COUNTERPOINT: Men should be treated for hormone refractory prostate cancer with systemic chemotherapy when they are symptomatic, and not before

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The benefits of chemotherapy in men with symptomatic HRPC include pain relief, better physical functioning and improved quality of life. These have been well established in randomized trials. A meaningful or statistically significant improvement in survival has yet to be demonstrated. In the absence of a survival benefit, there is concern that treating men when they are free of symptoms may have a negative impact upon quality of life due to drug related toxicity. It will also limit or eliminate any therapeutic options when symptoms eventually develop and therapy is needed most.

Key Words: chemotherapy, HRPC, symptomatic

It is not difficult to justify the use of chemotherapy to treat *symptomatic* hormone refractory prostate cancer [HRPC]. As a medical oncologist who focuses on the treatment of prostate cancer, I have seen many patients who receive benefit from chemotherapy. This benefit has been gratifying for the patients, and for me as their treating physician. I have seen men previously disabled with progressive pain and fatigue return to normal activities, sometimes for long periods of time. There is toxicity associated with the agents used to treat HRPC; mitoxantrone is generally well tolerated but can cause some fatigue, nausea and myelosuppression, docetaxel has a somewhat higher rate of these problems. However, in patients who respond to therapy, the benefits associated with the improvement in the cancer usually outweigh the negative effects from drug toxicity. This personal experience is consistent with the literature on

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chemotherapy in HRPC, which has demonstrated that chemotherapy can significantly improve pain, physical functioning and overall quality of life in men with symptomatic prostate cancer.

The situation is different in men who are feeling perfectly well, but have a rising PSA, or other evidence of disease progression despite hormonal therapy. There are potential justifications for treating someone with cancer who is asymptomatic. The most important would be if there were evidence that the treatment improved overall survival. There is good evidence that patients are willing to experience unpleasant and complex therapies at a time they are feeling well, in order to lengthen their life by even modest amounts. As someone who has been working to find new and better therapies for prostate cancer, I really wish that we had found something that did improve survival in HRPC. Unfortunately the truth is otherwise, and despite numerous phase II and III studies there is no reliable evidence that chemotherapy will improve overall survival. The treatment of an asymptomatic man with HRPC could still be justified in the absence of a survival benefit if it could be demonstrated that the earlier use of treatment could improve quality of life as compared to waiting until patients develop symptoms. It would also be justifiable if it could be demonstrated that earlier treatment could delay or prevent serious complications such as spinal cord compression, as has been seen in studies of early use of hormonal therapy. No such data for quality of life improvement or prevention of serious complications exists for the use of chemotherapy in *asymptomatic* men with prostate cancer, and as such the use in this setting cannot be justified by the data we presently have available. It is clear that the PSA response rate is better when chemotherapy is used earlier, however unless this translates into some outcome of meaningful clinical benefit, such as survival or quality of life, then it is not an appropriate justification for early treatment.

There are potentially negative effects that can occur from treating men when they are feeling well. There is toxicity associated with the agents used to treat HRPC. In Canada our standard of care, mitoxantrone, is generally well tolerated but can cause some fatigue, nausea and myelosuppression. Docetaxel has a somewhat higher rate of these problems, and if combined with Estramustine the rates of severe and sometimes lethal toxicities are even higher. There is also a limit both to the amount of these drugs than can be given, and the number of useful agents that we have. The median duration of response [until resistance occurs] is around 8 months; also chronic cumulative toxicities such as cardiomyopathy and neurotoxicity occur if therapy is continued beyond this period. Thus the use of therapy when a patient is asymptomatic will limit or eliminate any therapeutic options when symptoms eventually develop and therapy is needed most.

The type of patients with HRPC that we are seeing in clinic has changed over the past 10 years. When we did our original studies with mitoxantrone most patients were referred when symptoms had developed. Now we are seeing many patients who have a low but rising PSA, no clear evidence of metastatic disease and are feeling well other than anxiety about the PSA. It may be between 6 and 24 months before these patients develop symptoms and given the limitations of current therapy the best we can do for these men is to allow them to enjoy this period of good quality time. Asymptomatic men do need to be closely monitored. The PSA doubling time is a critical parameter in determining how to approach these patients. If the PSA value is low, the doubling time is 2 months or greater and the bulk of disease is low then these patients should be followed, reserving chemotherapy for when symptoms develop. A reasonable argument can be made that chemotherapy should be used in an asymptomatic patient with a moderate to high volume of disease, and a rapid [< 1month] PSA doubling time as the duration of this period of feeling well is likely to be very short. However outside of this situation the use of chemotherapy in asymptomatic men cannot be recommended based on currently available data. □