

Encouraging data for survival and fertility in some cancers

The American Society of Clinical Oncology marked its 50th anniversary at this year's annual conference in Chicago, where it showcased the latest scientific advances in oncology and explored the translation of research findings into practice under its umbrella theme, Science and Society.

Drug combo extends survival by more than 1 year in metastatic prostate cancer patients

Key clinical finding Adding docetaxel to hormonal therapy at the time of diagnosis of metastatic prostate cancer extends survival. **Major finding** Patients receiving docetaxel and androgen deprivation therapy at the time of diagnosis had median overall survival that was 13.6 months longer than men who received androgen deprivation therapy alone. **Data source** Randomized trial in 790 men with newly diagnosed metastatic hormone-sensitive prostate cancer.

The answer was nearly a decade in coming, but worth the wait: adding docetaxel to initial hormonal therapy in men with metastatic, hormone-sensitive prostate cancer can extend overall survival (OS) by more than a year. In a randomized phase 3 trial, median OS for men who received upfront androgen deprivation therapy (ADT) alone for 18 weeks was 44 months, compared with 57.6 months for men who received ADT plus docetaxel, reported Dr Christopher Sweeney of the Lank Center of Genitourinary Oncology at the Dana-Farber Cancer Institute, Boston.

"The certainty of the data is strong for patients with a high volume of metastatic disease and clearly justifies the treatment burden. This is one of the biggest improvements in survival we have seen involving patients with an adult, node-metastatic solid tumor," he said.

In this study of 790 men with newly diagnosed metastatic prostate cancer, those with more extensive disease at study entry (520 patients) experienced the greatest benefit from the docetaxel-ADT combination, with a median OS of 49.2 months, compared with 32.2 months for men with extensive disease who received ADT alone. Median OS for men with less invasive disease, has not yet been reached.

The CHAARTED study began enrolling patients in 2006. Because there was evidence to show that docetaxel improves OS of men with metastatic prostate cancer who had disease progression while on ADT, the investigators wanted to see whether starting docetaxel earlier might provide additional benefit. They randomly assigned men on a 1:1 basis to receive either ADT alone, or ADT plus docetaxel 75 mg/m² every 3 weeks for 6 cycles within 4 months of starting ADT. Patients were stratified by low- or high-volume disease.

Of the patients assigned to ADT alone, 124 received docetaxel at the time of disease progression. Of those in the combination group, 45 who had disease progression received additional docetaxel.

At the fourth planned interim analysis in September 2013, when 53% of planned information had been accrued, the data-monitoring committee determined that the ADT-docetaxel combination had crossed the O'Brien-Fleming upper boundary, signaling statistically significant efficacy, and decided to release all available data. As of January 16, 2014, with a median follow-up of 29 months, there had been 137 deaths in patients treated with ADT alone, compared with 104 treated with ADT-docetaxel.

As already noted, median OS was 44 months for patients on ADT alone, compared with 57.6 months for those on the combination ($P = .0006$). This translated into a hazard ratio for death of 0.61 ($P = .0003$). The hazard ratio was similar for the subset of men with high-volume disease (0.60; $P = .0006$) who received ADT-docetaxel. The hazard ratio for men with low-volume disease was not significant, but as already noted, median OS in this group has not yet been reached, likely because men with low-volume disease tend to derive greater benefit from ADT, which suggests it may take longer follow-up for an added effect of docetaxel to be seen.

In addition to the survival advantage, the combination was better than ADT alone at driving down prostate-specific antigen (PSA) levels, with 27.5% of patients on the ADT-docetaxel arm having a PSA below 0.2 ng/mL at 6 months, compared with 14% of patients treated with ADT alone ($P < .0001$). At 12 months, the respective percentages were 22.7% and 11.7% ($P < .0001$).

The combination was also better at delaying the median time to development of castration-resistant prostate cancer (20.7 vs 14.7 months; $P < .0001$), and the median time to clinical progression (32.7 vs 19.8 months).

The most serious adverse events were febrile neutropenia and neuropathy. Of the 101 patients in the combination group who died, 84 of the deaths (83.2%) were from prostate cancer, 8 were from unknown causes, and 1 was attributed to the study protocol. Of the 136 in the ADT-alone arm who died, 112 deaths (83.6%) were from prostate cancers, and 22 were from other or unknown causes. Data on the causes of death in 2 patients were missing.

“The clinical interpretation of the data is that 6 cycles of docetaxel in addition to ADT represents an appropriate option for men with metastatic prostate cancer commencing ADT who are suitable for docetaxel therapy,” Dr Sweeney said.

