

New treatment modalities with vaccine therapy in renal cell carcinoma

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Abstract

The aim of implementing vaccine therapy is to activate immune response against malignant cells by overcoming the tolerance triggered by the tumor. These treatments are effective using the immune response against cancer. Not every type of cancer is suitable for vaccine therapies. For a vaccine therapy to be implemented, cancer should be immunogenic and contain tissue-specific proteins, should have a slow progression, and treatments should be feasible. For that reason, studies regarding urological cancers are mostly focused on the kidneys and the prostate. Vaccine therapies used in renal cell carcinoma (RCC) can be categorized under the following titles: autologous tumor cells, dendritic cells, genetically modified tumor cells, and protein/peptide. Although there are old studies on the implementation of vaccine therapies in RCC, researches have only been intensified recently. In addition to their effective potential for lengthening general survival, decreasing tumor burden and cancer development in long term, vaccine treatments are especially effective in metastatic RCC patients. We think that vaccine treatments would be applied more in near future since RCC are immunogenic. In this compilation, we will discuss vaccine therapies used in RCC, which urologists are not so familiar with, in the light of the up-to-date literature.

Keywords: Autologous tumor cell, dendritic cell, immunotherapy, renal cell carcinoma, vaccine therapy

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INTRODUCTION

Not every type of cancer is suitable for vaccine therapies. For a vaccine therapy to be implemented, cancer should be immunogenic and contain tissue-specific proteins, should have a slow progression, and treatments should be feasible. For that reason, studies regarding urological cancers, most of which are phase 1/2 and phase 3, are mostly focused on the kidneys and the prostate.^[1,2]

The aim of implementing vaccine therapy is to activate immune response against malignant cells by overcoming

the tolerance triggered by the tumor. These treatments are effective using the immune response against cancer. The first oncological vaccine therapy ever published in the literature belongs to Coley dating back to 1893. In that study, it is demonstrated that inoperable soft tissue sarcomas regressed by stimulating nonspecific immune response with streptococcal toxins.^[3] Vaccine therapies used in renal cell carcinoma (RCC) can be categorized under the following titles: autologous tumor cells, dendritic cells (DCs), genetically modified tumor cells, and protein/peptide.^[4] Although there are old studies on the implementation of vaccine therapies in RCC, researches

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have only been intensified recently. In this compilation, we will discuss vaccine therapies used in RCC, which urologists are not so familiar with, in the light of the up-to-date literature.

METHODS

Search strategy

We searched the following electronic databases from inception until September 2017: PubMed, Medline, and Embase (Excerpta Medica Database). The following search strategy was modified for the various databases and search engines: RCC, immunotherapy, vaccine therapy, autologous tumor cell, DC, and genetically modified tumor cell. We also searched among the references of the identified articles. If it was not clear from the abstract whether the paper might contain relevant data, the full paper was assessed. Along with MeSH terms and relevant keywords, we used the Cochrane Highly Sensitive Search Strategy for identifying reports of articles in PubMed. We restricted the search to articles published in English.

Types of studies

Original articles, systematic reviews, and meta-analyses.

Inclusion and exclusion criteria

Based on the key questions, we came up with inclusion and exclusion criteria. Included were abstract and full articles written in only English language and reporting on RCC, immunotherapy, vaccine therapy, autologous tumor cell, DC, and genetically modified tumor cell. Full text of inaccessible studies and articles not written in English were excluded. A total of 44 studies were included in this review.

Data extraction and management

Based on the predetermined selection criteria, two authors (MGS, LÖS) independently selected all trials retrieved from the databases and bibliographies. Studies were reviewed for relevance based on the RCC, vaccine therapy, and outcomes.

We retrieved full-text copies of the articles identified as potentially relevant by review author. The flow of study selection is described in preferred reporting items for systematic reviews and meta-analyses diagram [Figure 1]. Data are reported in a narrative manner.

HOW DOES IMMUNE RESPOND AGAINST CANCER OCCUR?

First, the macrophages phagocytose cancer cells as the cancer cells start to reproduce and at the same time, other cancer

