[News * Analysis * Commentary * Controversy]

August 25, 2013 * Vol. 35 * No. 16

oncology-times.com

Oncology Times

Lippincott Williams & Wilkins
Wolters Kluwer Health

The Independent Hem/Onc News Source

Celebrating 35 Years of Publishing 35

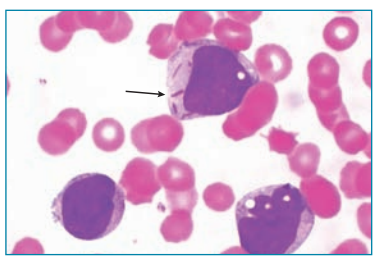
Survey: Most Oncologists Avoid the Word 'Cure' in Discussions with Patients

BY KURT SAMSON

In what is believed to be the first such study to give quantitative as well as qualitative data on this topic, oncologists said both that their patients are hesitant to ask whether they are cured, and that they as cancer care clinicians try not to use the word with patients. The implications are many, those interviewed for this article said, and open up multiple avenue of research. *Page 24*

Call for Oncologists to Be Far More Aggressive on Tobacco Control p.10

Jeffrey Sosman and Douglas Johnson on Treating Patients with BRAF Wild-Type Metastatic Melanoma p.16



APL: ATRA + ATO Shown as Better than Chemo p.18

Lynn Matrisian's Evolutionary Transition from Science to Advocacy p.30

[ALSO]

@OncologyTimes /OncologyTimesNews

PERIODICALS

ID Statement on page 9

aTTom Study

Extending Adjuvant Tamoxifen to 10 Years Shown to Reduce Breast Cancer Recurrence and Death

BY MARK FUERST

"Five years of adjuvant tamoxifen is already an excellent treatment, but we thought that longer treatment might be even better because women with ER+ breast cancer can have recurrences long after treatment is completed."

CHICAGO—Extending adjuvant treatment with tamoxifen from five to 10 years affords women with estrogen receptor-positive (ER+) breast cancer greater protection against late recurrence and breast cancer death, according to data reported at the American Society of Clinical Oncology Annual Meeting (***Abstract 5***).

"Five years of adjuvant tamoxifen is already an excellent treatment, but we thought that longer treatment might be even better because women with ER+ breast cancer can have recurrences long after treatment is completed," said lead author Richard G. Gray, MA, MSc, Professor of Medical Statistics at the University of Oxford. Until now, though, there have been doubts about whether continuing tamoxifen beyond five years is worthwhile. This study and its international counterpart, ATLAS (***OT, 2/10/13***), confirm that there is definitely a survival benefit from longer tamoxifen treatment, and many doctors will likely recommend continuing tamoxifen for an extra five years."

Prior studies have shown that five years of tamoxifen reduces breast cancer death rates by about a third over a 15-year period following diagnosis. In the randomized, Phase III aTTom study, the benefits of longer treatment emerged later on, with reductions in recurrence seen after year 7 and reductions in mortality becoming evident after year 9, Gray said. The continued use of tamoxifen resulted in an additional 24 percent reduction in mortality after year 10.

"What is really impressive is the effect on breast cancer mortality: 10 years of tamoxifen compared with no tamoxifen reduces breast cancer mortality by a third in the first decade and a half in the second decade."

Trial Data

For the study, between 1991 and 2005, a total of 6,953 women in the United Kingdom who had been taking tamoxifen for five years were randomly assigned to continue treatment with tamoxifen for another five years or to stop immediately. The women were contacted yearly to assess treatment compliance, recurrence, hospital admissions, and death rates. Compliance was good, with about 75 percent of women in the 10-year group continuing to take tamoxifen.

With 5,000 women followed for more than 10 years after randomization, and some for as long as 20 years, there were 580 recurrences among women who had taken tamoxifen for 10 years, compared with 672 recurrences among those who took the drug for five years. There were 392 breast cancer deaths after disease recurrence in the 10-year arm compared with 443 deaths among those in the five-year arm.

A pooled analysis of the 17,477 patients enrolled in both the aTTom and ATLAS trials showed a nine percent reduction in the risk of death after patients received 10 years versus five years of tamoxifen for the entire follow-up period. The relative risk reduction increased to 16 percent starting at year 10.

There was an increased risk of endometrial cancer with the use of extended tamoxifen: 102 cases and 37 (1.1%) deaths attributed to endometrial cancer in the 10-year tamoxifen arm, compared with 45 cases and 20 (0.6%) deaths in the five-year group. The researchers estimated, though, that for every endometrial cancer death that occurs as a side effect of long-term tamoxifen, 30 deaths from breast cancer are prevented.

"The benefits of continuing tamoxifen to 10 years greatly outweigh the risks," Gray said.

In conclusion, he said, "the aTTom and ATLAS trials together provide proof beyond reasonable doubt that continuing tamoxifen beyond five years reduces recurrence over the following years."

ASCO/Silas Crews 2013

RICHARD G. GRAY, MA, MSC: "This study and its international counterpart, ATLAS, confirm that there is definitely a survival benefit from longer tamoxifen treatment, and many doctors will likely recommend continuing tamoxifen for an extra five years."

He said that he and his colleagues are now planning to follow women in both of the studies for at least five more years to see if there is additional long-term benefit. A retrospective analysis of combined data from aTTom, ATLAS, and three smaller trials will be conducted to determine if there are subgroups of women who benefit the most from longer tamoxifen treatment.

