Effectiveness of Maximal Androgen Blockade (MAB): illusion or reality?

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Two decades have passed since the concept of Maximal Androgen Blockade (MAB) was first applied to the clinical treatment of prostate cancer. The theory is that by cutting off the supply of androgen from the adrenal gland, androgen blockade of the prostate could be made more complete. However, to date the clinical benefit of MAB has failed to live up to the theoretically expected effect. Having said that, fundamental research and clinical trials in recent years do indicate that the benefit of MAB is not merely an illusion.

Key Words: advanced prostate cancer, hormone therapy, maximal androgen blockade, combined androgen blockade

Introduction

In 1982, Labrie et al[1] proposed a new hormonal therapy for prostate cancer. Since then, this therapy has undergone numerous clinical trials in the form of Combined Androgen Blockade (CAB) or Maximal Androgen Blockade (MAB). More recently, a number of meta-analyses of a group of randomized prospective studies have been published.[2-4] Nevertheless, the results of these trials have not necessarily yielded results comparable to what would be expected from theoretical predictions. Consequently, were there any flaws in the MAB theory? Alternatively, were there errors in the methods or interpretations of clinical trials? This paper will investigate these questions in the light of research findings released recently.

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Recent fundamental studies indicate that the MAB theory is valid and that developing a new type of MAB therapy is possible

Mohler et al[5] published an important finding about the impact of adrenal androgen. He did a comparative study of 22 samples of prostate cancer tissue and 48 benign prostate hypertrophy tissue samples presenting with local recurrence during androgen depletion therapy. The benign prostate cases had not been given hormonal therapy. Androgen Receptor (AR) expression and androgens within the prostate tissues were compared. Epithelial nuclei androgen receptor immunostaining in recurrent prostate cancer samples (mean optical density, 0.284 +/- SD 0.115 and percentage positive nuclei, 83.7 +/- 11.6) was similar to that of benign prostate samples (mean optical density, 0.315 +/- 0.044 and percentage positive nuclei, 77.3 +/- 13.0). Tissue levels of testosterone were similar in recurrent prostate

cancer (2.78 +/- 2.34 pmol/g tissue) and benign prostate samples (3.26 +/- 2.66 pmol/g tissue). Tissue levels of dihydrotestosterone, dehydroepiandrosterone, and androstenedione were lower (Wilcoxon, P = 0.0000068, 0.00093, and 0.0089, respectively) in recurrent prostate cancer than in benign prostate samples, while the mean dihydrotestosterone levels, although reduced, were 1.45 nM. Androgen receptor activation in recurrent prostate cancer was suggested by the androgen regulated gene product, prostate-specific antigen, at 8.80 +/- 10.80 nmol/g tissue. These findings indicate the following. First, testosterone and dihydrotestosterone occur in recurrent prostate cancer tissue at levels sufficient to activate androgen receptors. This means that adrenal androgen has a strong impact on migration for apparent hormone refractory prostate cancer (HRPC); this is a finding that justifies therapy to remove adrenal androgen in combination, in other words, MAB therapy. Furthermore, Chen et al[6] studied the mechanism that would lead to resistance to anti-androgen therapy at the molecular level. They created an androgen- resistant sub-strain from seven groups of human prostate cancer strains and compared it with the parent, androgen- sensitive strain using a cDNA array. Among 12,559 genes, it was discovered that only the expression of AR genes in the sub-strain had increased greatly.

In addition, in all the sub-strains, increases in AR protein were seen. The androgen- resistant cell strains that had AR genes inserted multiplied quickly in castrated mice. By contrast, multiplication slowed down in AR knockdown mice. At this point, the cells that had multiplied in a low-androgen environment escaped from knockdown and expressed AR. These findings indicate that an increase in AR expression is the cause of, and pre-requisite for, androgen resistance acquisition. Also, Chen et al studied the ligand dependency of AR using RI labeling. They found that even in non-dependent multiplication, AR showed ligand bonding. Therefore, even in a low-androgen environment, this suggests that a certain level of increase in expression of AR is necessary. It is thought that this induction towards androgen resistance through AR is dependent on endonucleic signals. Research by Chen CD et al proved that the increase in AR expression switches AR antagonists to AR agonists and changes the distribution of coactivators and corepressors.
These two studies open up the following vista for MAB:

- the importance of eliminating adrenal androgen;
- conventional anti-androgen drugs sometimes work as agonists so there is a need to develop a new drug to overcome androgen withdrawal syndrome;
- MAB as it exists is theoretically inadequate;

If accurate control of adrenal androgen were to become possible, MAB may well become a powerful method of treatment.

Could previous MAB trials have accurately assessed the outcome?

There have been many results published for MAB trials. Several excellent meta-analyses have been made and assessments have been made on MAB in one sense. That is to say, "MAB in combination with an LHRH agonist or surgical castration and antiandrogen drugs only give a short-term survival benefit for advanced prostate cancer patients who have not yet been given hormone therapy. What is more, the deterioration of QOL is serious due to the side effects of the additional antiandrogen drug, and it is not reasonable to recommend MAB across the board." Now, are these judgments correctly assessing MAB? For the following reasons, we believe they are not: 1) in most MAB trials, the patients were aged over 70 so, 2) many of their deaths were not due to prostate cancer, and in addition, even in cases of death caused by prostate cancer, it was not necessarily easy to make that judgment; 3) many patients that were experiencing disease progression who were randomized by a castration single arm were thought likely to receive additional treatment with antiandrogen drugs; 4) due to adverse reactions, treatment had to be withdrawn for a relatively large number of patients allocated to the MAB group; 5) besides, as regards the judgment that the MAB group had an inferior QOL, many cases were probably due to an adverse reaction to flutamide. These observations point to the need for resolving all the above issues in order to make an appropriate clinical evaluation of MAB.

