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Review

Transforming pancreaticobiliary cancer treatment: Exploring the frontiers of adoptive cell therapy and cancer vaccines

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Pancreaticobiliary cancer, encompassing malignancies of both the pancreatic and biliary tract, presents a formidable clinical challenge marked by a uniformly bleak prognosis. The asymptomatic nature of its early stages often leads to delayed detection, contributing to an unfavorable 5-year overall survival rate. Conventional treatment modalities have shown limited efficacy, underscoring the urgent need for alternative therapeutic approaches. In recent years, immunotherapy has emerged as a promising avenue in the fight against pancreaticobiliary cancer. Strategies such as therapeutic vaccines and the use of tumor-infiltrating lymphocytes have garnered attention for their potential to elicit more robust and durable responses. This review seeks to illuminate the landscape of emerging immunotherapeutic interventions, offering insights from both clinical and research perspectives. By deepening our understanding of pancreaticobiliary cancer and exploring innovative treatment modalities, we aim to catalyze improvements in patient outcomes and quality of life.

INTRODUCTION

Pancreaticobiliary cancer affects both the pancreas and the biliary tract, including the intrahepatic and extrahepatic bile ducts. Despite distinct etiology, these malignancies exhibit a uniformly dismal prognosis, characterized by a 5-year overall survival rate ranging from 9% to 10% for pancreatic cancer and 5% to 15% for bile duct cancer.[1] Projections indicate that pancreatic and bile duct cancers will ascend to the second and third positions, respectively, among the leading causes of cancer-related mortality by 2040.[2]

Pancreatic ductal adenocarcinoma (PDAC) accounts for about 90% of pancreatic cancer cases.[3] Patients with PDAC frequently manifest nonspecific symptoms such as vague abdominal pain and weight loss, contributing to delayed diagnosis of this aggressive tumor. Compounded by the absence of readily available biomarkers and the suboptimal performance of existing diagnostic tools, 40%–60% of newly diagnosed patients present with metastasis at the outset.[4] Once metastasis occurs, treatment options are severely constrained, substantially diminishing the prospects of patient survival. PDAC is notably characterized by rapid progression, with an average temporal span of 14 months between stage I and stage IV diagnoses.[5] Understanding the mechanistic underpinnings of pancreatic cancer development is critical for the development of targeted therapies and early detection strategies. Key genetic alterations in genes like KRAS, TP53, CDKN2A, and SMAD4 drive the initiation and progression of PDAC. These mutations often arise in ductal and acinar cells, leading to the development of precursor lesions such as pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms, and mucinous cystic neoplasms. The progression from normal pancreatic tissue to invasive cancer involves a series of molecular and histological changes. However, the heterogeneous nature of pancreatic cancer, coupled with conflicting research findings, underscores the need for further research to elucidate its intricate pathogenesis.[6]

Similar to the challenges posed by pancreatic cancer, cholangiocarcinoma (CCA) emerges as another aggressive cancer within pancreaticobiliary malignancies. This malignancy manifests in three distinct subsets, namely, perihilar cholangiocarcinoma (pCCA), intrahepatic cholangiocarcinoma (iCCA), and distal cholangiocarcinoma (dCCA). The prevalence of these subsets varies based on their anatomical locations, with pCCA being the most common, accounting for 50%–60% of all cholangiocarcinoma, followed by dCCA (20%–30%) and iCCA (10%–20%).[7] CCA typically remains asymptomatic in its early stages, contributing to delayed detection and limited therapeutic interventions. Consequently, the prognosis is unfavorable, with a 5-year overall survival ranging from 7% to 20%.[7] Although accounting for a modest 3% of all gastrointestinal cancers, the global incidence of CCA is on the rise, painting a concerning epidemiological picture.[8]

The heightened aggressiveness of these tumors is exacerbated by their poor response to conventional treatments such as chemotherapy. Given the increasing application and promising outcomes observed in solid tumors, immunotherapy emerges as a hopeful adjunct for managing these malignancies. While immune checkpoint inhibitors

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(ICIs) have demonstrated limited efficacy in comparison with other solid tumors like melanoma, there is a need to further explore novel immunotherapeutic approaches. This review aims to shed light on emerging avenues in immunotherapy for pancreaticobiliary cancer, encompassing vaccine therapy and tumor-infiltrating lymphocyte (TIL) therapy. Additionally, the review provides an overview of the current treatment landscape for these tumors, delving into the tumor environmental characteristics that contribute to their aggressiveness.

OVERVIEW OF CURRENT TREATMENT OF PANCREATICOBILIARY TUMORS

Surgical resection and adjuvant therapy in pancreatic ductal adenocarcinoma

Despite significant advancements in biomedical science, effectively treating these tumors remains a challenge with existing therapeutic modalities. The initial assessment for pancreatic cancer involves a dedicated abdominal computed tomography (CT) scan utilizing a pancreatic protocol to evaluate both the disease's stage and vascular anatomy.[3] Approximately half of the patients present with disseminated disease that features distant metastasis at the time of diagnosis, while the remaining half exhibit localized disease. Within this latter category, distinctions can be made based on the extent of cancer and its interaction with visceral vasculature, classifying it into resectable, borderline resectable, and locally advanced pancreatic ductal adenocarcinoma (PDAC). Additionally, further subclassification can be undertaken based on biological parameters, including biopsy and tomographic imaging, as well as serum carbohydrate antigen (CA 19-9) levels. The patient's performance status serves as a pivotal conditional criterion that is factored in when classifying localized PDAC disease.[9] For cases in which the cancer is deemed resectable, surgery remains the primary treatment choice.[10] The preponderance of PDAC lesions is situated in the pancreatic head (60%–70%), with the remaining distributed in the body (15%) and tail of the pancreas (15%).[11] Depending on the tumor's localization, surgical interventions may encompass a pylorus-preserving pancreaticoduodenectomy (PPPD) (Kausch-Whipple procedure), a distal pancreatectomy, or a total pancreatectomy. Despite surgery being the only curative option, fewer than 20% of newly diagnosed patients are deemed eligible for resection. Furthermore, even post-surgery, the majority of patients experience disease recurrence within the first year.[12]

