[News * Analysis * Commentary * Controversy]

September 25, 2011 * Vol. 33 * No. 18

oncology-times.com

ONCOLOGY TIMES

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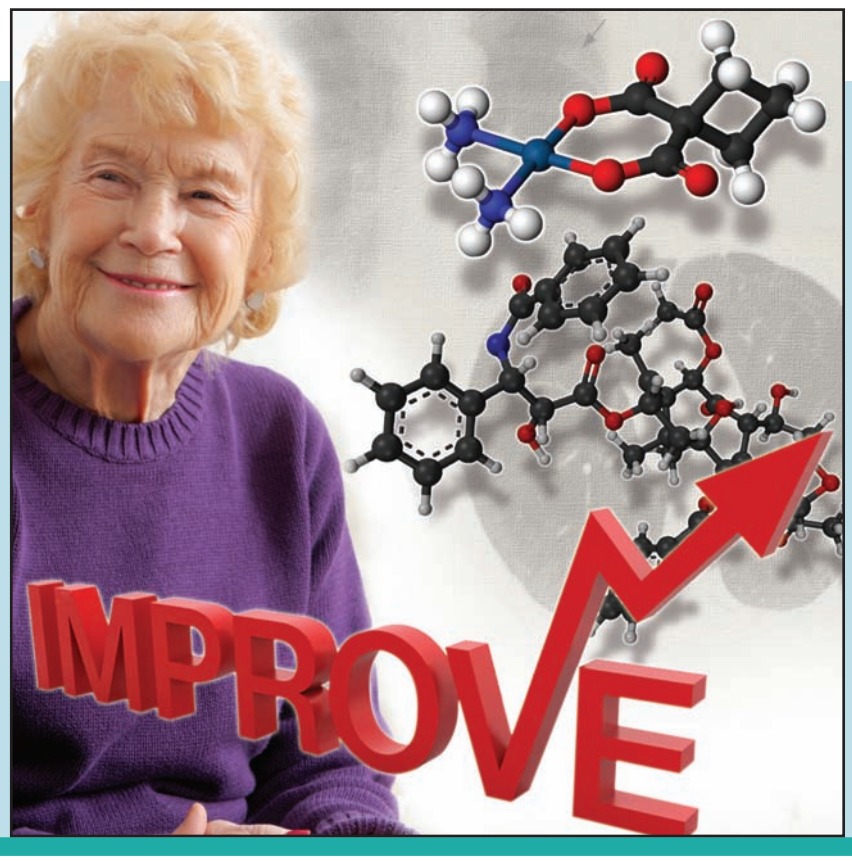
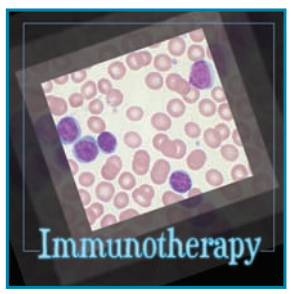


NSCLC: Doublet Therapy Shown as OK for Fit Older Patients

BY KURT SAMSON

For years, younger patients with advanced non-small-cell lung cancer have benefited from combined chemotherapy using platinum-based doublet chemotherapy, but the treatment was usually not given to older patients due to concerns about potential toxicity. A new study, though, shows that many patients over age 70 can also have increased survival without prohibitive toxicity. "At the end of the day," one expert told us, "age is just a chronological number, and performance status always trumps age. This Phase III trial validates what some of us have already been doing with carefully selected and monitored elderly NSCLC patients. These new results are not just positive, but significantly so."

Page 19



CLL T-Cell Therapy Approach Shows the Progress in Immunotherapy p.9

Warnings about Hormone Therapy for Men with High-Risk Prostate Cancer & Heart Disease p.26

CML: When Imatinib Fails, What's to Do Next: Second-Generation TKIs or Transplant? p.44

[ALSO]

PERIODICALS

Warnings about Hormone Therapy for Men with High-Risk Prostate Cancer and Heart Disease

BY MARK FUERST

Men with high-risk prostate cancer and pre-existing heart conditions who are treated with androgen-deprivation therapy (ADT) along with radiation therapy may be at increased risk of dying, according to the results of a large, retrospective cohort study now available online ahead of print in *International Journal of Radiation Oncology*Biology*Physics (10.1016/j.ijrobp.2011.04.067)*.

Over the past five years, studies have shown that hormone therapy could induce metabolic, cardiovascular side effects, including weight gain, loss of muscle mass, a worsening lipid profile, an increase in the risk of diabetes, and increased cardiac events. Clinicians face a dilemma about whether to offer ADT to men with congestive heart failure (CHF) or myocardial infarction (MI) who have high-risk prostate cancer.

