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Development of Treatments for Localized Prostate Cancer in Patients Eligible for Active Surveillance: U.S. Food and Drug Administration Oncology Center of Excellence Public Workshop

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Abstract

Purpose: The following is a summary of discussion at a United States FDA (Food and Drug Administration) public workshop reviewing potential trial designs and end points to develop therapies to treat localized prostate cancer.

Materials and Methods: The workshop focused on the challenge that drug and device development to treat localized prostate cancer has been limited by the large trial sizes and lengthy timelines required to demonstrate an improvement in overall or metastasis-free survival and by the lack of agreed on alternative end points. Additionally, evolving treatment paradigms in the management of localized prostate cancer include the widespread use of active surveillance of patients with low and some intermediate risk prostate cancer, and the availability of advances in imaging and genomics.

Results: The workshop addressed issues related to trial design in this setting. Attendees discussed several potential novel end points such as a delay of morbidity due to radiation or prostatectomy and pathological end points such as Gleason Grade Group upgrade.

Conclusions: The workshop provided an open forum for multiple stakeholder engagement to advance the development of effective treatment options for men with localized prostate cancer.

Keywords

prostatic neoplasms; United States Food and Drug Administration; drug development; equipment design; research design

ON July 11, 2018 the FDA held a public workshop to discuss general principles regarding the development of new drugs, biologics or devices to treat localized prostate cancer.[1] Invited experts represented the urology, medical oncology, radiation oncology and patient advocacy communities.

In the last 40 years despite advances in many areas of oncology no treatments of localized prostate cancer have been approved. While devices have been approved as surgical tools to ablate prostate tissue, they are not indicated to treat any specific prostatic disease and were not studied in trials which would meet drug approval standards. Drug and device development for localized prostate cancer is difficult, given the long natural history of this disease, which makes trials with accepted end points such as OS or MFS difficult to perform in a timely manner. At a FDA/AUA (American Urological Association) public workshop held in May 2013 alternative practical or meaningful measures of clinical benefit to accelerate the development of treatment for localized prostate cancer could not be identified. [2] Despite this, there is still interest in developing devices and drugs in this space to reduce the morbidity of surgery and radiation.

The 2018 FDA workshop focused on identifying pathways to develop new products to treat localized prostate cancer with an emphasis on trial designs and potential alternative end points. Panelists identified key areas which would benefit from further study.

MATERIALS AND METHODS

The workshop morning session covered the role of focal therapy in treating patients with low risk prostate cancer. Presentations addressed regulatory considerations for localized prostate cancer, regulation of devices in this setting, and the appropriate use and patient population for focal therapy. Certain questions were posed. 1) Is there a role for focal therapy in the treatment of patients with low risk prostate cancer? 2) What should the eligibility criteria be for a focal therapy study and what is the ideal patient population to study? 3) How much weight should a delay in morbidity due to radiation or prostatectomy be given in the setting of potentially curable localized prostate cancer?

The afternoon session covered statistical issues surrounding trial design and end points for localized prostate cancer. Specifically the issues included whether delaying the morbidity of prostatectomy or radiation is clinically meaningful and, if so, how to design a trial to assess this end point. In 3 presentations trial design and end points, trial design considerations for

low risk localized prostate cancer and statistical considerations were discussed. Certain questions were posed. 1) What end points other than OS and MFS could be used in localized prostate cancer trials? 2) Does delaying morbidity due to prostatectomy or radiation represent a clinically meaningful end point? If so, a) How would you design a trial to prospectively evaluate this end point? b) Are there objective triggers for definitive therapy for patients on active surveillance? c) How would you minimize bias in this end point? 3) What pathological variables would you consider using as the basis of a trial end point in this setting, eg a Gleason Grade Group upgrade at a fixed time point? How would you incorporate other parameters (imaging, serologic and/or genomic)? 4) What magnitude of effect on the above end points would be clinically meaningful? 5) What minimum duration of followup for oncologic outcomes (eg MFS) should be built into trials of localized prostate cancer?