The landscape of treating resectable patients has undergone a transformative shift with the implementation of multimodal therapy, integrating surgical resection and adjuvant systemic chemotherapy. This approach has redefined the standard of care, elevating the median disease-free survival from 6.7 months with surgery alone to 13.4 months when coupled with adjuvant gemcitabine, as evidenced by the CONKO-001 trial.[13] Subsequent advancements have been achieved by incorporating various adjuvant therapies in conjunction with surgery. The ESPAC-4 trial demonstrated a survival benefit through the combination of gemcitabine with capecitabine compared with gemcitabine alone, resulting in an overall survival of 28.0 months compared with 25.5 months, respectively.[14] Presently, for individuals with resected PDAC and a favorable functional status, the modified FOLFIRINOX regimen stands as the standard of care, exhibiting an enhanced overall survival of up to 54.4 months when contrasted with 35 months observed with gemcitabine alone (PRODIGE-24 trial).[15] The difference in overall survival between the ESPAC-4 (25.5 months) and PRODIGE-24 (35 months) trials, both using gemcitabine-based adjuvant therapy for pancreatic cancer, can be attributed to variations in patient selection criteria, postoperative management protocols, and treatment response based on resection margin status. ESPAC-4's inclusion of patients regardless of CA19-9 levels and its lack of mandatory surveillance CT scans may have led to a less homogeneous cohort with potentially poorer disease biology. Meanwhile, PRODIGE-24's stringent criteria and mandatory scans likely enriched its population with patients more likely to respond favorably to treatment, thus yielding better overall survival outcomes.[16] In accordance with the guidelines set forth by both the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), gemcitabine, either as a standalone option or in combination with capecitabine, is considered an alternative regimen for patients exhibiting a lower performance status.[17]

Neoadjuvant therapy in pancreatic ductal adenocarcinoma

A distinctive approach in the treatment of PDAC involves neoadjuvant therapy, aiming to enhance the completion rate of chemotherapy. This approach becomes particularly crucial given that up to 40% of patients may not be deemed suitable for adjuvant chemotherapy due to surgical morbidity.[11] For cases categorized as borderline resectable PDAC, the NCCN guidelines advocate for a neoadjuvant treatment strategy for all patients, including chemotherapy with or without radiation.[17] Subgroup analysis from the PREOPANC trial shows an overall survival advantage in borderline resectable PDAC patients who underwent neoadjuvant gemcitabine combined with radiation therapy compared with those undergoing upfront surgery (17.6 vs. 13.2 months).

Additionally, this approach demonstrated an improvement in achieving R0 resection when surgery was complemented by neoadjuvant therapy for this patient subgroup.[18] Similar positive outcomes were observed in the Alliance A021501 trial, where the neoadjuvant regimen involved modified FOLFIRINOX with or without radiation therapy. The inclusion of neoadjuvant radiation did not yield discernible benefits; however, neoadjuvant chemotherapy alone demonstrated superior 18-month overall survival compared to upfront surgery (66.7% vs. 50).[19]

Locally advanced and metastatic PDAC

In the context of locally advanced pancreatic cancer, the standard of care involves systemic therapy, with only 5% of patients progressing to surgical resection.[17] Treatment protocols comprise systemic chemotherapy utilizing gemcitabine plus nab-paclitaxel or FOLFIRINOX.[20] The median overall survival in locally advanced pancreatic cancer treated with FOLFIRINOX is 24.2 months.[21] Similarly, these regimens are applied in the setting of metastatic PDAC, with survival durations ranging from 11.1 months with FOLFIRINOX to

6.8 months with gemcitabine.[22] Notably, combining gemcitabine with nab-paclitaxel resulted in a slight increase in overall survival, as evidenced by the findings of the MPACT trial (median survival 8.5 vs. 6.7 months).[23] Local tumor control may be attained in patients who are deemed unsuitable for surgical intervention. Various modalities, such as short-course stereotactic body radiotherapy and long-course external beam radiation therapy, have been investigated for this patient cohort.[24] A recent retrospective analysis demonstrated that high-dose radiotherapy ($\geq$98 Gy) can provide comparable disease control in locally advanced PDAC when compared with surgical resection.[25]

