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Review Article

GVAX vaccine as a treatment for pancreatic cancer: an overview of its clinical history and current immunotherapeutic outcomes

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ABSTRACT

With few available treatments and a dismal prognosis, pancreatic cancer is among the most aggressive and deadly cancers. Immunotherapy has become a potential strategy to increase anti-tumor immunity, especially cancer vaccines. GVAX, an allogeneic pancreatic cancer vaccine employing granulocyte-macrophage colony-stimulating factor as an immune adjuvant, has emerged as a promising therapeutic strategy to enhance anti-tumor immunity. Initial trials of GVAX showed mixed results, with some patients exhibiting immune responses and prolonged survival. Subsequent studies explored combinations with chemotherapy and immune checkpoint inhibitors, such as ipilimumab and nivolumab. While these combinations demonstrated promising immunological effects and improved clinical outcomes in some cases, the overall survival benefit has been inconsistent, especially in advanced disease stages. Recent trials are further investigating optimal combinations and dosing regimens to maximize the efficacy of GVAX-based immunotherapy in pancreatic cancer. In conclusion, GVAX holds promise as a component of immunotherapy for pancreatic cancer. However, further research is needed to optimize its use in combination with other therapies and to identify patient populations that may benefit most from this approach.

Keywords: Cancer vaccines, GVAX, Immunotherapy, Pancreatic cancer

INTRODUCTION

Pancreatic cancer is one of the most aggressive malignancies with a 5-year survival rate below 10% globally.[1] A key characteristic of pancreatic cancer is its complex tumor microenvironment (TME). This TME is constantly changing as the tumor develops and is made up of various non-cancerous cells, including fibroblasts, immune cells, blood vessel cells and nerve cells. Additionally, the TME contains a large amount of extracellular matrix, which contributes to its dynamic and poorly vascularized nature.

These components interact with each other in numerous ways to encourage tumor growth and resistance to treatment.[2,3] While significant advancements have been made in the treatment of localized, surgically resectable cancers over the past decade, the majority of patients present with regional or distant metastases. Despite therapeutic interventions, disease progression remains the predominant clinical course for these patients.[3]

Currently, the mainstay of pancreatic cancer treatment involves surgery, chemotherapy and radiation therapy.[4] Surgical resection remains the only curative treatment modality; however, its applicability is restricted to approximately 20% of patients due to widespread disease at the time of initial diagnosis. The type of surgery for pancreatic cancer depends on the tumor's location.

Tumors in the pancreas's head often require a pancreaticoduodenectomy, while those in the tail can be removed with a distal pancreatectomy. Complete resection combined with chemotherapy offers the best chance of curing pancreatic cancer. Patients with advanced or metastatic disease are treated with palliative care. Moreover, adjuvant radiation therapy is commonly used, despite inconclusive evidence of its effectiveness.[5,6]

Immunotherapy has emerged as a promising approach to enhance cancer treatment outcomes. Well-recognized immunotherapeutic strategies include immune checkpoint blockade therapies, oncolytic viral therapies, adoptive T cell therapies and vaccination strategies.

While cancer vaccines have been successful in treating certain cancers (e.g., prostate, cervical and vulvar cancers), developing a vaccine for pancreatic cancer remains an ongoing challenge.[6] The most extensively researched and tested vaccine is GVAX, a heterologous vaccine made of irradiated allogeneic pancreatic cancer cell lines.[7] This article aims to provide an overview of the mechanism, clinical history and immunotherapeutic efficacy of GVAX vaccine as a treatment for pancreatic cancer.

REVIEW

GVAX vaccine invention and mechanism

GVAX is a cancer vaccine that leverages the immunomodulatory properties of granulocyte-macrophage colony-stimulating factor (GM-CSF). This cytokine stimulates the production and activation of immune cells, which are then primed to attack tumor cells. In GVAX, GM-CSF is genetically engineered into tumor cells, which are subsequently administered to patients. These genetically modified tumor cells serve as a "danger signal," attracting immune cells to the vaccination site and inducing their activation against tumor-associated antigens.[8]

The vaccine was first introduced in 1993 by Glenn Dranoff, a cancer researcher, who compared various cytokine genes to identify the most effective inducer of protective immunity against tumors. The research revealed that GM-CSF was superior to other cytokines like IL-2 and IL-4 in inducing sustained high levels at the vaccination site, which are crucial for triggering effective anti-tumor immune responses, leading to the development of GVAX.[9,10]

Clinical history of GVAX vaccine and it's efficacy for pancreatic cancer treatment

Jafee et al, initiated the first clinical trial in 2001 to test GVAX on 14 human individuals diagnosed with different stages of pancreatic ductal adenocarcinoma. The vaccine induced a local immune response in some patients, characterized by infiltration of immune cells at the vaccination site.