"Despite Phase III data supporting hormone therapy for men with high-risk disease, the subgroup of men with a history of heart disease may be harmed by hormone therapy," said the lead author of the study, Paul L. Nguyen, MD, Director of Prostate Brachytherapy at Dana-Farber/Brigham and Women's Cancer Center.

"We found that for men with localized prostate cancer and a history of heart problems, treatment with hormones plus radiation was associated with higher all-cause mortality than treatment with radiation alone, even for patients with high-risk malignant disease."

Asked for his opinion for this article, A. Oliver Sartor, MD, Medical Director of the Tulane Cancer and Professor of Cancer Research in the Departments of Medicine and Urology at Tulane Medical School, said, "Clearly, there is now a greater understanding of how ADT may alter mortality in those with high levels of comorbidity. This interesting study goes an additional step. It demonstrates unequivocally that ADT increases all-cause mortality in a substantial way in a subset of patients with CHF or MI.

"This paper will make me look at ADT very carefully for patients with a history of CHF or MI, and should impact broadly, including at the community oncology level. With the risk-benefit now being segregated to this high-risk subset, before you start ADT, I advise: pause and consider the risk-benefit ratio."

PAUL NGUYEN, MD: "If you see a patient with a history of CHF or prior MI, even if he has high-risk prostate cancer, approach ADT with some caution. Weigh the risks and benefits, because you may still need to use it. And send the patient to a cardiologist to optimize his heart disease."

Study Details

In the study, from 1991 to 2006 a total of 14,594 men with prostate cancer were treated at some 20 community-based practices with brachytherapy-based radiation therapy. Of these, 1,378 of the patients (9.4%) had a history of congestive heart failure or myocardial infarction. Among these men with heart conditions, 22.6% received supplemental external-beam radiation therapy and 42.9% had four months of neoadjuvant ADT.

For the entire group of men with a history of heart problems, adding hormone therapy led to a significant increase in overall mortality. For men with pre-existing heart conditions and high-risk prostate cancer, the researchers found that by five years, 31.8% of the men who received hormones had died compared with 19.5% of the men who did not receive hormone therapy.

> "Using ADT when there is no demonstrable survival benefit should proceed only for highly selected low-risk patients."

A multivariate analysis found that ADT was associated with significantly increased all-cause mortality (adjusted hazard ratio of 1.76), with five-year estimates of 22.71% with ADT and 11.62% without ADT. The impact of ADT on all-cause mortality by risk group showed a higher

continued on page 28

Broader Theme

Dr. Sartor noted that the study by Dr. Nguyen and colleagues fits into a broader theme of interactions between patient comorbidities and the risk of prostate cancer itself.

"In low-risk prostate cancer, over-treatment is a critically important issue, given that the benefits of therapy are questionable," he said. Dr. Sartor also pointed to PIVOT, the Prostate Intervention and Observation Trial presented at the American Urological Association Annual Meeting earlier this year, a prospective trial randomizing patients to observation versus prostatectomy.

After 10 years of follow-up, there was no increase in overall survival with radical prostatectomy. "Low-risk prostate cancer patients had no benefit with surgery," he said. "The only group that benefited had high-risk prostate cancer and a PSA greater than 10. This broaches the question of who needs treatment and who doesn't. A clinician who utilizes therapies that have potential morbidity attached to them for low-risk patients may be engaging in questionable practice."

Dr. Sartor also noted the large Prostate, Lung, Colorectal and Ovarian Prostate Cancer screening study, in which researchers interviewed more than 73,000 men who were randomly assigned to usual care or intervention at 10 US centers. The reported results *(Crawford ED et al: JCO 2011;29:355-61)* showed a significant decrease in the risk of prostate cancer-specific mortality in men with no comorbidities, versus no decreased risk among men with at least one significant comorbidity. The researchers concluded that selective use of PSA screening for men in good health appears to reduce the risk of prostate cancer-specific mortality with minimal overtreatment.

Similarly, men with high-risk prostate cancer with prior CHF or MI may be unlikely to benefit from ADT. "This calls into question our choice of therapies in prostate cancer moving forward. This is the tip of the iceberg of a much larger question," Dr. Sartor said.

"We found that for men with localized prostate cancer and a history of heart problems, treatment with hormones plus radiation was associated with higher all-cause mortality than treatment with radiation alone, even for patients with high-risk malignant disease."

→ADT RISKS

continued from page 26

adjusted hazard ratio for high-risk patients (2.57) than intermediate-risk (1.75) and low-risk patients (1.52).

Particularly Important Finding

"This finding is particularly important, because neoadjuvant ADT is not typically used for low-risk disease except for gland volume reduction to enable brachytherapy, but it is widely accepted as the standard of care for high-risk clinically localized prostate cancer managed by radiation because it has been shown to improve overall survival," Dr. Nguyen said.

"Our data suggest that although most patients with high-risk disease probably benefit from the addition of ADT, the subgroup of patients with a prior history of CHF or MI—nine percent of the patients in this study's total population—may actually be harmed by the addition of ADT."