The workshop discussion is summarized.

RESULTS

Regulatory Background

Device regulation in the premarket setting includes a 3-tiered classification system based on complexity and risk.[3] A device with an indication to treat prostate cancer would be considered life sustaining and of substantial importance to prevent human health impairment and would likely be classified as Class III (high risk). A successful PMA (Premarket Approval) application (typical for a Class III device) to allow marketing a FDA approved device requires valid scientific evidence to provide a reasonable assurance of safety and efficacy.

In general device approval does not require demonstrating superiority in cancer control compared to existing therapies. Data to support adequate cancer control with an acceptable toxicity profile would likely be enough in this setting. Due to the lack of accepted and practical surrogate or intermediate clinical end points to reliably predict the long-term clinical benefit of treatment of patients with localized prostate cancer, demonstrating reasonable assurance of efficacy has been a significant hurdle for device development.[4,5]

To overcome this obstacle high intensity focused ultrasound devices were recently brought to the United States market via the De Novo process as Class II surgical tools with a claim to ablate prostate tissue. The evidence to support this indication was a demonstration of ablated tissue in the targeted region, which was measured by histology, imaging and biochemical changes, without significant ablation to nontargeted tissue, which was measured by adverse events. These prostate ablation devices are not indicated to treat any specific prostatic disease and clinicians in consultation with patients may decide how best to apply this ablation tool.[6] Anticipating that device manufacturers will pursue treatment claims of localized prostate cancer in the future, the FDA continues to explore trial designs to enable the appropriate study of such indications.

Drug approval is contingent on the demonstration of substantial evidence of safety and effectiveness based on adequate and well controlled studies. Direct clinical benefit is

demonstrated based on prolongation of life or a better life (eg increased survival, symptomatic or functional improvement) or an established surrogate end point. For drugs which treat serious and life threatening conditions accelerated approval is possible based on the demonstration of improvement over available therapies in an end point reasonably likely to predict clinical benefit and with the requirement to ultimately demonstrate direct clinical benefit in a confirmatory study or studies.[7]

Treatment Considerations

Given recent advances in imaging and ablative technology for localized prostate cancer since the 2013 workshop, the 2018 workshop revisited questions regarding treatment of localized prostate cancer and the potential for novel drug and device development. Although the majority of patients with low risk prostate cancer can be treated with active surveillance, a subset may be at higher risk for progression, including those with high volume disease, high prostate specific antigen density, high risk histological features such as intraductal cancer or cribriform histology and/or those with a high risk genomic profile. Approximately 50% of patients initially classified at low risk and who are placed on active surveillance proceed to treatment despite careful preselection.[8,9] Thus, there is room for improvement in patient classification and treatment. In some cases progression in an active surveillance population in the first 2 years may be due to misclassification at the time of initial diagnosis rather than to true clinical progression. New imaging modalities such as multiparametric MRI are becoming increasingly integrated into active surveillance algorithms in an attempt to reduce morbidity attributable to the frequency of on-study biopsies.

Patient Population

Criteria defining the appropriate patient population for enrollment in a randomized trial evaluating focal therapy vs active surveillance are not well established. This population may be best characterized as including patients considered at the higher end of the low risk category and a subset of patients at intermediate risk with Gleason 3 + 4 disease as defined by an intermediate risk CAPRA (Cancer of the Prostate Risk Assessment) score. This population would be best identified by the incorporation of multiple modalities in addition to clinical characterization, such as genomic profiling and MRI. Further data are necessary to establish the usefulness of genomic risk stratification at biopsy to determine patients at greatest risk for progression. Appropriate tumors, eg a tumor primarily confined to 1 lobe with a microfocus or no tumor in the contralateral lobe, would require identification based on imaging.

A potential concern is that randomizing patients with small Gleason 3 + 4 lesions to an active surveillance arm of a randomized study might be associated with an opportunity cost since the treatment margin might enlarge with the potential for increased morbidity and decreased likelihood of cure at the time of delayed definitive therapy.

