Maximum Androgen Blockade: A Clinical Update

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Maximal androgen blockade (MAB) therapy for metastatic prostate cancer has advanced in recent years with the discovery of luteinizing hormone–releasing hormone agonists (LHRH), the development of LHRH analogues, and the discovery of antiandrogens. Of 36 studies of MAB therapy performed from 1980 to 1991, 3 showed a statistically significant increase in survival with MAB versus castration alone. Because of the large number of studies showing no benefit from MAB, a meta-analysis was performed on 27 studies. This meta-analysis demonstrated a survival benefit from MAB of only 3%; however, a critical review of the analysis revealed major flaws that raise serious questions regarding the validity of its findings. In addition, the fact remains that the longest survival reported for patients with stage M1 prostate cancer was 35 to 36 months, whereas the longest survival for castration alone was 32 to 33 months. Therefore, when physicians discuss treatment choices for patients with metastatic disease, MAB should remain a reasonable option.

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Despite improvements in early detection, some men still present with metastatic prostate cancer, and despite improvements in chemotherapy, the primary therapy remains androgen ablation. Huggins and Hodges[1] first reported this therapy more than 60 years ago. They found significant palliation for men who had symptoms of bone metastases. The reason androgen ablation has been so effective is that prostate cancer is a hormone-dependent disease. The original methods used to achieve androgen ablation were bilateral orchiectomy

and oral estrogen. The primary effect was to eliminate the production of testosterone by the testes, which accounts for approximately 95% of the androgens produced in boys. The remainder is produced in the adrenal glands.

Despite the initial benefit of castration, patients ultimately have prostate cancer progression. However, Huggins and Scott[2] derived a secondary benefit in these men by performing a surgical adrenalectomy. Apparently, even a small amount of testosterone can stimulate prostate cancer cell growth. The finding of a clinical benefit from eliminating all androgens produced in the body was the first demonstration of the benefit of maximum or total androgen blockade.

Years later, the concept of total androgen ablation was revisited following 3 important developments. The first was the discovery of the structure of luteinizing hormone–releasing hormone, or LHRH. This peptide is responsible for regulating the production of luteinizing hormone, or LH, which controls the production of testosterone in the testes. This regulation is maintained by a pulsed rather than a continuous release of LHRH.

The second development was the production of synthetic LHRH analogues. These peptides have slightly altered structures compared with LHRH and when administered continuously, have the paradoxic effect of completely suppressing the production of LH and testosterone. This finding created a form of medical castration as effective as bilateral orchiectomy.[3]

The third development was the discovery of a new class of compounds called antiandrogens,[4,5] which block the binding of dihydrotestosterone to the androgen receptor in the nucleus of prostate cancer cells. Antiandrogens also result in castration, although these agents are less effective than LHRH agonists or bilateral orchiectomy in men with metastatic disease.[6]

Results from Positive Clinical Trials of Maximal Androgen Blockade

In the 1980s, the concept of maximal androgen blockade (MAB) was revisited by simultaneously combining 1 of the antiandrogens with either medical or surgical castration in men with advanced prostate cancer.[7] These studies used either flutamide (Eulexin; Schering Corp., Springfield, NJ), nilutamide (Nilandron; Aventis Pharmaceuticals, Kansas City, MO), or cyproterone acetate as the antiandrogen. Cyproterone acetate is a steroidal antiandrogen in contrast to the other two drugs, which are nonsteroidal antiandrogens. From 1980 to 1991, approximately 36 prospective, randomized studies were performed, of which 27 were available for reevaluation. All patients had a minimum of 1 year of therapy with MAB. Three of the 27 showed a statistically significant increase in survival compared with medical or surgical castration alone.

The first study showing a benefit compared flutamide (250 mg 3 times a day) plus daily leuprolide (Lupron; Abbott Laboratories, Abbott Park, IL; 1 mg/d) to placebo plus leuprolide in men with stage M1 prostate cancer.[8] More than 600 patients were enrolled in this trial. The combination of flutamide and leuprolide resulted in a significantly longer progression-free survival ($P = .039$) and overall median survival (35.6 vs 28.3 months; $P = .035$) when compared with the control.[8] The authors performed an exploratory analysis to determine the impact of MAB according to the extent of metastatic disease. Minimal disease was defined as the absence of metastases in the skull, ribs, long bones, and soft tissues excluding lymph nodes. Patients with minimal disease who received MAB had an even greater difference in survival compared with men receiving monotherapy.