The mechanism of this harm remains unknown, but it is possible that the adverse effects of ADT on cardiovascular mortality for this vulnerable subgroup outweigh the beneficial effects on prostate cancer-specific outcomes.

For men with unfavorable risk, clinically localized prostate cancer and a history of congestive heart failure or myocardial infarction, oncologists need to carefully weigh the known prostate cancer-specific benefits of ADT against the suggested potential for harm due to ADT, he said. For this vulnerable subgroup, dose-escalated radiation alone might provide a superior overall outcome versus radiation plus ADT, although this needs to be tested in a future randomized trial, Dr. Nguyen said.

"We are always trying to balance the aggressiveness of prostate cancer treatment with the risks of cardiac disease. At the moment, there is no way to stratify patients. Future studies may tease out these patients more carefully."

Other subgroups also at risk may be men with pre-existing diabetes or other cardiovascular risk factors, he added. Studies may also look at providing medication to minimize cardiovascular changes—for example, metformin to block the insulin changes associated with ADT.

For the moment, Dr. Nguyen's advice is "if you see a patient with a history of CHF or prior MI, even if he has high-risk prostate cancer, approach ADT with some caution. Weigh the risks and benefits because you may still need to use it. And send the patient to a cardiologist to optimize his heart disease."

Still Needs Randomized Trial

Dr. Nguyen cautioned that this is a retrospective study and needs to be confirmed with a randomized trial that stratifies patients by cardiovascular morbidity.

Stratification by cardiovascular risk is being built into clinical trials—for example, RTOG 0815, now enrolling patients, is examining intermediate-risk prostate cancer patients and randomizing them to dose-escalated radiation with or without six months of ADT. The patients are being stratified by comorbidity, mainly cardiovascular morbidity, he said.

A. OLIVER SARTOR, MD: "This paper will make me look at ADT very carefully for patients with a history of CHF or MI, and should impact broadly, including at the community oncology level. With the risk-benefit now being segregated to this high-risk subset, before you start ADT, I advise: pause and consider the risk-benefit ratio."

Utilization of ADT in low-risk patients is questionable when using external-beam radiation, Dr. Sartor said. Data recently published in RTOG 9408 show that low-risk patients do not benefit from the addition of ADT. "I would say that using ADT when there is no demonstrable survival benefit should proceed only for highly selected low-risk patients," he said.

Science Advisory

The issue of the heart risks of ADT has been under scrutiny recently. For example, a science advisory on ADT in prostate cancer and cardiovascular risk by the American Heart Association, American Cancer Society, and American Urological Association, and endorsed by the American Society for Radiation Oncology, was released last year *(Circulation 2010;121:833-840;* also available on the websites of each of the organizations).

The multidisciplinary writing group reviewed and summarized the metabolic effects of ADT, evaluated the data regarding a possible relationship between ADT and cardiovascular events in patients with prostate cancer, and generated suggestions regarding the evaluation and management of patients, both with and without known cardiac disease.

The conclusion was that ADT could increase cardiovascular risk on the basis of its adverse impact on risk factors for cardiovascular disease and that there may be a relationship between ADT and cardiovascular risk. "Future clinical trials of ADT should prospectively assess cardiovascular risk factors before and after ADT is begun and should prospectively monitor patients for adverse cardiovascular events and mortality," wrote the committee, which was led by Glenn N. Levine, MD.

In addition, in October 2010 the FDA asked manufacturers to add new warnings to labeling for the use of ADT, in particular gonadotropin-releasing hormone (GnRH) agonists, a class of drugs primarily used to treat prostate cancer. Earlier last year, in May, the FDA said that a preliminary and ongoing analysis found that patients receiving GnRH agonists were at a small increased risk for diabetes, heart attack, stroke, and sudden death.

"Now we know that patients with history of CHF or MI are a special subgroup that has increased mortality from ADT," Dr. Sartor said. "In these patients, utilization of ADT should proceed with extreme caution. Before you start therapy, be sure the risk-benefit ratio is appropriate and that the patient is managed from a cardiovascular prospective."

The study fits into a broader theme of interactions between patient comorbidities and the risk of prostate cancer itself.

Clinicians need to better understand the risks and benefits of hormone therapy in the high-risk patient where ADT has been shown to be of benefit along with radiation therapy. "This group of men now becomes a target for more intensive medical management related to cardiovascular risk factors," Dr. Sartor said. "A well-qualified internist or cardiologist who is adept at managing risk is an appropriate consultant for those receiving ADT, particularly if the patient has a history of cardiovascular disease.

"Now we have to put these data into practice and learn how to utilize ADT and mitigate the risks. Prospective validation and stratification of men by comorbidity and cardiovascular risk will be important to assess how these results affect patients not only with CHF but other comorbidities."