Surgical resection and adjuvant therapy in CCA

Similar to pancreatic cancer, CCA presents with limited early symptoms, leading to the majority of patients being diagnosed at an advanced stage (70%). While surgery remains a curative option, only 25% of patients qualify for resection, primarily due to the prevalence of metastatic or locally advanced stages at presentation.[7] The management of CCA is contingent on the anatomical location of the disease. Intrahepatic CCA typically presents as a sizable liver mass, identified through imaging studies, and is often accompanied by elevated serum biomarkers such as CA 19-9. Surgical resection in these cases involves extended hepatectomy and dissection of regional lymph nodes. However, fewer than 30% of patients undergo curative surgery with negative margins. The challenges in early detection and the high proportion of patients presenting at advanced stages underscore the complexities involved in the effective management of CCA.[26] The 5-year overall survival following curative surgical resection varies between 30% and 40%, and it diminishes to 20% when lymph node involvement is present.[27] Liver transplant emerges as a potential option for small intrahepatic CCA (iCCA) measuring less than 2 cm, particularly in patients with cirrhosis. Studies have reported 5-year overall survival rates of up to 65% with a liver transplant for such cases.[28] However, this approach is associated with a recurrence risk, particularly in patients with large iCCA tumors. Patients with locally advanced iCCA may benefit from locoregional therapies, such as *trans*-arterial chemoembolization, which yields a median overall survival of 13.2%.[29] A recent phase II clinical trial demonstrated enhanced overall survival, reaching up to 35 months, with hepatic arterial infusion of floxuridine in combination with systemic gemcitabine and oxaliplatin.[30] Nevertheless, the absence of high-quality phase III clinical trials poses a challenge in establishing the standard of care for this specific patient group, underscoring the need for further research and evidence-based guidelines.[31] Surgical interventions for perihilar CCA (pCCA) typically entail complex procedures involving major hepatectomy, vascular and bile duct resection, and reconstruction. Advances in surgical techniques have contributed to an increased number of R0 resections, elevating the 5-year overall survival to 32.5% for this subgroup of patients.[32] In specific cases of pCCA, particularly those with masses smaller than 3 cm and without intrahepatic or extrahepatic metastasis, liver transplantation with neoadjuvant chemoradiation can be considered. This approach has shown a 5-year disease-free survival rate of 68%.[33] However, for patients with unresectable disease, palliative care options, including biliary stenting and systemic chemotherapy with gemcitabine and cisplatin, are recommended. Similar to iCCA, there is a lack of established standards of care for this patient category.[31] Surgical procedures for distal CCA (dCCA), resembling those for PDAC, involve pancreaticoduodenectomy, encompassing the removal of the pancreas head, duodenum, gallbladder, and bile duct. Resection of the hemi liver with extrahepatic bile duct is the standard procedure for perihilar cholangiocarcinoma (pCCA), with some extensive cases treated with a hepatopancreatoduodenectomy (HPD), including the simultaneous resection of part of the liver, pancreas, and duodenum.[34] Despite the anatomical similarities, prognosis for dCCA is comparatively better than that for PDAC at the pancreas head.[35] Post-surgical relapse remains frequent across all three types of CCA, prompting investigations into the efficacy of adjuvant chemotherapy. Three phase III clinical trials, namely the BCAT trial using gemcitabine,[36] the PRODIGE-12[37] with gemcitabine and oxaliplatin, and the BILCAP trial[38] examining capecitabine, compared their respective chemotherapy arms to observation alone. Only the BILCAP trial demonstrated a benefit in overall survival and disease-free survival with capecitabine in the adjuvant setting, establishing it as the standard of care for resected CCA.[39] In the context of metastatic CCA, systemic chemotherapy takes precedence as the first-line approach. The ABC-02 trial confirmed the combination of gemcitabine and cisplatin as the recommended first-line therapy, with a median overall survival of 11.7 months.[40]

Despite significant advancements, the therapeutic options available for pancreatic cancer and CCA remain severely constrained, predominantly relying on a combination of chemotherapy and surgical interventions. The dismal prognosis associated with these cancers necessitates urgent research efforts to unravel novel therapeutic targets, innovative treatment strategies, and personalized interventions.

IMMUNOTHERAPY IN PANCREATICOBILIARY CANCERS

Given the unfavorable outcomes observed in pancreaticobiliary cancers following surgery and chemotherapy, immunotherapy is emerging as a promising treatment strategy for these aggressive tumors. Cancer immunotherapy harnesses the body's own immune cells, activating them to counteract cancer immune evasion and eliminate tumor cells. Among the various types of immunotherapies, ICIs are the most widely used. These molecules, typically monoclonal antibodies, function by blocking one or more surface proteins, specifically targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PDL-1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). By doing so, ICIs facilitate the killing of tumor cells by T lymphocytes and prevent T cell anergy, thereby enhancing the immune system's ability to combat these aggressive cancers. Following the initial application of ipilimumab (anti-CTLA-4) in the treatment of metastatic melanoma in 2011,[41] which yielded impressive results, there has been significant progress in utilizing ICIs in the adjuvant or neoadjuvant treatment of cancer. However, the clinical experience with these therapies in pancreatic ductal adenocarcinoma has been notably disappointing. In a phase II clinical

trial, ipilimumab as a monotherapy did not demonstrate any clinical benefit.[42] Similarly, combining two ICIs, anti-PDL-1, and anti-CTLA-4 in patients with metastatic PDAC resulted in an objective response rate of only 3%.[43] Despite these discouraging outcomes, there are glimpses of hope for the use of immunotherapy in PDAC. The phase II trial KN046, which employed a combined antibody targeting PDL-1 and CTLA-4 alongside gemcitabine and nab-paclitaxel in 17 patients with locally advanced and metastatic PDAC, showed a more promising objective response rate of 55.6%.[44] In contrast, a larger cohort of 110 patients in a phase III clinical trial combining sintilimab (anti-PD-1) with FOLFIRINOX did not yield significantly different overall survival compared with the chemotherapy alone group (10.9 vs. 10.8 months).[45]

In the context of CCA, the application of ICIs as monotherapy has yielded similar results to those observed in PDAC. Objective response rates remain modest, with nivolumab[46] showing a rate of 22% and durvalumab[47] (anti-PDL-1) exhibiting a rate of 5%. However, the clinical efficacy of durvalumab improved significantly when combined with the gemcitabine and cisplatin regimen in the TOPAZ-1 trial, conducted in patients with advanced biliary tract cancer. This combination therapy elevated the 24-month survival to 24.9%, as opposed to 10.4% for chemotherapy alone.[48] These favorable results prompted the Food and Drug Administration (FDA) to approve the combination of durvalumab with gemcitabine-cisplatin as the first-line therapy for advanced CCA. Despite this approval, the overall response rate of CCA tumors to the combination of chemotherapy and ICIs remains relatively low at 26%. The lack of significant progress in immunotherapy for PDAC and CCA could be linked to the intrinsic immunosuppressive nature of the disease and the intricate dynamics within the tumor microenvironment. There is a need for in-depth exploration into the immune microenvironment of these tumors and the identification of new therapies to overcome therapy resistance.

