Editorial

Personalized peptide vaccine in prostate cancer: capitalizing on existing immunity

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As immunotherapy takes the center stage among emerging cancer strategies, recent data in prostate cancer was striking at first glance. Dr. Yoshimura and colleagues enrolled men with castration resistant prostate cancer (CRPC) from two institutions in Japan to either treatment with 1 mg dexamethasone alone or in combination with immunotherapy (1). The immunotherapy strategy in this trial was personalized to the existing anti-tumor humoral responses existing within each patient. Once existing IgG responses were detected and matched to at least one of 24 "warehouse peptides", the appropriate peptides were administered subcutaneously every 2 weeks until progression, death, or intolerance. Patients could receive up to four peptides matching existing IgG findings in their blood. Progression was determined based on PSA parameters. Patients on the control arm were allowed to cross over.

This study randomly assigned 37 patients to the vaccine arm and 36 patients to the dexamethasone arm. All patients were required to have progressive CRPC, HLA-A02, A03, or A24, and positive IgG responses to at least one of the 24 stock peptides. The primary endpoint was time to PSA progression which substantially favored the vaccine cohort (22.0 *vs*. 7.0 months; 95% CI, 0.222–0.684; P=0.0076) even though major PSA response rates (>50% decline) were not statistically different (59.6% *vs*. 54.3%). Median time to chemotherapy initiation also favored the vaccine cohort (52.4 *vs*. 23.8 months; P=0.047) as did overall survival estimates (73.9 *vs*. 34.9 months; HR =0.412; P=0.00084). Post-study treatments reported in the manuscript appear balanced with 14 in the vaccine cohort *vs*. 19 in the dexamethasone alone arm getting docetaxel. Use of enzalutamide and abiraterone was rare (only 1 patient in the vaccine arm and 2 patients in the dexamethasone cohort), likely because the study preceded the approval of those agents (1).

These findings are remarkable on many levels. Perhaps most surprising for practitioners who struggle in treating CRPC is the major PSA response rates in both groups, thereby suggesting this was an effect of 1 mg of dexamethasone. The fact that dexamethasone alone could have this large an impact (20% of whom had PSA responses greater than 90%) is somewhat unexpected. The other finding of note, is the timelines for overall survival surpass what has been seen in phase 3 trials with abiraterone and enzalutamide in metastatic CRPC by almost 2-fold (32–35 *vs*. 73.9 months in this trial) and most patients did not receive these agents after this study (2,3).

Although not completely clear from the data presented, there are several possible explanations for the remarkable findings in this study which seem discordant with other trials in metastatic CRPC. The most likely explanation, however, is that this was a very early population of CRPC patients without metastasis on conventional imaging at the time of enrollment mixed in with metastatic CRPC patients. The baseline patient characteristics suggest that 22 of the 73 patients were not metastatic at enrollment and with another 23 having "lymph node" sites of metastasis. It remains unclear how many of those sites were diagnosed and resected at surgery since eligibility allows "regional lymph nodes and/or distant metastasis at diagnosis." Thus it seems likely that the data from this study are most

appropriately compared with the CHAARTED study where patient survival beyond 5 years was common and even more likely if those patients had low volume of disease, a distinction not defined by Yoshimura *et al*. (1,4). Early CRPC could also explain the exquisite sensitivity of PSA to 1 mg of dexamethasone seen in both groups. Another study that could be a relevant comparison was study of denosumab in CRPC patients without metastasis. In that trial of 1,432 men, metastasis free survival ranged from approximately 25–30 months. This may help better understand some of the time to progression data provided by Dr. Yoshimura and colleagues, although that seems to have primarily been based on PSA (5).

