Androgen Deprivation Therapy Could Protect Men Against COVID-19

BY PETER M. GOODWIN

A study of 9,280 patients infected with COVID-19 in the northern Veneto region of Italy found a strong association with reduced risk for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients who had prostate cancer treated with androgen deprivation therapy (ADT). Findings published in the *Annals of Oncology* found markedly fewer patients infected with the virus whose prostate cancer had been treated with ADT than those receiving other therapies (2020; doi: https://doi.org/10.1016/j.annonc.2020.04.479).

"Patients with prostate cancer receiving androgen-deprivation therapies had a significant four-fold reduced risk of COVID-19 infections compared to patients who did not receive ADT," said Andrea Alimonti, MD, a full professor at both the Università della Svizzera Italiana in Bellinzona, Switzerland, and the Department of Pharmaceutical and Pharmacological Sciences in the Università degli Studi di Padova in Italy.

"An even greater difference was found when we compared prostate cancer patients receiving ADT to patients with any other type of cancer. There was a more than five-fold reduction in risk of infection among the prostate cancer patients on ADT," he said.

In addition, the study found that in patients whose prostate cancer had been treated with ADT the virus infection had been less severe.

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The findings prompted Alimonti to propose clinical trials of ADT among patients with severe COVID-19 symptoms because it could theoretically improve outcomes in men to bring them more in line with the less severe form of the disease experienced by women.

Study Findings

The investigators found that out of 4,532 men infected with COVID-19 430 of them (9.5%) had cancer and in 118 (2.6%) this had been prostate cancer. Male patients with cancer were found to have had a 1.8-fold increased risk of COVID-19 infection as compared with the whole male population and to have developed more severe disease.

When Alimonti and his colleagues looked at all patients with prostate cancer in the Veneto region, they found that only four out of 5,273 men on ADT had been infected with COVID-19 and none of them had died. But from 37,161 men with prostate cancer who had not been receiving ADT, 114 developed COVID-19 and 18 died. Among 79,661 patients with other types of cancer, 312 had developed COVID-19 and 57 died.

"This is the first paper to suggest a link between ADT and COVID-19," said Alimonti. "We collected data from a large population of patients infected by the coronavirus and have found that those being treated with ADT for prostate cancer are protected, even though all patients with cancer have a greater risk of COVID-19 infection than non-cancer patients."

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Clinical Implications

"I think this study is important because it gives an additional piece to this puzzle that tries to establish a link between androgen and SARS-CoV infection," Alimonti told *Oncology Times*. "It is the first time that we have reported that patients who are deprived of androgen by ADT are at decreased risk."

While he acknowledged that it had been a retrospective study, he believed it was acceptable to think about moving the hypothesis that ADT was protective into the clinic by setting up clinical trials to validate whether it could even protect male patients infected by the virus who did not have cancer.

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> —Andrea Alimonti, MD, at the Università della Svizzera Italiana in Bellinzona and the Università degli Studi di Padova

"So the idea would be to, for instance, look into male patients just infected with the virus who had comorbidities—cardiovascular disorder or other type of disorder—which bring them to a high or increased risk of hospitalization or be admitted to ICU or even to die," said Alimonti. "These patients could be treated transiently with androgen deprivation therapy—I say transiently because the disorder is fast—everything happening within 1 month from the infection. We think that this could be a valid approach to cure these patients.

"There are several clinically approved therapies that decrease the levels of androgens and that can be administered to patients. For instance, luteinizing hormone-releasing hormone (LHRH) antagonists can decrease the levels of testosterone in patients in 48 hours and the effect of this therapy is transient. Once a patient stops taking the drug, his testosterone levels go back to the previous levels. These treatments to lower testosterone levels, if given for no more than a month, do not have major side effects," said Alimonti.

Examining Research

The study had been prompted partly by recent research showing that the enzyme TMPRSS2 (one of a family of Type II Transmembrane Serine Proteases) helped COVID-19 to infect healthy human cells.