This study also included a crossover design. Once patients met the criteria for progression based on changes in the bone scan, their treatment was unblinded; those receiving placebo could then receive flutamide, whereas those initially receiving flutamide were treated according to doctor preference. This is the only study that provides any information about the impact of early versus delayed MAB.

In the second study, all men had stage M1 disease and underwent a bilateral orchiectomy. Then they were randomized to receive placebo or nilutamide 300 mg/d for 1 month followed by 150 mg/d.[9] After 8.5 years of follow-up, the MAB group showed a longer median time to progression (21.2 vs 14.7 months, respectively; $P = .002$) and significantly higher overall survival (37 vs 29.8 months; $P = .13$).[10]

The last study to show a significant benefit from MAB compared bilateral orchiectomy to monthly depot goserelin acetate (3.6 mg Zoladex) combined with flutamide (250 mg 3 times a day).[11] More than 450 men with stage M1 disease were enrolled in this trial. The study showed a 23% reduction in mortality; similar to the National Cancer Institute (NCI) trial[8], this translated into a 7-month increase in overall survival. This study also found that men with good prognostic factors had a reduction in mortality of 39%.

Meta-Analysis of MAB

Given the controversy over MAB and the large number of studies that showed no benefit from MAB, a large meta-analysis was performed combining the results from all 27 studies.[12] More than 8000 men served as

subjects in these combined trials, and approximately 90% had metastatic disease. The study was quite comprehensive, with the authors obtaining updated information from many of the studies, including those that were never published. The authors found that MAB using the steroidal antiandrogen cyproterone acetate was significantly inferior compared with the outcome using the nonsteroidal agents. In fact, using the combination of castration and cyproterone acetate, the survival was significantly inferior to that of castration alone.[12] When the analysis combined only the studies using nonsteroidal agents, a small but significant improvement in the 5-year survival rate was observed (27.6% vs 24.7%; $P = .005$).[12] Based on this report, many experts in the United States have felt that a survival benefit of only 3% from MAB is overshadowed by its cost and side effects. With so much emphasis placed on the findings of the meta-analysis, some questions regarding the reliability of these findings have evolved.

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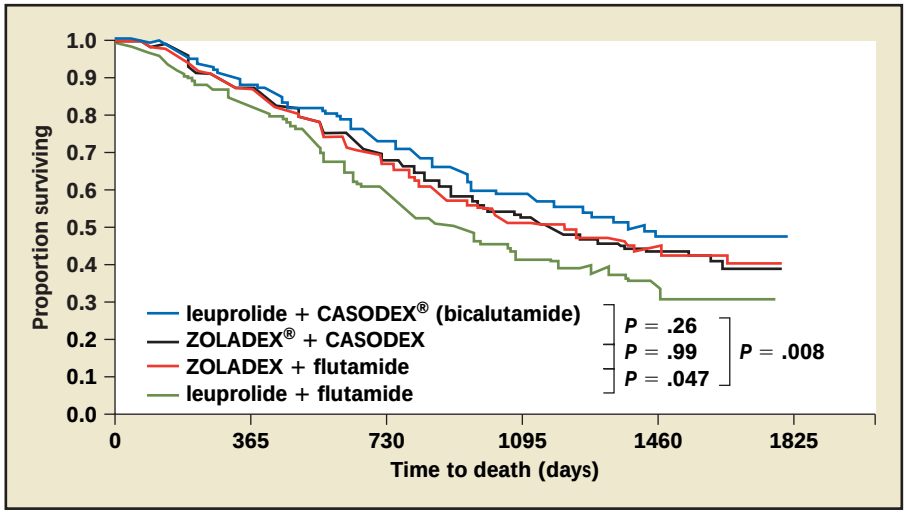
Is the Meta-Analysis of MAB Valid?

A critical review of the meta-analysis reveals 5 flaws that raise serious questions about whether its findings and conclusions are valid. The most important of these is the fundamental premise that all the combinations of castration and antiandrogens are equal. If they were not similar, however, then combining the different studies into the meta-analysis would not be justified. Unfortunately, the only data available suggest that not all MAB regimens are equally effective. For example, combining the studies comparing orchiectomy plus nilutamide with orchiectomy plus placebo had a relative survival risk of 1.68,[12] meaning that combination improved survival. In contrast, the same comparison using flutamide in place of nilutamide yielded a relative risk of only 1.22.[12] Given these differences, the studies involving flutamide should not have been combined with the studies using nilutamide.