THE IMMUNE MICROENVIRONMENT IN PANCREATICOBILIARY CANCERS

The resistant nature of pancreaticobiliary cancer to various treatments can be attributed to the immunosuppressive microenvironment within the tumor. The tumor microenvironment (TME) consists of the neoplasic cells and the tumor stoma, which includes cancer-associated fibroblasts (CAFs), endothelial cells, myeloid-derived suppressor cells (MDSCs), and various immune cells such as $CD8^+$ T cells, regulatory T cells (Tregs), and tumor-associated macrophages (TAMs). PDAC manifests a distinctive immune landscape characterized by limited immune cell infiltration and recruitment of immunosuppressive entities such as Tregs, immature dendritic cells, MDSCs, and type 2 macrophages.[49] Additional immune suppression mechanisms are achieved through the secretion of immunosuppressive chemokines (such as stromal cell-derived factor 1, also known as CXC motif chemokine 12) and different cytokines (interleukin [IL]-1, IL-6, IL-10, transforming growth factor [TGF]-β, tumor necrosis factor α, and granulocyte-macrophage colony-stimulating factor).[50] TAMs constitute the predominant immune population in PDAC and predominantly exhibit an immunosuppressive phenotype characterized by the expression of CD206 and CD163 receptors and the secretion of IL-10.[51] An increased number of TAMs in PDAC tumors has been associated with poor prognosis.[50] Immune cell infiltration is further constrained by the dense stroma, comprising up to 80% of the PDAC tumor.[52] CAFs, activated by tumor cells, generate a dense desmoplastic stroma, establishing a mechanical barrier around the tumor that hinders access to therapeutic agents.[53] The immunosuppressive attributes of immune cells within the tumor and the abundant stroma collectively impede the infiltration and cytotoxic activity of T lymphocytes. Analysis of patient tumor samples has revealed increased expression of exhaustion markers on CD8 T cells in advanced stages of the disease, contributing to progressive immune dysfunction. On the other hand, higher infiltration with cytotoxic CD8 T cells is associated with improved survival.[54]

The significance of stroma in PDAC tumors is underscored by the identification of two stroma-specific subtypes of pancreatic cancer. Moffitt et al., through comprehensive gene expression analysis of 145 primary and 61 metastatic PDAC tumors, delineated samples into distinct "classical" or "basal-like" stroma types. The basal-like subtype, also referred to as the activated stroma, demonstrated a more heterogeneous gene profile associated with macrophages and other genes implicated in tumor progression. The disparity in gene expression signatures between classical and basal-like stroma subtypes correlated with clinical outcomes, where patients with samples belonging to the activated stromal subtype exhibited a poorer median survival time compared with patients with samples belonging to the normal stromal subtype (15 vs. 24 months).[55] Additionally, findings from the COMPASS Trial indicated a more favorable objective response to chemotherapy among patients with the classical subtype compared with those with the basal-like subtype.[56]

In CCA tumors, a defense mechanism similar to that observed in PDAC is orchestrated through a dense stroma barrier and an immunosuppressive microenvironment. CAFs play a pivotal role in this process by generating an extracellular matrix (ECM) that mirrors the desmoplastic stroma observed in PDAC. The CAFs not only create a physical barrier limiting tumor access[57] but also modulate the immune response by secreting cytokines such as transforming growth factor B1 (TGF-B1) and epidermal growth factor, thereby promoting CCA progression.[58] Furthermore, the CCA TME is enriched with myeloid cells, particularly TAMs, with a predominance of M2 macrophages associated with a pro-tumor effect and adverse outcomes in CCA patients.[59] These M2 macrophages release suppressive cytokines and chemokines, contributing to the recruitment of immunosuppressive cells like tumor-associated neutrophils (TANs), MDSCs, and Tregs.[59] Activation of TAMs by IL-6 and TGF-β produced by CCA tumor cells further enhances invasion and migration through IL-10 secretion and STAT3 pathway activation.[60] Conversely, the presence of TILs, particularly CD8 cytotoxic T cells and CD4 helper T cells, constitutes a crucial defense mechanism against CCA progression. A high tumor infiltration by CD8 cytotoxic T cells and CD4 helper T cells is associated with a better prognosis in