However, systemic immunity, as measured by DTH (delayed-type hypersensitivity) responses to autologous tumor cells, was only observed in a few patients. Interestingly, these patients also showed a significant increase in DTH reaction size and were disease-free for over 25 months. While the study was not designed to assess efficacy, these findings suggested a potential correlation between immune response and clinical benefit.[11] Later in 2008, a pilot study conducted by Laheru et al, investigated the efficacy of GM-CSF-secreting pancreatic cancer cell lines as immunotherapy for advanced pancreatic cancer. The immunotherapy was administered alone or in combination with cyclophosphamide. While both regimens showed some anti-tumor activity, the combination therapy with cyclophosphamide demonstrated a more pronounced effect, with a higher rate of mesothelin-specific T-cell responses and longer survival.

These findings suggested that the combination of GM-CSF-secreting tumor cell immunotherapy with cyclophosphamide was a promising approach for treating advanced pancreatic cancer.[12] In 2011, the vaccine was also tested as an adjuvant therapy in a phase I/II clinical trial by Eric et al, the study evaluated the efficacy of the GM-CSF-based immunotherapy in treating patients with resected pancreatic adenocarcinoma.

The immunotherapy was administered in sequence with chemoradiotherapy. The results showed that the median disease-free survival was 17.3 months and the median overall survival was 24.8 months. The induction and maintenance of enhanced post-immunotherapy mesothelin-specific T cell responses were associated with prolonged disease-free survival.

These findings suggested that the immunotherapy approach integrated with chemoradiotherapy may improve outcomes for patients with resected pancreatic cancer.[13] Researchers continued to investigate the efficacy of the vaccine compared to chemotherapy. In 2017, Le et al, conducted a phase II clinical trial that evaluated the efficacy of GVAX combined with CRS-207 immunotherapy against standard chemotherapy in patients with advanced pancreatic cancer who had already undergone multiple treatments.

Unfortunately, the study concluded that this combination did not significantly improve overall survival compared to standard chemotherapy. The study did highlight the potential benefit of immunotherapy in a specific subset of patients with stable disease. Their trial suggested that further research and exploration of different immunotherapy strategies and combinations was necessary to effectively target pancreatic cancer.[14]

As the immune responses triggered by GVAX alone were often not strong enough to overcome the highly immunosuppressive environment of pancreatic cancer, further trials were conducted to assess the efficacy of combined regimens, particularly combining GVAX with immune checkpoint inhibitors. In 2013, Le et al, investigated the efficacy of Ipilimumab, a CTLA-4 inhibitor, in combination with GVAX in patients with previously treated pancreatic ductal adenocarcinoma. The combination therapy demonstrated superior clinical outcomes, including longer overall survival and a higher rate of disease stabilization.

Enhanced mesothelin-specific T cell responses and diversification of the T cell repertoire were associated with improved survival.

These findings suggested that combining immune checkpoint blockade with the cancer vaccine holds promise for treating pancreatic cancer and warranted further investigation by clinical trials.[15] Later in 2020, a phase II clinical trial conducted by Wu et al, assessed the efficacy of a combination therapy involving GVAX and ipilimumab as a maintenance treatment for metastatic pancreatic ductal adenocarcinoma in patients who had responded to initial chemotherapy.

The study revealed promising immunological effects and patients experienced clinical responses although no increase in survival rate was concluded. The combination therapy stimulated a robust immune response, characterized by increased T cell differentiation and activation and a shift towards an M1 macrophage-dominant tumor microenvironment.

Despite the lack of significant survival benefit, the observed immunological changes and clinical activity suggested that further investigation into innovative combination therapies for the maintenance treatment of metastatic PDA was warranted.[16]

In addition, Tsujikawa et al, conducted a clinical trial in 2020 to assess the combination of the GVAX pancreas vaccine and nivolumab, an Anti–PD-1/PD-L1 and another a checkpoint inhibitor, for treatment of metastatic pancreatic cancer. Similar to the findings of Wu et al, about GVAX and ipilimumab, the combination with nivolumab demonstrated potential efficacy in treating pancreatic cancer.

Although the primary endpoint of improved overall survival was not met, this combination also showed signs of clinical activity, including increased T-cell infiltration in tumors and a slight improvement in response rates.[17]

Furthermore, a 2021 phase II clinical trial investigated a combination therapy for locally advanced pancreas cancer. Patients who remained disease-free after standard chemotherapy received cyclophosphamide, GVAX, pembrolizumab (another Anti–PD-1/PD-L1 and a checkpoint inhibitor) and stereotactic body radiation therapy.

While the primary endpoint of distant metastasis-free survival was not met, 44% of patients underwent surgical resection and 42% of these had a significant pathologic response. This suggested that the combination therapy may prime the immune system and improve surgical outcomes in pancreatic cancer patients.[18]

To enhance survival rate, a third drug was added to this combination. A recent trial in 2023 by Heumann et al, evaluated the efficacy of neoadjuvant and adjuvant GVAX-based immunotherapy in patients with resectable pancreatic adenocarcinoma.