Also absent were the implications of the 4-arm double-blinded comparison of MAB regimens: leuprolide plus flutamide, leuprolide plus bicalutamide, goserelin plus flutamide, and goserelin plus bicalutamide. This study found that the 2 arms using flutamide resulted in an inferior survival curve compared with the bicalutamide arms ($P = .047$) (Figure 1).[13] Also, the combination of flutamide and leuprolide gave significantly inferior results ($P = .008$) compared with the other 3 combinations. The authors never acknowledge this potential shortcoming in their report.

The next problem relates to the antiandrogen withdrawal phenomenon that was discovered years after the MAB trials were completed. Kelly and Scher[14] reported that approximately 50% of men with a rising prostate-specific antigen (PSA) level on an antiandrogen would have at least a 50% decline in PSA within 1 to 2 months of discontinuing the antiandrogen. PSA testing was not available when the MAB trials were designed. Patients continued on the antiandrogen until demonstrating objective evidence of disease progression on bone scan or computed tomography, or until death. Thus, patients were maintained on the antiandrogen much longer than is now known to be appropriate. In effect, the prolonged use of an antiandrogen may have

Figure 1. *Probability of survival in four groups receiving combined androgen blockade therapy. An exploratory analysis assessed the efficacy and tolerability of bicalutamide (Casodex; AstraZeneca Pharmaceuticals, Wilmington, DE) 50-mg tablets and flutamide, each in combination with a luteinizing hormone–releasing hormone (LHRH) agonist: goserelin acetate implant (Zoladex; AstraZeneca Pharmaceuticals) or leuprolide. A second exploratory analysis compared the combined antiandrogen regimens that were yielded by the two-by-two factorial design. Administration was double-blind for antiandrogen therapy and open label for LHRH agonist therapy. Reproduced with permission from Sarosdy MF.*[13]



accelerated disease progression in the patients on MAB. Had patients stopped the antiandrogen sooner, many of the trials might have detected a significant increase in survival in the MAB group.

The third problem was the failure to stratify patients according to the extent of metastatic disease. The assumption was that the effect of MAB would be similar for men with minimal versus extensive metastases. However, 2 of the 3 positive studies suggested that much greater differences occurred with MAB for patients with minimal metastases compared with those with more extensive metastases.[8,11] Because most of the studies were conducted in countries where men would likely be diagnosed with advanced metastatic disease, they would be less likely to find a significant improvement in survival. This problem also was not acknowledged.

Another reason to question the meta-analysis is that it combined both published and unpublished studies without showing similar outcomes. Klotz,[15] however, reanalyzed the results and found significant differences. Combining the published studies showed a significant benefit from MAB, whereas combining the unpublished studies failed to show a difference. Therefore, the results should have been shown stratified according to whether a study was published.

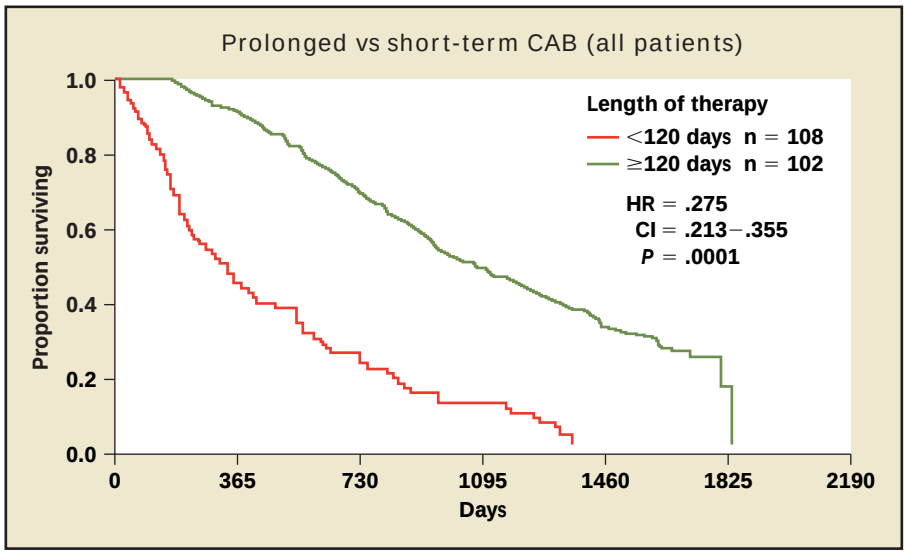
The last problem is that sample size from the individual trials was not addressed. Many of the trials enrolled too few patients to be capable of detecting a small but statistically significant difference. Combining several underpowered studies into one analysis does not eliminate the possibility that properly powered trials would have shown a benefit. Three of the 5 largest studies demonstrated a statistically significant improvement in survival.[8-11] The largest study compared orchiectomy plus flutamide to orchiectomy plus placebo.[16] Although this study showed a 10% difference in survival, the study had been powered to show a 24% difference. Hence, the difference of 10% did not reach statistical significance and for that reason, was considered negative. This problem could also explain the lack of greater differences between MAB and androgen suppression alone.