Dr Michael J Morris, the invited discussant, pointed out that the superior OS seen with the combination in this study far outstrips that of other drugs tried in this population, with median OS benefits ranging from 2.2 to 5.2 months. “The investigators have adequately shown that high-volume patients with castration-sensitive metastatic disease can benefit from upfront docetaxel,” he said. “But there is insufficient data at this after 29 months of median follow-up to recommend that low-volume patients with castration-sensitive disease undergo chemotherapy. We need to optimize the distinction between those who benefit from chemotherapy and those who don’t.” Dr Morris, of Memorial Sloan-Kettering Cancer Center and of Weill Cornell Medical College in New York, was not involved in the study.

Disclosures The study was funded by the National Cancer Institute. Dr Sweeney disclosed serving in a consulting or advisory role to Astellas Pharma, BIND Biosciences; Biomimics, Exelixis, Genentech, Janssen Pharmaceuticals, Roche, and Sanofi. Dr Morris disclosed consulting/advising Astellas, Bayer, Janssen, Millennium, and Progenics, stock ownership in Biogen Idec, Procter & Gamble, and Teva, and research funding from Agensys, Algeta, Bayer, Medivation, and Sanofi.

– Neil Osterweil

Goserelin improves fertility in HR-negative breast cancer

Key clinical point Goserelin may be offered to young patients with hormone receptor-negative breast cancer who desire to preserve fertility or prevent premature menopause. **Major finding** The risk of ovarian failure was reduced 70% with goserelin (odds ratio, 0.30; two-sided $P = .04$). **Data source** A phase 3 randomized trial in 257 premenopausal women with hormone receptor-negative breast cancer.

Use of the gonadotropin-releasing hormone agonist gosere-

lin during chemotherapy for early hormone receptor-negative breast cancer was associated with lower rates of ovarian failure and more pregnancies in the phase 3 POEMS study, Dr Halle Moore reported at the meeting. At 2 years, 22% of women receiving standard neoadjuvant or adjuvant chemotherapy alone and 8% of those receiving chemotherapy plus goserelin experienced ovarian failure, defined as amenorrhea for the previous 6 months and follicle-stimulating hormone (FSH) in the postmenopausal range.

In logistic regression analysis that accounted for age and chemotherapy regimen, the risk of ovarian failure was reduced by 70% with goserelin (odds ratio, 0.30; two-sided $P = .04$). Risk was further reduced using the less stringent definition of ovarian failure of amenorrhea for the previous 6 months or FSH in the postmenopausal range (45% vs 20%; OR, 0.29; $P = .006$).

The 2-year ovarian dysfunction rate was 33% with standard chemotherapy and 14% with chemotherapy plus goserelin (OR, 0.35; $P = .03$). Dysfunction was defined as amenorrhea for the previous 3 months and FSH, estradiol, and/or inhibin B levels in the postmenopausal range.

Small studies have shown high rates of ovarian preservation in women with hematologic malignancies with the use of a luteinizing hormone release hormone (LHRH) analogue. Results of randomized trials in breast cancer have been mixed; the studies commonly used only return of menses as an endpoint, and few provided data on pregnancy outcomes, said Dr Moore of the Cleveland Clinic.

The intergroup POEMS-S0230 randomly assigned 257 premenopausal women, aged 18-49 years, with operable stage I-IIIa estrogen receptor- or progesterone receptor-negative breast cancer to curative-intent standard cyclophosphamide containing neoadjuvant or adjuvant chemotherapy alone or with subcutaneous injections of goserelin 3.6 mg every 4 weeks starting at least 1 week before the first chemotherapy dose and ending within 2 weeks of the final dose. The average age of the groups was 38.7 and 37.6 years, respectively.

The study was closed before full accrual of the target 416 patients, with 218 women evaluable for pregnancy and survival outcomes and 135 for ovarian failure.

In all, 18 of 113 evaluable controls and 25 of evaluable 105 women who were given goserelin reported attempting pregnancy, with 12 and 22 women, respectively, becoming pregnant over the 5-year study period (OR, 2.45; $P = .03$). Compared with controls, women who received goserelin were twice as likely to have a successful delivery (8 vs 16; OR, 2.51; $P = .05$) and to have a successful delivery or an ongoing pregnancy at the time of the analysis (10 vs 19; OR, 2.45; $P = .04$). Twelve babies were born to women on chemotherapy alone, and 18 to those given goserelin, with 3 and 5 pregnancies, respectively, ongoing at the time of analysis. Of note was that there was no evidence that gos-

erelin increased adverse pregnancy events such as miscarriage (5 controls vs 4 goserelin), elective termination (3 vs 2), and delivery complications (2 vs 2).

Grade II-IV endocrine toxicity was reported in 24% of the chemotherapy-alone arm and 48% of the goserelin arm ($P = .006$). One grade IV thromboembolic event occurred with goserelin. The most common added toxicities with goserelin were hot flashes, mood changes, vaginal dryness, and headache.