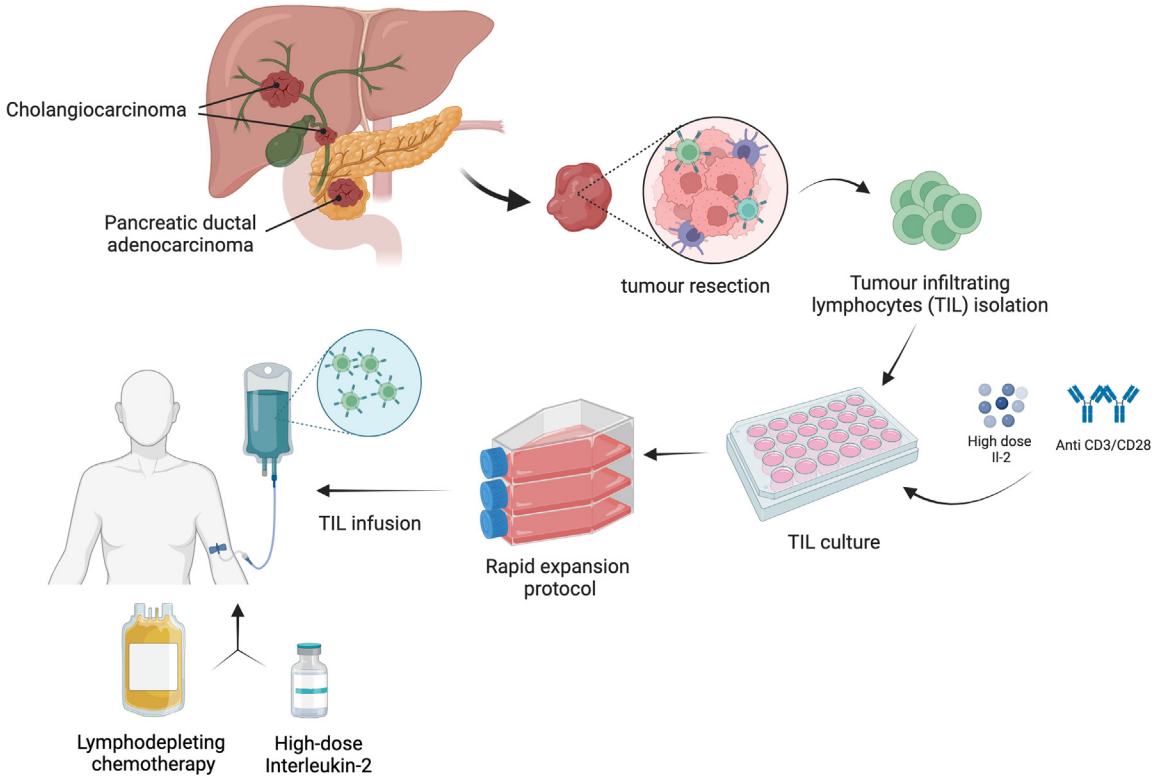

Figure 1. Schematic representation of the adoptive T cell therapy workflow

The process involves sequential steps, including surgical resection of tumor tissue; TIL isolation; rapid expansion protocol (REP), utilizing IL-2 and anti-CD3/CD28 monoclonal antibodies; lymphodepleting chemotherapy; TIL infusion; and adjuvant IL-2 administration to support the infused TILs.
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CCA patients.[61] However, it was shown that these infiltrating lymphocytes are present predominantly in the peritumor region while Treg accumulate in the intra-tumoral region.[59] This T cell subtype strongly accumulates in late stages of CCA disease and has been linked to the immune escape and progression of the tumor.[62]

The intricate interplay among the desmoplastic stroma, immune cell composition, and cytokine signaling is similar in the CCA and PDAC TME. The balance between pro-tumor and antitumor mediators emerges as a critical determinant of prognosis in these pancreaticobiliary cancers. Understanding these mechanisms holds promise for developing targeted therapeutic strategies aimed at disrupting the immunosuppressive milieu and enhancing antitumor immunity.

EMERGING AVENUES IN IMMUNOTHERAPY FOR PANCREATICOBILIARY CANCER

In light of the constrained therapeutic alternatives and suboptimal treatment outcomes for pancreaticobiliary tumors seen when using ICIs, there has been a growing focus on exploring targeted and personalized therapeutic strategies. Emerging as promising avenues are cell-based therapy and cancer vaccine interventions, designed to address various challenges posed by the TME. Previous findings have demonstrated that the infiltration of T lymphocytes into pancreaticobiliary tumors correlates with improved prognosis. Consequently, these novel therapies represent a potential approach to enhance T-cell-mediated tumor surveillance and infiltration.

Adoptive cell therapy: A cutting-edge approach

Adoptive T cell therapy involves the extraction and isolation of T lymphocytes from the patient's tumor or blood. These cells are expanded *in vitro* and then reinfused to the patients following lymphodepleting chemotherapy. Such therapies can exist in the form of autologous TIL infusion or chimeric antigen receptor T cell (CAR-T) therapy targeting specific surface tumor antigens.

TILs in PDAC

Melanoma is often described as a clinical model for immunotherapy and was the first cancer treated with tumor-infiltrating lymphocytes.[63] Drawing from the precedence of endogenous TIL transfer in melanoma, the adoptive cell transfer approach in solid tumors necessitates the execution of a preparative regimen. This regimen requires lymphodepleting chemotherapy, succeeded by the expansion and transfer of substantial quantities of autologous T cells, coupled with the systemic administration of high-dose IL-2 (Figure 1). Adverse effects are typically minimal, allowing patients to successfully complete the treatment. While high-dose IL-2 may elicit symptoms

ranging from rash and diarrhea to pulmonary edema, symptom control is achieved through supportive care and discontinuation of IL-2. Conversely, the infusion of TIL itself is generally well tolerated.[64] Objective response rates range from 49% to 72% in metastatic melanoma and up to 28% of metastatic patients were able to achieve a complete response.[65] The isolation of TIL from pancreatic cancer specimens was initially documented in preclinical investigations in 2016. In a pioneering study, a research cohort presented an optimized methodology for TIL isolation and expansion, involving 17 pancreatic cancer patients. This method employed a distinct combination of cytokines, such as IL-2, IL-5, and IL-21, resulting in the successful acquisition of TIL from the entire patient cohort.[66] Notably, the majority of these TILs were $CD8^+$ T cells with the capacity to recognize commonly shared tumor-associated antigens and autologous tumor cells. Conversely, another research group successfully expanded TILs from 19 patients with resected PDAC, wherein the predominant TIL subset comprised $CD4^+$ T cells. Purified $CD8^+$ T cells from this population exhibited interferon (IFN)-γ production in response to HLA-matched pancreatic tumor targets. Furthermore, the implementation of 4-1BB stimulation was identified as an effective strategy to enhance the yield of functional TIL, thereby augmenting the production of tumor-reactive pancreatic TIL.[67]