In addition, he noted, ongoing clinical trials are comparing five and 10 years of use of aromatase inhibitors (AIs) to see if longer use of those agents also leads to additional benefits.

Late Recurrences

The Discussant for the study, Ann Partridge, MD, MPH, Director of the Program for Young Women with Breast Cancer at Dana-Farber Cancer Institute, noted that late recurrences in HR+ breast cancer are a major problem and remain a challenge as early treatment increases.

continued on page 13

→ASCO TOBACCO STATEMENT

continued from page 11

adults, which means that the burden of smoking in the general population—where 20 percent of Americans smoke—is passed forward from youth to older adulthood. By the time an oncologist sees an older patient who smokes, the patient may have had decades of exposure to tobacco.

The IOM report also makes the point that many health professionals are still unaware of tobacco-cessation clinical practice guidelines and the availability of quit-lines for smokers.

'Lead by Example'

The new statement by ASCO also specifically calls on all oncology professionals to "lead by example" and refrain themselves from using all tobacco products. The ASCO survey found that despite the overwhelming evidence about the dangers of tobacco use, nearly one quarter of respondents reported smoking cigarettes at some point during their lifetime.

"Treat tobacco dependence as aggressively and compassionately as cancer," the ASCO statement says, and help patients and their families end tobacco dependency.

→ATTOM

continued from page 12

"Even with recent advances, including AIs and trastuzumab, there appears to be a persistent risk of late recurrences.

"Five years of tamoxifen continues to improve the risks beyond five years. There is a carry-over effect. As time goes on, we are more likely to see a difference in breast cancer mortality out to 15 years," she said.

Several studies have addressed the issue of whether extending tamoxifen would be helpful, she continued. There are suggestions that tamoxifen continuation may be better, but also that continued tamoxifen may worsen breast cancer outcomes.

In the aTTom trial, the absolute reduction of recurrence was four percent out to 15 years, and the absolute reduction of breast cancer mortality was two percent, which is of borderline significance, she said. "But this is impressive given that the majority of these patients were ER-unknown. Undoubtedly some of them were ER-negative and would not be expected to respond to tamoxifen. Also, women followed the longest do appear to have a mortality benefit."

Making Decisions

How should clinicians use this data to make decisions with early breast cancer survivors? "When assessing the anti-cancer benefit in an individual patient, stage clearly matters for early and late recurrence, and tumor biology matters tremendously," Partridge answered. "Can gene expression profiling help us here? How can we better understand tumor dormancy and endocrine resistance mechanisms? For the individual patient, we also need to consider comorbidity and age."

The Discussant for the study, Ann Partridge, MD, MPH, said future research priorities should include improved understanding of the biology of late recurrence, identification of markers of late recurrence, and improved strategies to reduce late recurrences.

She also encouraged clinicians to assess the risks of therapy, such as endometrial cancer: "Especially five years out, symptoms and quality of life become important. A patient's preferences and values also need to be considered."

Extended endocrine therapy options are largely driven by menopausal status as well as prior treatment experience. Partridge recommended that most postmenopausal women should consider receiving an AI in the first five years of therapy. "Consider tamoxifen if a patient has a contraindication or intolerance to AIs. Beginning tamoxifen after completing five years of AI might be reasonable," she said, adding that the data do not support continuing AIs beyond five years.

DOUGLAS YEE, MD: "In many places in the world, AIs are not used routinely in adjuvant therapy for breast cancer, partially due to cost. The aTTom trial provides validation of an alternative for extended endocrine therapy, and identifies an option for certain subgroups of women, particularly premenopausal women, for whom AIs would not be effective."

For women who remain premenopausal, "extended tamoxifen is a great option where there has been no prior standard," she said. These women have higher risk disease and therefore potentially the greatest risk reduction. "But the personal cost may be great, with a greater effect on long-term quality of life and future plans for fertility. Continued tamoxifen is a new option, but it also is reasonable to stop therapy, take a break, and have a woman think about the options.

"For some women, these are very difficult decisions. We need ways to better support our patients to make these decisions not only at diagnosis but also in long-term survivorship. Ultimately, decisions must be tailored to the individual patient based on her own risk/benefit profile."

Future Research

Future research priorities should include improved understanding of the biology of late recurrence, identification of markers of late recurrence, and improved strategies to reduce late recurrence, she said.

The Chair of the Scientific Program for the meeting, Douglas Yee, MD, Professor of Medicine and Pharmacology and Director of the Masonic Cancer Center at the University of Minnesota, said the aTTom trial was "well-designed and provides additional data from a large number of patients to really settle the question of efficacy and safety of 10 years of tamoxifen."

He noted that until now, extended tamoxifen regimens have been used infrequently in the U.S. because a smaller National Surgical Adjuvant Breast and Bowel Project (NSABP) study had suggested that 10 years of therapy was not beneficial. "However, it was recognized that this study was very underpowered to demonstrate benefit, so the NSABP was supportive of this larger trial," he said.

Many places in the world are not using AIs routinely in adjuvant therapy, partially due to cost, Yee continued. "The aTTom trial provides validation of an alternative for extended endocrine therapy. In addition, it identifies an option for certain subgroups of women, particularly premenopausal women, for whom AIs would not be effective. It also shows that some women with ER+ breast cancer have an extended risk over time and provides an additional way to manage that risk."

"What is really impressive is the effect on breast cancer mortality: 10 years of tamoxifen compared with no tamoxifen reduces breast cancer mortality by a third in the first decade and a half in the second decade."