Is the Duration of MAB Important?

One other aspect of the studies on MAB that could have had an impact on the results is the duration of MAB. Many patients who initiated this treatment discontinued the antiandrogen prior to reaching 1 of the study endpoints. In the largest study of MAB, 5% discontinued flutamide because of diarrhea.[16] This may have contributed to a smaller improvement in survival than that observed in the NCI 0036 trial,[8] in which no patient discontinued the drug because of side effects. Sarosdy and colleagues,[17] using data from the 4-arm trial of different MAB regimens, assessed the impact of the duration of MAB. They found a very significant difference in survival for men on MAB for longer than 120 days compared with those with a shorter duration (Figure 2). Although the study was not designed for this analysis, which precludes firm conclusions, it suggests that another reason some studies of MAB could have failed to show a benefit is that the drop-out rate was significant.

Taken together, these problems provide strong evidence that the findings and conclusions of the meta-analysis are not valid. The fact remains that the longest survival ever reported in the literature for patients with stage M1 disease was 35 to 36 months, and that was achieved using MAB. The longest survival for castration alone was 32 to 33 months. As a result, when physicians discuss the options

Figure 2. *Prolonged versus short-term combined androgen blockade (CAB) therapy. An exploratory analysis looked at the effect of prolonged CAB, ≥ 120 days, versus short-term CAB on survival. The two groups analyzed were based solely on the duration of treatment. Using the Cox proportional hazards regression model, researchers analyzed survival data from a controlled trial that evaluated the safety and efficacy of bicalutamide (Casodex; AstraZeneca Pharmaceuticals, Wilmington, DE) 50-mg tablets and flutamide, each combined with leuprolide or goserelin acetate implant (Zoladex; AstraZeneca Pharmaceuticals), in 813 patients with stage D2 prostate cancer. An additional subanalysis involving patients who survived at least 2 years beyond the date of randomization (n = 544) was included to reduce study bias associated with shortened duration of therapy due to early death. Reproduced with permission from Sarosdy MF et al.*[17]



for treating patients with metastatic prostate cancer, MAB should remain a reasonable option. Although the overall benefit may be small, a subset of patients, most likely those in a favorable risk group, are likely to have a more substantial improvement in survival compared with androgen suppression alone. Many of those individuals may want to do everything possible to improve their outcome. For them, the benefits of the therapy will outweigh the cost and potential side effects. ■

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Main Points

- The finding of a clinical benefit from eliminating all androgens produced in the body was the first demonstration of the benefit of maximum or total androgen blockade.
- Total androgen ablation therapy has progressed with the discovery of luteinizing hormone–releasing hormones (LHRH), the development of LHRH analogues, and the discovery of antiandrogens. All 3 agents result in medical castration, but antiandrogens are not as effective as LHRH agonists or bilateral orchiectomy in men with metastatic prostate cancer.
- Two studies comparing flutamide, nilutamide, or cyproterone with placebo have shown significant increases in progression-free survival and overall survival with maximal androgen blockade (MAB) versus control. Another study demonstrated a reduction in mortality with MAB versus bilateral orchiectomy.
- Because a large number of studies showed no benefit from MAB, a meta-analysis was performed combining the results from all 27 MAB studies. The analysis showed a survival benefit for MAB of only 3%, leading many experts to believe the benefit was overshadowed by the therapy's cost and side effects.
- A critical review of the MAB meta-analysis found 5 flaws: 1) the fundamental premise that all combinations of castration and antiandrogens are equal, 2) the fact that patients may have been on antiandrogens longer than what is now considered appropriate, 3) the failure to stratify patients according to the extent of metastatic disease, 4) the combination of both published and unpublished studies without showing similar outcomes, and 5) the fact that sample size from the individual trials was not addressed.
- The longest survival ever reported for patients with stage M1 prostate cancer was 35 to 36 months, and that was achieved with MAB. The longest survival for castration alone was 32 to 33 months. Although the overall benefit of MAB may be small, it should remain a reasonable option when discussing treatments for metastatic prostate cancer.