With the context of this trial better defined, the apparent treatment effect of the peptide vaccine cocktail can be appreciated. All patients enrolled were required to have existing evidence of circulating IgG antibodies against peptides thought to be relevant in prostate cancer. Although no subsequent immune data is presented with regard to how either dexamethasone or the peptide-based therapies augmented those immune responses, the strategy is noteworthy. Currently, a subset of immunotherapy in clinical development is focused on developing personalized immunotherapy, but in a more labor intensive manner that will cost substantial time and money. Those strategies often involve biopsying tumor, identifying (neo)antigens in the tumor *ex vivo* and directing immune cells against those immunologic targets. The alternative strategy that Dr. Yoshimura and colleagues propose is more elegant in its simplicity. Once existing immune responses are identified perhaps they could be amplified by peptide-based or other immune strategies.

Despite the possible imbalances in the two arms that may not have been accounted for (true metastatic disease at study entry and/or disease burden) the PSA progression of 22 *vs*. 7 months is noteworthy and may appear to contradict existing data with sipuleucel-T in metastatic CRPC where PSA declines are not common (6). It is, however, important to realize that the dexamethasone in this population was very capable of decreasing PSA values in the majority of patients. Thus, this data is not directly comparable to the sipuleucel-T phase III trials which did not allow other agents that lowered PSA. Perhaps the sipuleucel-T data most similar to this study comes from the castration sensitive setting where that sipuleucel-T was combined with one dose of androgen deprivation therapy. The results of the study showed that after testosterone recovery, patients treated with sipuleucel-T had 48% decrease in PSA rate of rise as measured by PSA doubling time (155 *vs*. 105 days, P=0.038) (7). The ability for immunotherapy to slow PSA growth rates has also been demonstrated retrospectively with pox-viral based vaccine prostvac (8). Therefore, although sipuleucel-T and other immunotherapies in prostate cancer have yet to demonstrated a time to progression benefit in large studies, based on the potential to decrease tumor growth rates, it has been hypothesized that combining immunotherapy with agents that decrease PSA could alter PSA progression in ways similar to was reported in this study by Dr. Yoshimura and colleagues (9). Despite the controversies surrounding PSA and the fact that it is no longer the primary means to measure disease progression in metastatic prostate cancer, the PSA progression findings in this study is buttressed by the overall survival data which also favors the vaccine cohort (73.9 *vs*. 34.9 months).

Given the questions that remain regarding this study and its design, an additional study with a better defined and a more uniform patient population is required. Perhaps, early CRPC prior to metastasis would be reasonable with a PSA progression endpoint that could provide greater confidence in the findings presented in this study.

At the current time, this study is important and raises broader questions in the burgeoning field of immune-oncology. Could other vaccine strategies or checkpoint inhibitors be used as part of this approach or in a similar manner to augmenting an existing immune response? Perhaps, but the concern would be how many patients have underlying immune responses present? Based on the data presented in this paper, only 10 of 83 did not meet eligibility criteria, suggesting that at most only 12% of the screened patients did not have pre-existing immunity, under the presumption that all patients were excluded for that reason (1). These findings would require broader assessment for confirmation.

If the findings of this study can be confirmed, current immunologic strategies may change or evolve in a different direction. Current approaches either favor providing the immune system with general target (such as prostatic acid phosphatase with sipuleucel-T) or selecting a target *ex vivo* after a biopsy. There is logic, however, to identifying the immune responses each patient has already generated against the tumor and further augmenting them as was done in the study by Dr. Yoshimura and colleagues. While the counter argument could be that the cancer has already grown despite this underlying immune recognition, it is likely that that those existing immune cells are still

capable of an anti-tumor response. Indeed, this is likely the mechanism by which therapies targeting PD1/PDL-1 have their effect, by unlocking immune cells that are mitigated in the tumor microenvironment by PD1/PDL-1 interactions between the tumor and local immune cells.

The greatest, and perhaps as yet untapped, strength of the immune system is that it has many facets and components. Thus future immunotherapy strategies will likely seek to activate different aspects of the immune system. In this context, a component of therapeutic approach could simply augment on-going humoral responses could be appealing. Regardless of the confirmatory studies for the data presented by Dr. Yoshimura and colleagues, optimizing immune responses in patients may logically begin by enhancing existing immune activity and adding additional therapies to capitalize on them.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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