The application of TIL therapy in PDAC patients is predominantly explored in preclinical investigations, with clinical trial data awaiting to be published. Ongoing research involves two basket trials actively investigating the efficacy of TIL therapy in PDAC. A Phase II clinical trial (NCT01174121) is currently under way, focusing on evaluating the effectiveness of TIL therapy in conjunction with anti-PD-1 in metastatic gastrointestinal, hepatobiliary, and genitourinary cancers. Simultaneously, a second trial (NCT03610490) includes cohorts of osteosarcoma, platinum-resistant ovarian cancer, and pancreatic cancer patients who have either progressed on or derived maximal benefit from front-line therapy.[68]

TILs in CCA

Adoptive cell therapy utilizing TILs in CCA has been sparsely documented, primarily in the form of case reports. The exploration of TILs in the context of CCA dates back to 2006 when a case report demonstrated the efficacy of this therapeutic approach in a patient with metastatic intrahepatic cholangiocarcinoma (iCCA). Employing a combination of surgical resection and treatment involving CD3-activated T cells along with tumor lysate or peptide-pulsed dendritic cells, the patient remarkably remained free from recurrence for over 3 years. Notably, the overall survival rate for patients with lymph node metastasis in this context is strikingly low, ranging from 0% to 8%.[69] Another noteworthy case report, conducted by Rosenberg's group, documented the successful application of TIL treatment in a patient with metastatic CCA. The TIL infusion in this instance was enriched with $CD4^+$ T cells targeting a mutation expressed on the cancer cells (erbb2 interacting protein), identified through a comprehensive whole-exome sequencing approach.[70] This tailored treatment approach resulted in a reduction in lesion size and a concomitant extension of survival. Importantly, this patient was enrolled in an ongoing phase II trial (NCT01174121) investigating the use of TIL therapy in various solid tumors, including CCA. The detailed results of this trial are pending disclosure. Two pivotal clinical trials focusing on CCA patients are currently in progress. The first trial is a phase II study, led by Kammula's group, investigating the adoptive transfer of TILs for metastatic biliary tract carcinoma (NCT03801083). Most recently, a second trial is under way in Canada, representing the first-of-its-kind initiative for the CCA population in the country. This trial, led by Dr. Simon Turcotte and the Canadian Cholangiocarcinoma Collaborative (C3), aims to evaluate TIL therapy in 15 patients with CCA. The outcomes of these trials are anticipated to contribute valuable insights into the efficacy and potential applicability of TIL-based therapies in the context of CCA.

Current barriers and future directions for adoptive therapy in biliopancreatic tumors

Nevertheless, the prospects for TIL therapy in non-melanoma solid tumors may not be as encouraging as in melanoma patients. The absence of clinical trial data from pancreatic and biliary tumors concerning the application of this adoptive therapy has led to growing concerns about its actual efficacy in solid cancers. The overall response rates range from 8% to 24% across different cancers, encompassing human papillomavirus (HPV)-associated malignancies and non-small cell lung carcinomas.[71] Higher response rates in melanoma are attributed to its elevated mutational burden and extensive T cell infiltration[72,73] resulting from an abundance of somatic mutations and a correspondingly high mutational burden, leading to an increased number of neoantigens.[74] These neoantigens, recognized by specific T cell receptors (TCRs) on TILs, contribute to the therapy's efficacy. Importantly, human $CD8^+$ TILs can be non-tumor specific, marked by the absence of CD39 expression.[75] Notably, the proportion of non-tumor-specific TIL is higher in non-melanoma tumors compared with melanoma.[76] These findings suggest that the diminished efficacy of TIL therapy in solid tumors other than melanoma may be linked to a lower proportion of tumor-reactive T cells. However, ongoing developments in the next generation of cell therapy and TILs aim to enhance T cell selection and selectively expand tumor-reactive T cells.

A novel manufacturing methodology is currently under evaluation for the augmentation of neoantigen-specific TILs. This process entails the extraction of TILs from the patient's tumor, followed by their co-culture with autologous dendritic cells loaded with patient-specific neoantigens. This technique enables the rapid expansion of TILs specifically targeting the tumor, facilitating subsequent infusion back into the patient. The efficacy of this innovative approach is presently being investigated in two clinical trials focused on non-small cell lung cancer (NCT04032847) and melanoma (NCT03997474). Alternative strategies involve the identification of tumor-specific TILs based on their phenotypic markers. Notably, markers such as PD-1, CD39, and CD103 exhibit high expression within this TIL sub-population. Magnetic bead sorting of TILs from the tumor sample, expressing the $CD8^+PD\text{-}1^+$ markers, has demonstrated increased tumor specificity. Similar results were observed in melanoma patient samples,