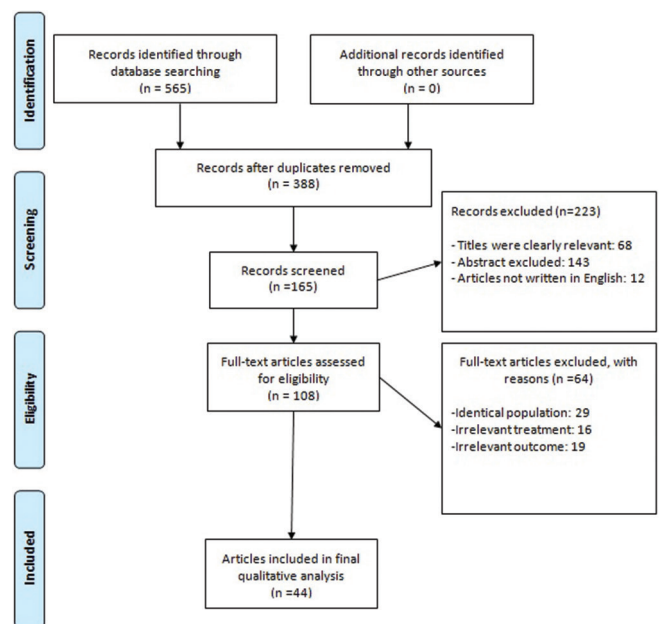


Figure 1: The search strategy and the selection process

cells also occupy the tissues and cells nearby. Macrophages suppress cancer cells and demonstrate the antigenic parts of cancer cells on the surface. T helper cells then recognize the presented antigens through binding with macrophages (DCs). This binding causes the release of many cytokines from both cells. Thus, an antigen presentation occurs as an immune response to cancer. The released cytokines induce the formation of more cytokines and antibodies by stimulating interleukin 2 (IL-2), T helper, cytotoxic T and B cells, especially. Induced cytotoxic T cells lead toward cancer cells carrying the same antigen and start to form holes on them. Thus, a cytotoxic effect is presented against cancer. Finally, the antibodies released from B cells bind to free-floating cancer cells and a target to be destroyed is shown to the macrophages and the complement system is activated. When cancer cells are taken under control, B and T cells are pacified by suppressor T cells. Memory T and B cells stay ready to respond fast if antigens for cancer cells are noticed.^[5,6]

AUTOLOGOUS TUMOR CELL VACCINES

Cell-based vaccines basically consist of nonviable autologous tumor cells and antigens to form immune response. These vaccines induce cytotoxic T lymphocyte (CTL) response by expressing tumor-related antigens in RCC. As adjuvant to increase immune response provided by vaccines, IL-2, IL-12, granulocyte monocyte colony-stimulant factor (GM-CSF), and bacillus Calmette–Guerin (BCG) can be given.^[7,8]

After giving BCG as adjuvant in the phase 2 study made with 120 T3a-b N0 M0/T2-3 N1 M0 RCC patients with

nephrectomy, irradiated mixed autologous tumor cells were given intradermally as vaccine, and the patients were followed up for 61 months in average and the 5-year progression-free survival was reported as 63% in these patients.^[9] In the phase 3 study including 379 T2-3b N0 M0 RCC patients, the patients were given irradiated autologous tumor cell lysate “RENIALE” after nephrectomy. 5-year progression-free survival was measured as 77.4% in medicine group and as 67.8% in control group.^[10] In the phase 3 updating study made with 477 patients who were given RENIALE treatment, no difference was observed in general survival although progression-free survival was better than the control group.^[11]

A significant general survival improvement was detected in especially phase T3 patients in the 10 year-retrospective evaluation of 692 T2-3 NX-2 M0 RCC patients who took RENIALE.^[12]

Autologous tumor cell vaccines metastatic studies

In phase 2 study made on 33 metastatic RCC (mRCC) patients given autologous tumor cell vaccine, objective response was observed in eight patients. While the general survival was 17 months, average survival was measured as 32 months in these patients. However, this was stated to be statistically insignificant.^[13]

Irradiated tumor cells were used in 14 patients with mRCC (patients were applied BCG, interferon alpha and beta as adjuvant) and it was reported that five patients had stable disease and minor response was acquired in three patients.^[14] It was not possible to acquire an objective response to the vaccine in a similar study.^[15]

In phase 2 study made on 31 phase 4 RCC patients, autologous large multivalent immunogen (LMI) acquired through the application on immobile autologous tumor cell on 5 mm diameter silica particles was given to the patients. The aim here is to increase the tumor-specific CTL response. Decreasing repressor T cell activation and increasing the immune response were aimed by giving adjuvant cyclophosphamide, IL-2 to the patients. Patients were separated into three groups, and stable disease was detected in five patients in LMI group and in four patients in LMI + cyclophosphamide group, and in LMI + cyclophosphamide + IL-2 group, stable disease was detected in three patients and partial response in one patient. Although a positive clinical response was observed in this study, no explicit proof was reported to evaluate the immune response.^[16,17] Based on these studies, we can conclude that autologous cell vaccines are safe and effective as adjuvant in kidney tumors, but more studies are needed on this subject.^[17]

Obara *et al.*^[18] applied HLA-A 0201/0206-restricted epitope peptide (HIG2-9-4) vaccine on nine patients who had metastatic or unresectable RCC after failure of the cytokine and/or tyrosine kinase inhibitor (TKI) therapies in the phase 1 study. Peptide-specific CTL responses were detected in eight out of nine patients. The disease control rate (stable disease for ≥ 4 months) was reported as 77.8%, and the median progression-free survival time as 10.3 months.