Trial End Point

Considering the impracticalities of using OS or MFS as end points for localized prostate cancer trials, a potential novel trial end point which may demonstrate early evidence of clinical benefit would be to examine the delay in radiation or prostatectomy. While delaying

a major procedure and its associated morbidity may be considered a clinical benefit, an issue regarding this putative end point is the subjectivity associated with the decision whether to proceed to treatment with curative intent. Therefore, demonstrating a delay in an objective measure of cancer control (eg Gleason grade progression, an increase in the number or extent of cores, etc) could mitigate these concerns of bias. A path forward could include demonstrating a delay or prevention of cancer progression (cancer control) coupled with a delay or prevention of definitive therapy and its associated morbidities, including urinary incontinence and sexual dysfunction. This type of trial design would ideally require predefined criteria for triggers which would lead to intervention (surgery or radiation). These triggers could be based on histology, tumor volume, imaging, genomics or a combination.

DISCUSSION

Based on these factors, an example of a clinical trial was proposed for a therapy not shown to be curative (eg focal therapy) in an active surveillance population (see figure). The proposed trial design randomizes patients eligible for active surveillance to a novel therapeutic intervention plus active surveillance vs active surveillance alone at or shortly after diagnosis. The primary end point could be objective local disease progression and a key secondary end point would be time to local therapy with curative intent (ie prostatectomy or radiation therapy).

Because the true clinical benefit associated with delaying local therapy with curative intent is avoidance of morbidity, the safety profile must be carefully assessed and the tolerability of the therapy must be significantly better than that of the therapy which is avoided (prostatectomy or radiation therapy). Any improvement in the delay or prevention of local definitive therapies must be balanced by the potential for missing the window for cure. The trial would need to follow patients to collect data on the recurrence rate in those who eventually receive definitive treatment. Finally, long-term followup would be important to assess the cumulative toxicity of the intervention and whether therapy during active surveillance increases the morbidity associated with definitive prostatectomy or radiation, or subsequent salvage therapy should the disease recur.

Careful assessment of acute and longer term safety would be critical to ensure that the therapy did not result in worse toxicity than expected for local curative therapy. Because many toxicities associated with these therapies are symptomatic, emphasis would need to be placed on patient reported outcomes of symptomatic adverse events and function, including urinary and sexual dysfunction. Given the importance of a clear understanding of long-term outcomes, a post-marketing requirement would require prolonged followup to ensure no delayed harm, including worsened oncologic outcomes. This might be evaluated as descriptive safety data and might not require powering for non-inferiority or superiority.

Ideally the patient population in such a trial would be enriched for men at risk for progression, which could be aided using genomic or imaging features. Enrolling patients with Gleason Grade Group 1 could be problematic with some of these patients having a low volume of disease and a lower risk of progression. However, many patients with Gleason Grade Group 1 tumors who are treated with active surveillance ultimately receive local

definitive therapy, making enrollment potentially acceptable. Patients with Gleason 3 + 4 with a low volume of pattern 4 disease (ie those at favorable intermediate risk) are another potentially appropriate population for randomization to AS vs AS plus focal/nondefinitive therapy.

Given that the primary objective end point of the trial would be pathological progression, the trial design should attempt to minimize bias for this measure. The biopsy schedule and type would need to be balanced between the arms to minimize differences in assessment times and tissue sampling. Because a pathology review would drive the events, standardizing the pathological read, including a potential central review, may mitigate challenges of interreader variability. While imaging, including multiparametric MRI, is considered a promising end point, performance and interpretation standards are currently inadequate to use imaging as part of an end point. Challenges with enrollment may be an additional consideration in such a trial design as enrolling patients in randomized trials of focal therapy of prostate cancer has been challenging.