wherein TILs expressing $CD39^+CD103^+$ markers were isolated. From the resultant expanded TIL product, 51% of the cells exhibited reactivity against the tumor.[77] This sub-population of TILs can also be identified through whole-exome sequencing or RNA sequencing of the tumor to recognize specific mutations and expand neoantigen-reactive T cell clonotypes. In a phase II clinical trial (NCT01174121), TIL therapy demonstrated effectiveness in metastatic epithelial cancer. A patient with metastatic breast cancer received neoantigen-specific TILs targeting mutant versions of four proteins (SLC3A2, KIAA0368, CADPS2, and CTSB), combined with checkpoint blockade, resulting in complete and durable regression of metastatic breast cancer.[78] Similar success was observed in metastatic colorectal cancer, where $CD8^+$ T cells targeting a mutant KRAS mediated effective antitumor immunity against lung metastasis.[79] Several clinical trials explore ways to enhance TIL therapy efficacy, particularly through combinations with ICIs. The combination of TIL therapy with anti-PD-1 showed success in preliminary data from trials in head and neck squamous cell carcinoma and cervical cancer (NCT03108495 and NCT03645928), achieving overall response rates of 43%–57%, respectively. Another promising avenue in adoptive cell therapy is the genetically modified TCR T cell therapy, involving the generation of T cells expressing TCR against specific neoantigens on tumor cells. In treating a patient with metastatic pancreatic cancer targeting mutant KRAS, this approach yielded an overall partial response of 72%, sustained at 6 months post-treatment.[80]

In conclusion, clinical trial data regarding TIL therapy efficacy in pancreatic and biliary cancers remain pending. Nevertheless, innovative strategies, including combining TILs with anti-PD-1 therapy and selecting neoantigen-specific TILs, show promise for improving outcomes in non-melanoma cancers.

Cancer vaccines: Harnessing the immune system

The induction of an immune response mediated by T cells through cancer vaccines represents a distinct approach in the field. These vaccines primarily target tumor-associated antigens (TAAs) present on cancer cells.[81] Cancer vaccines fall into four categories: peptide-based vaccines, dendritic cell vaccines, cellular vaccines, and personalized vaccines (Figure 2). The overarching objective of this therapeutic approach is to prime T cells, facilitating an effective response against tumors. In cancer vaccine strategies, dendritic cells (DCs) play a pivotal role. Their activation occurs either through the administration of selected tumor antigens or the infusion of activated DCs. The aim is to activate DCs and stimulate the patient's adaptive immune system, leading to a reduction in tumor growth. The success of this therapy hinges on the delivery of substantial antigen quantities to dendritic cells, activating these cells to engage and stimulate both CD4 and CD8 T cells. The meticulous selection of tumor antigens is a pivotal aspect of cancer vaccine development, distinguishing between two principal categories: TAAs and tumor-specific antigens (TSAs). TAAs represent self-antigens, which are naturally occurring and exhibit an elevated expression in cancer cells compared with normal cells. In contrast, TSAs encompass neoantigens, generated by genetic alterations in tumor cell genes. These neoantigens are perceived as non-self by the immune system, eliciting a robust immunogenic response. This category provides a foundation for developing vaccines that target these distinctive features. Vaccines designed to target patient-specific neoantigens necessitate the sequencing of the individual's tumor. This personalized approach allows for the identification and incorporation of unique neoantigens into the vaccine, enhancing its specificity and potential efficacy in inducing a potent immune response tailored to the patient's tumor profile.[82]

Peptide-based vaccines

Peptide-based vaccines are designed using synthetic peptides derived from TSAs or TAAs.[83] Short peptides are made with 8–12 amino acids and can bind to HLA class I without being processed by APCs. They usually have a short half-life and produce a short-term induction of $CD8^+$T cells. Long peptides can be up to 20 amino acids and can bind to either HLA class I or II. They induce a stronger immune response that involves a longer activation of $CD8^+$ T cells and the concomitant stimulation of $CD4^+$ T cells.[84] This therapy is usually well-tolerated, easy to apply, and can be combined with other therapies.[49] Even with all these advantages, the interest toward peptide-vaccine-based therapies has been declining due to lack of effectiveness in clinical trials. A 2006 case report showed near complete response for a patient with pancreatic cancer refractory to gemcitabine. The patient received a peptide-based vaccine with survivin peptides, an apoptosis inhibitor protein expressed in many malignancies. The patient experienced a complete remission of liver metastasis for up to 8 months but reoccurred when they were weaned of the treatment.[85] However, the results are not reproducible in larger clinical trials. Several phase I and II trials were developed from the early 2000s to test different peptide base vaccines in PDAC. Several peptides were used, including KRAS and MUC1 that are TAAs expressed in up to 90% of PDAC tumors.[86] Improved survival was reported in patients who developed an immunological response after the treatment. Yamamoto et al. reported a better survival up to 15.5 months in responders compared with 8 months in patients with locally advanced or metastatic PDAC treated with MUC1 peptide vaccine.[87] This therapy was also tested in an adjuvant setting after surgical resection in PDAC patients. A phase II clinical trial tested the KRAS peptide vaccine as an adjuvant after surgery with a mean overall survival of 44 months with a positive induced immune response specific to the mutant KRAS peptide.[88]

Peptide-based vaccine results were also less effective in CCA tumors. These vaccines mainly target Wilms tumor protein (WT1) and MUC1, which are widely expressed in CCA tumors.[89] A phase 1 trial of Wilms tumor 1 (WT1) vaccine and gemcitabine combination therapy for patients with advanced pancreatic cancer or biliary tract cancer was performed. The study enrolled 25 patients with a median survival of less than a year for both tumors. However, the study confirmed the safety of WT1 peptide vaccine in combination with gemcitibine.[90] MUC1 peptide vaccine was also tested with good safety result in three patients in a phase I clinical trial with no objective clinical results.[87] Multi-antigen vaccines seem to have better results in CCA tumors as proven by a phase clinical trial serval antigen