The primary endpoint of increased intratumoral CD8+ CD137+ cells was met with the combination of GVAX, nivolumab and urelumab. This combination therapy demonstrated numerically improved disease-free and overall survival compared to GVAX alone or GVAX with nivolumab, although not statistically significant due to the small sample size. These findings were in favour of a triple combination.[19]

Current trials on GVAX vaccine for pancreatic cancer treatment

Recent trials are still investigating the combinations of GVAX with immune checkpoint inhibitors and cyclophosphamide.

Table 1 summarizes the most recently published trials investigating this vaccine's efficacy in combined-therapy interventions. The results of these trials highlight the potential of GVAX-based immunotherapy combined with other treatments in improving outcomes for pancreatic cancer patients.

Notably, in resectable and locally advanced cases, the combination therapies significantly enhanced overall, disease-free and metastasis-free survival compared to standard approaches, emphasizing the role of multimodal regimens.

However, in metastatic pancreatic cancer, FOLFIRINOX chemotherapy outperformed immunotherapy with ipilimumab and tumor vaccine in terms of overall survival, suggesting that advanced disease stages may benefit more from intensive chemotherapy than from current immunotherapeutic strategies.

While promising, the small sample sizes in certain trials limit the robustness of these findings and highlight the need for larger studies to validate the efficacy and optimize the integration of immunotherapy in pancreatic cancer treatment (Table 1).

Currently, two more trials were completed in 2024 (NCT03161379 and NCT03767582) to further investigate the potential of combined GVAX and Nivolumab for the treatment of Resectable and Advanced Pancreatic Cancer, respectively. Yet the results of these trials are not publicly available.

Moreover, a clinical trial investigating neoadjuvant and adjuvant immunotherapies for resectable pancreatic cancer is recruiting in 2024 (NCT02451982). Once these studies are completed and results are published, they are expected to further support the current evidence on GVAX vaccine's efficacy and available combinations for pancreatic cancer management.

Table 1: Recent trials investigating the vaccine's efficacy in combined-therapy interventions.

Trial ID	Results published	Intervention	Condition	No. of participants	Outcomes
NCT03153410	2024	Cyclophosphamide, pembrolizumab, GVAX and IMC-CS4 (LY3022855)	Borderline resectable adenocarcinoma of the pancreas	9	Overall survival: 20.4 months (median) Disease free period: 12.6 months (median) Surgical resectability after neoadjuvant therapy: 100% (n=9) of patients. Participants with<10% residual viable tumor post resection: 77.8% (n=7).
NCT02648282	2024	Cyclophosphamide, pembrolizumab, GVAX pancreas vaccine and stereotactic body radiation therapy (SBRT).	Locally advanced pancreatic cancer	58	Distant-Metastasis-Free survival: 9.8 months (median).
NCT01595321	2024	Pancreatic tumor cell vaccine (GVAX), cyclophosphamide (CY), stereotactic body radiation therapy (SBRT) and FOLFIRINOX che motherapy.	Resected adenocarcinoma of the pancreas	19	Overall survival: 61.3 months (median) for patients treated with CY, GVAX, SBRT and Modified FOLFIRINOX chemotherapy compared to median of 27.5 months (median) for patients treated with SBRT and Modified Folfirinox chemotherapy only. Disease-free survival: 24.1 months (median) for patients treated with CY, GVAX, SBRT and Modified FOLFIRINOX compared to median of 14.5 months (median) for patients treated with SBRT and Modified Folfirinox only. Distant-Metastases-Free survival: 42 months (median) for patients treated with CY, GVAX, SBRT and Modified FOLFIRINOX compared to median of 19 months (median) for patients treated with SBRT and Modified folfirinox only.
NCT01896869	2024	Folfirinox chemotherapy compared to Ipilimumab with pancreatic tumor vaccine	Metastatic pancreatic cancer	82	Overall survival 9.38 months (median) for patients treated with Ipilimumab with vaccine compared to 14.7 months (median) for patients treated with folfirinox chemotherapy.

CONCLUSION

In conclusion, the GVAX vaccine has shown promise as a potential immunotherapy for pancreatic cancer, particularly when combined with other therapeutic modalities. While early trials demonstrated limited success as standalone treatment, subsequent studies have revealed the potential benefits of integrating GVAX with immune checkpoint inhibitors and chemotherapy. These combinations have demonstrated improved clinical outcomes, especially in locally advanced and resectable pancreatic cancer, including enhanced immune responses, increased tumor infiltration and prolonged survival. However, in metastatic pancreatic cancer, the benefits of GVAX-based immunotherapy have been less pronounced, with chemotherapy often remaining the standard of care. Further research is needed to refine these treatment strategies, identify patient subgroups who may benefit most and optimize the timing and sequence of therapies to maximize clinical benefit. As ongoing clinical trials continue to explore the potential of GVAX-based immunotherapies, it is anticipated that these approaches will play a significant role in the future management of pancreatic cancer, particularly in earlier-stage disease.

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