Into a new era of MAB

Although the hurdles described above have not been fully cleared, we have been conducting an MAB trial that has solved some of the problems. That is to say, we chose to use bicalutamide, an antiandrogen which has fewer adverse reactions compared to flutamide.[7,8] Moreover, our clinical trial has used this antiandrogen drug in a double

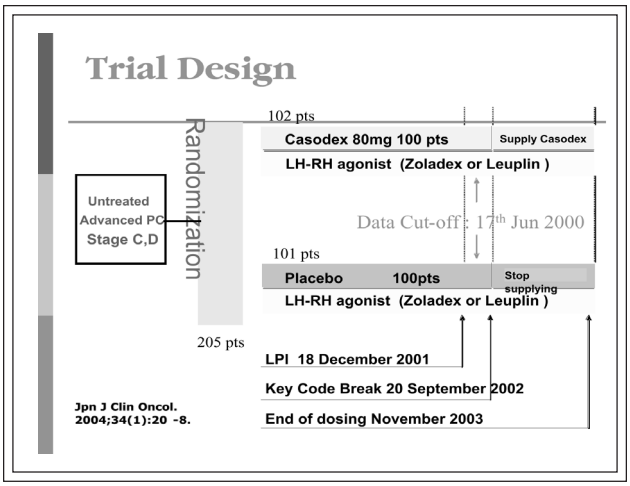

Figure 1. Casodex: product name of bicalutamide in Japan.

blind fashion. Figure 1 shows the protocol. The primary purpose of this trial is to investigate whether this treatment is appropriate; therefore, the primary endpoint is the response of the tumor to the drug in the 12th week after treatment starts and a comparison of treatment withdrawal due to adverse reactions. The secondary endpoint includes time to progression, time to treatment failure, survival, QOL and treatment safety. A total of 205 patients with previously untreated stage C/D prostate cancer were randomized (1:1) to receive once-daily bicalutamide 80 mg or a placebo, each combined with a luteinizing hormone-releasing hormone (LHRH) agonist. Primary study variables were the 12-week prostate-specific antigen (PSA) normalization (i.e. PSA level <or = 4 ng/ml) rate, the 12-week overall tumor response rate (proportion with a partial response or better) and the proportion of withdrawals due to adverse drug reactions (ADRs) at follow-up. The interim analysis was undertaken after a minimum of 6 months' follow-up (median 15 months).[9] The 12-week PSA normalization rate was 79.4% for MAB and 38.6% for LHRH agonist monotherapy (P < 0.001), while the 12-week overall tumor response rates were 77.5% and 65.3%, respectively (P = 0.063). The withdrawal rates due to ADRs were 8.8% and 10.9% respectively. There were differences in favor of MAB over monotherapy with respect to time to treatment failure (TTTF) (P = 0.038) and time to progression (TTP) (P = 0.016). There have been too few deaths (n = 10) to analyze survival. The profiles of adverse events and ADRs were broadly similar in the two treatment groups. This trial is ongoing.

In September 2002, we opened the key and the above analysis was made. After that, the administration of placebos to the placebo group was terminated. Until disease progression is witnessed, we will continue to give the LHRH agonist in principle. When disease progression has been observed in this group, bicalutamide 80 mg/day as a second therapy has been added. For the drug group, the administration of bicalutamide has been continued. At the point when disease progression has been noted, antiandrogen withdrawal syndrome has been observed. At 128 weeks after the clinical trial started (median point), out of the 101 cases receiving the placebo 40 showed disease progression and bicalutamide was added to their treatment. Of these, in 31 cases (77.5%) PSA was again observed to drop by 50% or more. In the drug group, 18 cases out of 102 showed disease progression and AWS observation was started. Of these, AWS was observed in seven cases (38.9%). In the comparison of QOL, FACT-G FACT-P[9,10] was used. Observations were made at four points, 1 week before the start of the trial, 1 week after the start of the trial, and 5 weeks and 24 weeks after the start. At present, we are preparing a report on the detailed findings, but under all the observation headings, the cases that were given actual drugs have been seen to have a good QOL. This trial is unique among comparable trials because we used a double-blind test in the allocation of antiandrogen drugs and because we used bicalutamide, a drug good drug compliance with fewer adverse reactions compared to similar drugs and because it has a long half-value time in the blood. At present, longer term observation is ongoing. In the near future, a clearer outcome is expected.

Conclusion

It is possible to eradicate testicular androgen by almost 100% using an LHRH agonist or surgical castration. However, a method to 100% control the production of adrenal androgen has yet to be perfected. The latest findings indicate that the cause of hormone receptor deviation in prostate cancer is actually chiefly due to the relatively small amount of androgen coming from the adrenal glands. In other words, these are not deviations from completed androgens, but merely apparent HRPC. This fact signifies that the MAB concept has not yet been accurately demonstrated. As was mentioned in the section above, the interim results of the

clinical trial conducted under a new trial design indicate that MAB can actually become a powerful method of therapy. By controlling the increased androgen receptors themselves or the signal transmission from them, ideal MAB looks one step closer. □

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