"We were really intrigued about a recent publication that showed that TMPRSS2 is involved in the SARS-CoV infection. TMPRSS2 is an enzyme that is frequently overexpressed in prostate cancer. And since we are a team that works on prostate cancer, we [have] know for many years that androgen deprivation therapy cuts TMPRSS2 almost to zero."

Furthermore, Alimonti said their findings from Italy confirmed the clear gender disparity in terms of COVID-19 severity.

"We have a higher prevalence of the infection in females compared to males in Veneto, but the infections in females were not severe. So, the rate of hospitalizations of the female population was really minor

Continued on page 19

ANDROGEN DEPRIVATION THERAPY

continued from page 18

compared to the one of males—and also the complication [rate] and the rate of death. So, we think that by lowering the level of androgen, we can reduce this risk [in men] and bring it to the level of a female. This would be a significant advantage if you think about this in a large scale," he noted.

Timely Treatment

Although the wider use of ADT in patients without cancer could not be endorsed before randomized study investigation, there was already a clear message for men who had the option of having their prostate cancer treated with any therapy, but had not yet decided which one. This evidence clearly pushed the choice in the direction of ADT, according to Alimonti.

"At the moment, there are many prostate cancer patients that are delaying this therapy because they don't have access to the hospital. For these patients, there is an indication for androgen deprivation therapy," he said. "But I strongly recommend that these people will start androgen deprivation therapy immediately because, of course, there is [already] an indication for that, plus they could be protected. Let's not delay the treatment."

Alimonti said the study findings prompted a promising line of investigation for managing COVID-19.

"We now have evidence based on this epidemiological study that patients affected by prostate cancer on ADT are protected. So, this should be used to run a prospective clinical trial. Although these data need to be further validated in additional large cohorts of patients with COVID-19, they provide an answer to the hypothesis that androgen levels can facilitate coronavirus infections and increase the severity of symptoms, as has been seen in male patients."

Editor-in-chief of the journal *Annals of Oncology*, Fabrice André, MD, PhD, Director of Research at the Institut Gustave Roussy in Villejuif, France, shared his thoughts on the study: "We decided to publish this study because it provides a rationale to evaluate the efficacy of ADT prospectively in patients infected with COVID-19. Nevertheless, the study does not provide a definitive conclusion about the role of ADT in patients infected with COVID-19, and this class of drugs should not be used for this purpose until prospective trials have confirmed its efficacy." OT

Peter M. Goodwin is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Distinguish the characteristics of androgen deprivation therapy (ADT) and of COVID-19 that lend support to the hypothesis that ADT might improve outcomes in men with COVID-19. 2. Synthesize the study findings and their implications for treatment and research.

Disclosure: The author(s), faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this activity, have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

MULTIPLE MYELOMA

continued from page 8

What further research needs to be done on this topic?

"The addition of selinexor to other backbone treatments has also shown promising results, whereas the SVd regimen has shown significant clinical activity in a randomized phase III study.

"Patient selection is necessary for determining the optimal selinexor-based combination according to disease status, previous exposure to anti-myeloma agents, and patient characteristics including age and comorbidities.

"Well-designed studies are needed to address the effect of selinexor in subgroups of patients of special interest such as those with ultra-high risk cytogenetics or extramedullary disease or involvement of the central nervous system or plasma cell leukemia.

"Ongoing and future studies will determine the exact position of selinexor-based treatments in the therapeutic continuum of patients with multiple myeloma."

Is there anything else about your research that you would like to share?

"There has been an unprecedented progress in multiple myeloma therapeutics with the introduction of several novel agents both in the upfront and the relapsed/refractory setting during the last decade.

"The availability of different agents poses two main challenges; the optimal sequence of treatment and the management of heavily pretreated patients. The introduction of novel agents from the bench to the bedside significantly contributes to the improvement of patient outcomes."

Editor's note: Ioannis Ntanasis-Stathopoulos, MD, MSc, PhD, a sub-investigator of the STORM clinical trial in the Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece, helped facilitate the interview with Dr. Gavriatopoulou and contributed to this article. OT

Chuck Holt is a contributing writer.