GENETICALLY MODIFIED TUMOR CELL VACCINES

In order to increase immunological response in these vaccines, autologous or allogeneic tumor cell vaccines are binded with cytokine and co-stimulatory molecules such as B7 (CD80), GM-CSF, IL-2, IL-12, and interferon-gamma. The aim here is to reveal the activation of T cell and natural killer cells through local cytokine release and to induce inflammatory response toward tumors at the same time.^[17]

GM-CSF transfer was made in 16 mRCC patients through retroviral vector on autologous tumor cells. A statistically significant clinical response was not observed although an increase was detected in immune response in the study.^[19]

In the phase 1 study made on 13 patients, genetically modified tumor cell vaccine (GMTV) was combined with B7-1 (CD80) gene as costimulator, and the patients were given IL-2 as adjuvant, and as a result, partial response and stable disease were detected in two patients each.^[20]

In the phase 2 study made on 30 mRCC patients, irradiated allogeneic GMTV and IL-2 mixture were given, and complete response was reported in one patient, partial response in four patients, and stable disease in nine patients.^[21]

In the phase 2 study made on 39 mRCC patients, autologous GMTV transduced with irradiated B7-1 (CD80) gene was given, and although there was a high rate of remission in tumor cells, complete response was reported in one patient, partial response in two patients, and stable diseases in 25 patients.^[22]

TG-4010, a recombinant modified vaccinia virus (MVA) expressing IL-2 and MUC1 antigen, has previously been investigated in a phase 2 study on 37 patients with treatment-naïve mRCC. However, TG-4010 showed low activity and was not developed further for this indication.^[23]

Hillman *et al.*^[24] TG4010 vaccine (MVA-MUC1-IL-2 cancer vaccine) therapy with radiotherapy on murine RCC

cells lead a significant delay on tumor growth, 55%–58% complete respond and a long-term survival in %60 of mice with combined treatment.

Buchner *et al.*^[25] reported that the application of RCC26/CD80/IL-2 vaccine cells was feasible and safe in mRCC patients. There was no evidence for severe local or systemic side effects, and the clinical effect of the vaccination protocol was limited in these very advanced mRCC patients and appeared to be associated with positive skin reaction.

These vaccines appear to be advantageous in these studies. Advanced researches are required for certain results.

DENDRITIC CELL VACCINES

Primary immune response is targeted by transferring DC-cultured tumor-related antigen or tumor cell lysates to the patient. Monocyte-derived DC applications are more common.^[26]

Van Poppel *et al.*^[27] combined all studies on this subject (21 studies) in a meta-analysis of 296 patients in 2009 and reported complete response in 4, partial response in 12, and clinical response in a total of 95 patients (37%) including 12 patients for partial response and 79 patients for stable disease.

Laurell *et al.*^[28] injected pro-inflammatory allogeneic DCs (INTUVAX) in the kidney tumor in 12 mRCC patients in intermediate- and poor-risk group twice a week before planned nephrectomy. A large amount of CD8+ T cells infiltration was detected in 5 out of 12 kidney tumors extracted. No objective tumor response was observed, and 6 out of 11 assessable patients had subsequently received additional treatment with standard TKI. Three of these six patients experienced an objective tumor response including one sunitinib-treated patient responding with a complete and durable regression of four brain metastases.

Zhang *et al.*^[29] evaluated the effectiveness of DCs pulsed with antigen derived from CD105+ human RCC cancer stem cells against renal cancer cells *in vitro* and *in vivo*. They reported that cancer stem cell-targeted DC therapy could be a potent strategy for the elimination of cancer stem cell and therefore the prevention of posttumor therapy tumor metastasis and relapse.

Amin *et al.*^[30] randomly compared sunitinib-combined autologous DC vaccine (AGS-003) treatment with just sunitinib treatment in the phase 2 study they made on 21 mRCC patients and reported that survival was significantly better in autologous DC vaccine + sunitinib

group (57 ± 1 months vs. 30 ± 2 1 months). This result inspired the phase 3 ADAPT study. ADAPT has completed enrollment and should report initial results soon.

Wei *et al.*^[31] applied DC-based vaccine and anti-CD69 antibody treatment in murine RCC and reported that anti-CD69 antibody increased antitumor efficiency of DC-based vaccine and caused significant decrease in tumor volume and significant increase in T-cell proliferation and activity.