An important consideration would be to obtain data to support that early intervention to delay prostatectomy or definitive radiation does not harm patients by reducing the cure rate or adding synergistic toxicity to subsequent local therapies. Such data could be captured in a post-marketing requirement concentrating on long-term followup for outcomes such as biochemical recurrence, the need for salvage therapy, long-term safety and other important outcomes such as the development of metastasis. The minimum followup needed might be approximately 15 years, given a median time to metastasis of approximately 11 years in patients treated with focal therapy.[10]

Biochemical failure was discussed as an early safety signal compared to MFS or OS. Such a followup study should include patient reported outcomes and other clinical outcome assessments to capture urinary and sexual function as well as other symptom and functional outcomes important to quality of life.

Other possible trials could be designed in similar clinical contexts, including in the salvage setting following definitive radiation therapy and in patients on AS with disease progression on biopsy. These trials might require comparison of curative therapies for which the relevant end points would be different. Generally trials of focal and other therapies in the salvage setting were considered beyond the scope of the workshop.

CONCLUSIONS

There may be a population of patients appropriate for enrollment in a randomized trial evaluating focal therapy in the setting of active surveillance, although enrollment in randomized trials of focal therapy has proved challenging in the past.[11] A randomized trial of AS with and without focal therapy could incorporate a well designed primary end point to evaluate a delay in objective local progression, in addition to a corresponding end point supporting a delay in morbidity due to radiation or prostatectomy. A putative end point that demonstrates local progression would be in line with the established and objective criteria generally used to recommend definitive treatment.

One example of a pathological upgrade might be the detection of Gleason pattern 4, which is considered a well established indication for a patient to undergo curative local therapy. Additional objective criteria to recommend definitive treatment would need to be accounted for in such a trial end point. A trial done in the active surveillance population must carefully assess harm in the form of standard safety and PRO (Patient Reported Outcomes) assessments in the acute and followup treatment periods.

Anticipating that multiple stakeholders will continue to develop treatments in the evolving landscape of localized prostate cancer, the FDA encourages continued discussion of trial designs to enable the development of safe and effective therapies in this challenging context.

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Abbreviations and Acronyms

AS	active surveillance
FDA	U.S. Food and Drug Administration
MFS	metastasis-free survival
MRI	magnetic resonance imaging
OS	overall survival

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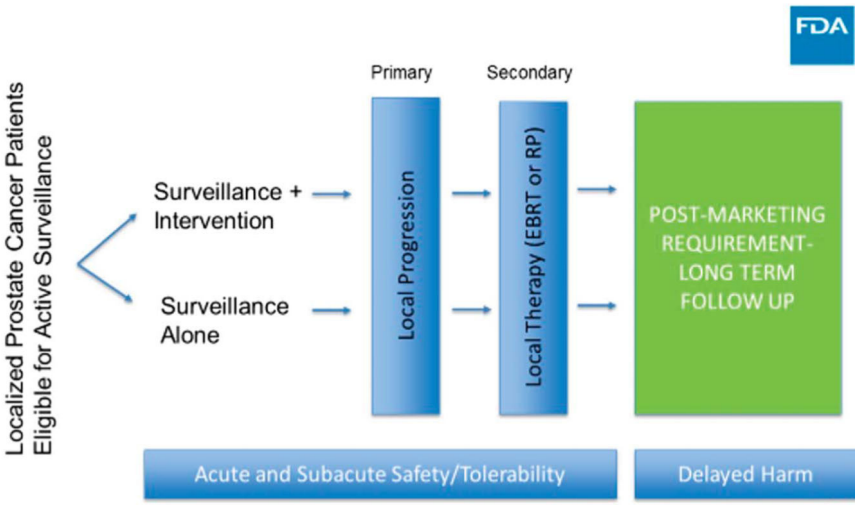

Trial design example shows how patients would be randomized to AS vs AS plus focal intervention and follow standard biopsy and clinical followup surveillance. Objective pathological and clinical progression criteria would be established to support primary end point. Key secondary end point would be reduction in number of patients who proceed to curative external beam radiation therapy (*EBRT*) or radical prostatectomy (*RP*). Safety and tolerability would be measured throughout and continue into postmarketing requirement followup.