A planned exploratory analysis revealed that 89% of women on goserelin and 78% on chemotherapy alone were disease-free at 4 years, with a hazard ratio of 0.47 after controlling for age and regimen ($P = .04$) and 0.49 after further adjusting for cancer stage ($P = .04$).

Overall survival at 4 years was 92% with goserelin and 82% with chemotherapy alone, with hazard ratios of 0.45 ($P = .06$) and 0.43 ($P = .05$), respectively. Dr Moore said that the favorable survival outcomes with the addition of goserelin were “intriguing and reassuring” regarding the safety of the approach, noting that one possible explanation for the finding is that there are a high number of LHRH receptors on hormone receptor-negative breast cancers.

Discussant Dr Sharon Giordano, chair of health services research at the University of Texas MD Anderson Cancer Center in Houston, said there were several limitations in the analysis. The most worrisome of these was missing endpoint data for 38% of participants. The study was also hampered by early close and low accrual, and excluded women with more than 10% estrogen or progesterone receptor positivity. “I don’t think we can consider these results definitive [but] having said that, and with these caveats and recognizing the uncertainty, I would be comfortable offering goserelin to my young patients with estrogen receptor-negative breast cancer who desire to preserve fertility or prevent premature menopause.”

Disclosures The study was supported by the National Institutes of Health. Dr Moore reported no disclosures; 3 coauthors have financial ties with AstraZeneca, maker of goserelin. Dr Giordano reported no relevant disclosures.

– Patrice Wendling

Obesity increased deaths only in premenopausal women with ER-positive breast cancer

Major finding Obesity was associated with a relative risk for death of 1.34 (95% confidence interval, 1.22-1.47) in premenopausal women; a weak, nonsignificant effect in postmenopausal, ER-positive women (RR, 1.06; CI, 0.99-1.14); and no effect in women with ER-negative tumors (RR, 1.00; CI, 0.93-1.08). **Data source** Analysis of pooled data on 80,000 patients enrolled in 70 clinical trials.

Obesity seems to increase the risk of breast cancer-related

deaths by about one-third in premenopausal but not postmenopausal women with estrogen receptor-positive disease, Dr Hongchao Pan reported on behalf of colleagues in the Early Breast Cancer Trialists’ Collaborative Group. An analysis of pooled data on 80,000 patients enrolled in 70 clinical trials showed that among 60,000 patients with estrogen receptor (ER)-positive disease, body mass index (BMI) was associated with risk for breast cancer mortality in both pre- and perimenopausal women. But after adjustment for patient factors and tumor characteristics, the association remained significant only for premenopausal women with ER-positive tumors, who had a 34% higher risk of dying from breast cancer,

“We found little independent adverse effects of obesity in the 40,000 postmenopausal women with ER-positive disease,” Dr Pan said at a media briefing in Alexandria, Virginia, highlighting research to be presented at ASCO 2014.

There was also no apparent effect among women of any age with ER-negative tumors. The findings suggest that the mechanisms by which obesity contributes to breast cancer prognosis are still unclear, Dr. Pan said.

Dr Peter Yu, president-elect of ASCO and a medical oncologist at Palo Alto Medical Foundation in Sunnyvale, California, noted that the study looked only at the role of obesity in breast cancer prognosis and did not consider its potential contributions to oncogenesis. Dr Yu comoderated the briefing but was not involved in the study.

The other moderator, Dr Clifford Hudis, president of ASCO and chief of the breast cancer service at Memorial Sloan-Kettering Cancer Center, New York, commented that both overweight and obesity are known to contribute to risk for postmenopausal, ER-positive breast cancer.

Obesity is associated with inflammation of white adipose tissue, including adipose tissue of the breast, through up-regulation of inflammatory mediators such as interleukin-6 and prostaglandin. The mediators activate the cytochrome P19 gene, which encodes for the aromatase enzyme, he explained. “People who have this low-grade inflammation will have increased aromatase activity, increased local production of estrogen, and that provides an explanation for the paradox of elevated ER-positive breast cancer with obesity after menopause, when the ovaries have stopped higher production of estrogen.”

Dr Pan and colleagues collected data on 80,000 individual patients in 70 early breast cancer trials, including information on BMI, ER status, menopausal status, recurrence, and cause of death. In Cox regression analysis adjusted for age, surgery type, trial treatment, HER2-receptor status, nodal status, tumor grade, and diameter, they looked at obesity as an independent factor associated with breast cancer mortality. They found that among premenopausal women, obesity was associated with a relative risk for death of 1.34 (95% confidence interval, 1.22-1.47). In contrast,

there was only a weak, nonsignificant effect in postmenopausal, ER-positive women (RR, 1.06; CI, 0.99-1.14), and no effect whatsoever in women with ER-negative tumors (RR, 1.00; CI, 0.93-1.08).