These studies show that DC vaccines constituted antigen-specific immune response in mRCC patients and can be used safely in most patients as they provide tumor regression in most patients.

PEPTIDE VACCINES

Synthetic peptide-based vaccines are more advantageous compared to other vaccines as they “are easy to manufacture, stabile, safe, cost-effective and don’t require tumor tissue.”^[32] Carbonic anhydrase 9 (CA9) is a tumor-related glucoprotein. It is in limited amounts in normal tissues including kidney in 90% of RCC patients. Tumor-associated antigen and human lymphocyte antigens (HLA) were also defined in RCC. The first peptide vaccines were made with CA9 antigen. Studies on peptide vaccines can be separated into two groups as metastatic and adjuvant.^[33]

Peptide vaccines metastatic studies

CA9 peptide vaccine was applied in phase 1 study on 23 progressive cytokine refractory HLA-A24+ mRCC patients. CA9-specific, CTL, and immunoglobulin G response was observed in nearly 70% of the patients. Clinical response ratio became 39%. But at least 12 vaccinations are required for CTL response due to the low immunogen effect of peptide.^[34]

In the phase 1 study made on eight mRCC patients, CA9 peptide vaccine was applied and specific, and CTL and immunoglobulin G response were not observed despite five intradermal injections.^[35]

In phase 1–2 study made on three mRCC patients, Wilms tumor (WT1) peptide vaccine was applied and long-term stable disease was observed in two patients. CTL response was observed after a 12-week treatment. But the vaccine was detected to cause severe leukopenia in myelodysplastic syndrome patients.^[36]

Patel *et al.* evaluated two phase 2 studies on mRCC patients together, one was a nonrandomized study on 60 patients

and the second was a randomized study on 36 patients and the patients were applied heat-killed Mycobacterium Vaccae SRL172 peptide vaccine. They reported SRL172 vaccine to be more effective than IL-2 and INF-alfa in the first study, and in the second study, they reported no superiority of the vaccine over IL-2.^[37]

Mutant Von Hippel–Lindau peptide vaccine was applied to the patients in Phase 1–2 study including six mRCC patients, and specific immune response was observed in four patients. General patient survival was measured as 30.5 months, and progression-free survival as 6.5 months. The vaccine was well-tolerated, and no vaccine-related side effects were observed.^[38]

TroVax

5T4 transmembrane glycoprotein is present in 95% of transparent and papillary RCCs, and it is present in normal kidney tissue in a limited amount. TroVax is a 5T4-based vaccine which is a tumor-related antigen. It was detected to be safe and well-tolerated in a total of 190 patients in nine phase 1–2 studies completed. Increased specific immune response and increased general survival were reported in all studies made.^[39]

In the phase 3 of double-blinded, placebo-controlled TRIST study on 732 patients, it was observed to be tolerated better than IL-2, INF-alpha and sunitinib treatments, and also IL-2+ TroVax treatment demonstrated a more significant survival over IL-2 treatment, but there was no difference in survival rates in all patients. General survival was measured as 20.1 months in the medicine group and 19.2 months in the placebo group, and there was no statistically significant difference.^[40]

IMA901

It is the first therapeutic vaccine for RCC, and it contains multiple tumor-related peptide which innately exists in innate human cancer tissue. In the phase 2 studies made, it was demonstrated to increase survival ratio and lengthen progression time. In two phase 1 and phase 2 studies including 96 mRCC patients, a T cell response proportional to the tumor-related peptide count and better disease control were reported in phase 1 study, and better immune response and thus longer general survival were reported in phase 2 study.^[41]

Rini *et al.*^[42] compared sunitinib + IMA901 to only sunitinib treatment in metastatic or locally advanced clear-cell RCC patients in Phase 3 of IMPRINT study and detected no significant difference in overall and progression-free survival rates amongst two groups.

Kirner *et al.*^[43] reported that T-cell response occurring with IMA901 was lower when compared to previous studies. These findings caused disappointment for IMA901.

PEPTIDE VACCINES ADJUVANT STUDIES

Autologous HSPCC-96 (oncophage)

Oncophage was given to the patients in the phase 3 study made on 371 patients who have high recurrence risk after nephrectomy, and no difference was detected in progression-free survival and recurrence rates between the observation group (37.7% and 39.8%). General survival data for this study are not enough.^[44] mRCC studies are not completed yet.

CONCLUSION

In addition to their efficient potential on prolonged overall survival, decreasing tumor burden and in long-term cancer development, vaccine treatments are especially effective in mRCC patients. We think that vaccine treatments would be applied more in near future since RCC are immunogenic. But more clinical data and studies are required to support the positive aspects of vaccine treatments.

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Conflicts of interest

There are no conflicts of interest.

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