixed-dose combination of pertuzumab and trastuzumab administered by subcutaneous injection at a patient’s home, for example, by a healthcare professional, and an evaluation of patient-reported outcomes regarding this “at-home” anti-cancer treatment experience.

Developing an “at-home” administration protocol for a subcutaneous formulation of a drug is an essential area of future research and can be advantageous for patients and infusion centers. However, this will require specific protocols to ensure the safety of this set up and needs to be rigorously tested before full implementation, she said.

Tan can also envision how a self-administered subcutaneous formulation of a therapeutic might potentially play a role to decrease patients’ exposure risk during the ongoing global battle with the novel coronavirus.

“When you consider the SARS-CoV-2 pandemic that is currently occurring, the option to have a subcutaneous medication either self-administered by the patient at home or administered by a health care worker in a patient’s home is very appealing, because it saves a patient a trip to the cancer center and thereby minimizes exposure risk,” she concluded.

Chuck Holt is a contributing writer.