MANISH KOHLI: I am Manish Kohli, Associate Professor of Oncology in the division of Medical Oncology, Department of Oncology at Mayo Clinic Rochester. Our article, "New Developments in the Medical Management of Prostate Cancer," co-authored by Dr. Don Tindall and myself, will be coming out in the January issue, 2010, of the *Mayo Clinic Proceeding.*

Prostate cancer has, of course, is a very large public health burden. Over the last decade, there have been some reasons for hope in the progress of prostrate cancer, diagnosis as well as treatments, although, none of these have been to the point that they have decreased mortality and morbidity from the cancer in appreciable ways. The progress on the good part, the progress part, we have seen earlier diagnosis of cancer being the one particular reason why it could have impacted the decrease in mortality from prostate cancer during this time. On the other hand, what we have also seen is, with PSA screening, far more over-diagnosis of cancers, which may not have been responsible for any morbidity or mortality during the patient's life.

So the picture is mixed. The lack of progress is an issue in prostate cancer, and more clinical trials is the only way to go forward in fine-tuning both these aspects in the treatment of prostate cancer.

Prostate-specific antigen, or PSA, screening is a important tool in prostate cancer in many ways, but most importantly it helps us in monitoring disease and treatment effects over time. The controversial role, although, of PSA is in its screening upfront. To be called a good screening test, it has to show that it has impacted mortality from the disease. And because the natural history of progression of prostate cancer is so indolent and takes 10 to 20 years, many times, to have seen an impact from PSA screening and to be used as a screening test, we have not quite gotten over there completely.

In this regard, there have been stellar attempts from the PLCO trial, as well as the European Study for the Reduction of Prostate Cancer, which were published in 2009 recently. The results were after seven years of follow-up in the PLCO trial and about nine years of follow-up in the European trial.

The results of the PLCO trial did not show us clear-cut cut evidence that PSA is a good screening test, which will impact mortality. On the other hand, there were some flaws in this trial in the sense that the level of follow-up, longitudinal follow-up was, perhaps, not as good as it should have been and as mature, given the fact that this is an indolent cancer, takes time for the mortality to actually show up.

On the other hand, the European trial, which had a slightly longer follow-up of approximately nine years, did show that there was some evidence for PSA screening as a tool for preventing prostate cancer mortality. However, it also showed that you would have to screen about over 1,400 patients to diagnose one cancer, and then treat an additional 49 patients to get the prostate cancer specific mortality down. So you have to do a lot of work for that one patient that you would save, and it has to come down to society and to medical fraternity and patients to come together to understand and to weigh the pros and cons in this argument, in terms of using PSA as a screening tool. I believe we need more follow-up from these trials to be absolutely sure about PSA as a screening test, at least in the year 2009.

The stellar developments that have occurred in identifying at-risk populations are that we know through clinical means that patients who have family members, immediate family members, like father and brothers, who have a history of prostate cancer, that increases the risk of the person himself suffering from this problem. So that is an at-risk population cohort. Also, we know that there is a high risk of prostate cancer incidence in African Americans, although we don't quite understand why.

Beyond these critical issues that we already know for quite some time, there have been recent developments in finding out the at-risk and defining at-risk populations based on germline SNP data. And emerging sciences, which have come out, are now showing us that there is a set of SNPs, which, when taken together, perhaps, may identify beyond the clinical factors of family history and race a at-risk population. This is, although, a work in progress and is not yet mature enough, again, to be identified in a clinic and although, only in a research setting.

After having identified an at-risk population or person, it is now pretty much a good idea to consider giving that person one of the 5-alpha reductase inhibitors, which decreases the activity of dihydrotestosterone moiety, which is implicated and well-implicated in the biology of this tumor formation. So that drugs like finasteride and possibly drugs like dutasteride are good chemopreventive medications, either in the present or together in the future.

The difference between the two drugs is that finasteride is specifically an inhibitor of type two isoenzyme of this particular protein, 5-alpha reductase while dutasteride is a type one and type two isoenzyme inhibitor. It has, therefore, a greater degree of inhibition and is currently being tested in the ongoing Reduce trial. The Prostate Cancer Prevention trial told us that there is a good role for decreasing prostate cancer incidence with chemo prevention using finasteride, at least a 25% reduction, at least. So that's a good proven treatment of a chemopreventer.

In terms of androgen deprivation, it is the first line of management of this testosterone-driven tumor and as far as advanced stage, or what we call hormone-sensitive stage disease is concerned. It is also, although, combined with radiation treatments in earlier stages, as well as combined many a times with radical prostatectomy in slightly high-risk populations. Immunotherapy has been a recent advance in the advanced stages, wherein blocking specific pathways in the immunotherapy profile of a tumor has shown that it will help in increasing longevity of life in the advanced stages only, although. And by that, I mean either hormone-sensitive or what we now call following hormone-sensitive disease, castration recurrent disease.

I think the most important thing to remember for prostate cancer is that a lot of work remains to be done, in terms of both finding out good screening tools. The follow-up of the PCLO trials, along with the EPSRC trial, over time, with more maturity of data, will tell us much more than what we already know, in terms of using it as a screening tool, number one.

Number two, it is absolutely imperative that prostate cancer patients be encouraged to take part in clinical research trials. This is what changed the paradigm in decreasing mortality in breast cancer from the 1970s to 1990s and continues to be the case, wherein thousands and thousands of breast cancer patients participated in clinical trials to bring new treatments to the clinic for future patients. That, unfortunately, has not happened that robustly in prostate cancer. So that's the second take-home message, wherein internal medicine physicians could encourage patients visiting them with this diagnosis to seek out such a clinical trial as is appropriate for their stage.

And number three, it is important to work with medical oncologists, as well as urologists and radiation oncologists on your patient to give a fullness of approach from all three different angles in educating the patient regarding his stage of disease and his type of prostate cancer, because there's a fund of information available in that situation.

The promising areas of research in medical oncology treatments and medical treatments of prostate cancer are some exceedingly exciting drugs, which we will find out when the trials are completed whether they actually work, but at least based on the biology of this tumor, two particular drugs, which focus on the androgen receptor and the testosterone axis, in terms of bringing out a new standard of care after the failure of standard line hormonal treatments, are those two drugs being-- those two-- there are many drugs coming out in clinical trials, but specifically abiraterone acetate in the future, is a drug that might be helpful to us. And it remains to be seen whether it will get FDA approval to the point of showing that it is effective enough and is useful enough in the clinic, but early evidence appears to be very promising in this regard.

In addition to these hormonally-driven agents, immunotherapy is a very active and hot area being pursued, which we will possibly see some new advances in 2010 with approval of new immunotherapy-based drugs as well.

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