Disclosures The study was funded by Cancer Research UK, the Medical Research Council, and the British Heart Foundation. Dr. Pan, Dr. Yu, and Dr. Hudis reported having no relevant financial disclosures.

– Neil Osterweil

Ibrutinib boosts survival of relapsed or refractory CLL

Major finding One-year overall survival for patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma treated with ibrutinib was 90%, compared with 81% for patients treated with ofatumumab.

Data source First interim analysis of a randomized phase 3 study in 391 patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma.

For the first time an oral drug, ibrutinib, has been shown to significantly improve both progression-free and overall survival of patients with relapsed or refractory chronic lymphocytic leukemia (CLL), compared with a systemic agent. The first interim analysis of a phase 3 randomized trial showed that 1-year overall survival for patients with previously treated CLL or small lymphocytic lymphoma (SLL) assigned to receive ibrutinib was 90%, compared with 81% for patients assigned to ofatumumab.

The hazard ratio (HR) for death for patients assigned to ibrutinib was 0.43 ($P = .005$), reported lead author Dr John Byrd, professor of medicine at the Ohio State University Comprehensive Cancer Center, Columbus, at a media briefing during the meeting. The median time to progression for patients on ibrutinib had not been reached, compared with 8.08 months for those on ofatumumab. At 15 months follow-up, the median progression-free survival (PFS) was 8.4 months in the ofatumumab group but had not reached for patients on ibrutinib.

Ibrutinib reduced by 78% the risk of disease progression or death when compared with ofatumumab.

The overall survival advantage shown with ibrutinib persisted even after 57 patients who had disease progression while on ofatumumab were crossed over to ibrutinib. “These patients who have a short response to first-line therapy, or who are elderly, have very few treatment options that induce durable remissions. Identifying new therapies in this patient population, particularly those that extend survival, is very important,” Dr Byrd said.

Dr Olatoyosi Odenike, a leukemia specialist from the University of Chicago, who was not involved in the study, described the drug as “transformative,” noting that “the issue now is how to best use the drug and how to most

effectively move this into the front-line setting.”

Ibrutinib is an oral inhibitor of Bruton’s tyrosine kinase, an enzyme essential for B-cell receptor signaling and adhesion that is present in many types of B-cell malignancies. On the basis of the results of phase 2 studies, ibrutinib was approved by the US Food and Drug Administration for relapsed mantle cell lymphoma in November 2013 and for CLL in February 2014.

Ofatumumab, a CD20 inhibitor, was approved for the treatment of CLL based on a single group study in which patients whose disease was resistant to fludarabine and alemtuzumab had an overall response rate of 58%.

In the RESONATE trial, Dr Byrd and his colleagues enrolled 391 patients with relapsed or refractory CLL or SLL and randomly assigned them to receive either oral ibrutinib 420 mg once daily until disease progression or unacceptable toxicity (195 patients) or to IV ofatumumab at an initial dose of 300 mg followed by 11 doses at 2,000 mg (196 patients).

At a median follow-up of 9.4 months, the median duration of PFS, the primary endpoint, had not been reached in ibrutinib-treated patients (88% of whom had PFS at 6 months), compared with 8.1 months for patients treated with ofatumumab. In all, 42.6% of patients on ibrutinib had a partial response rate, compared with 4.1% of those on ofatumumab. In addition, 20% of patients on ibrutinib had a partial response with lymphocytosis, which occurred in 69% of all patients treated with ibrutinib. The investigators did not consider lymphocytosis to be disease progression, and the condition resolved in 77% of these patients during follow-up.

Nonhematologic adverse events occurring in at least 20% of patients included diarrhea, fatigue, pyrexia, and nausea in patients on ibrutinib, and fatigue, infusion-related reactions, and cough in those on ofatumumab. In all, 4% of patients on ibrutinib and 5% on ofatumumab discontinued the assigned drug because of adverse events.

Richter’s transformation, that is, CLL evolving into an aggressive, rapidly growing large-cell lymphoma, occurred in 2 patients in each treatment arm. One patient on ibrutinib developed prolymphocytic leukemia.

Dr Byrd noted that the improved PFS, overall survival, and response rates with ibrutinib were seen across all patient subgroups, including patients who were resistant to chemoimmunotherapy and those with the notorious chromosome 17p13.1 deletion.

Ibrutinib is currently being explored in patients with previously untreated CLL or SLL.

Disclosures The study was supported by Pharmacyclics. Dr Byrd disclosed receiving research funding and serving as an unpaid advisor to Pharmacyclics. Dr Odenike reported having no relevant disclosures.

– Neil Osterweil