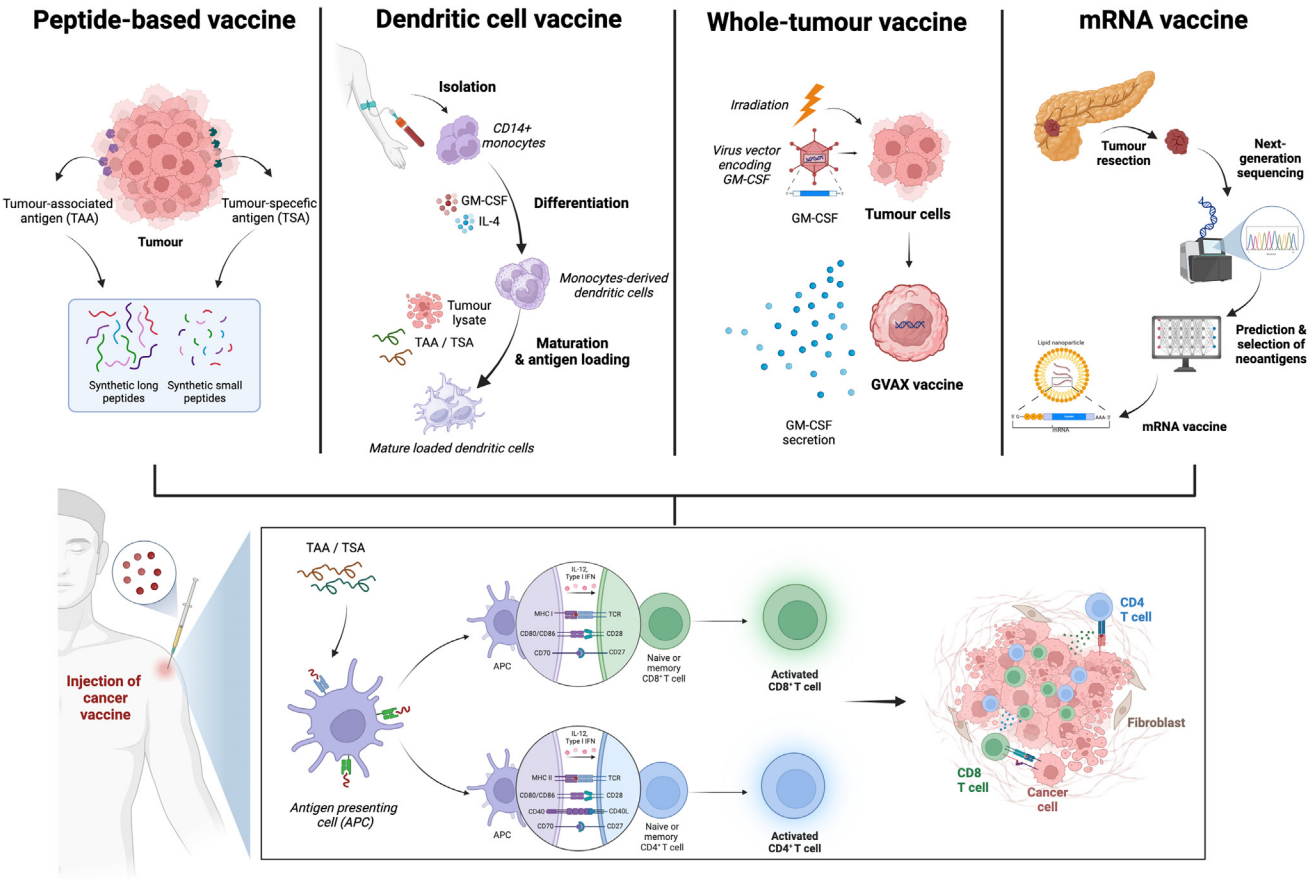

Figure 2. Visual description of four different types of cancer vaccines

Peptide-based vaccines use short or long chains of amino acids (peptides) that are derived from tumor antigens. These antigens are usually proteins that are overexpressed or unique to cancer cells (TAA/TSA). Dendritic cell vaccines involve isolating dendritic cells from the patient, loading them with tumor antigens (either whole-tumor lysate or specific antigens), and then reintroducing them into the patient. Whole-tumor vaccines utilize entire tumor cells or lysates, including various antigens expressed by the tumor, to stimulate an immune response. Messenger RNA (mRNA) vaccines involve introducing synthetic mRNA encoding tumor-specific antigens into the body. Through the vaccine injection, these antigens are presented by APCs to both $CD8^+$ and $CD4^+$ T cells. $CD8^+$ T cells are activated to directly target and destroy cancer cells, while $CD4^+$ T cells assist by secreting cytokines and enhancing the overall immune response.
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including cell division associated 1 (CDCA1), cadherin 3 (CDH3) and kinesin family member 20A (KIF20A) in patients with advanced biliary tract cancer. The median overall survival was up to 9.7 months with an objective targeted immune response.[91]

DC vaccines

DC-based cancer vaccines are designed to augment immunoreactivity within tumors, fostering the activation of $CD4^+$ and $CD8^+$ T cells through additional co-stimulation. DCs possess the capability to internalize diverse TAAs, effectively initiating antitumor responses in effector T cells. The infiltration of DCs into tumors has shown a positive correlation with T cell infiltration, indicating a favorable prognosis in various cancer types.[92,93] Notably, in 2007, the Swiss Institute of Public Health approved the world's first therapeutic vaccine for brain cancer, DCVax-Brain, while in 2010, the FDA sanctioned sipuleucel-T as a cancer vaccine for treating hormone-refractory prostate cancer. The activation of T cells by APCs necessitates antigen presentation coupled with stimulation signals, such as CD80 and CD86 on the APC's surface, in conjunction with a combination of proinflammatory cytokines. DC cell vaccines incorporate these crucial signals, facilitating an efficient induction of T cell responses directed toward specific antigens. This process entails isolating the patient's DCs, loading them *in vitro* with a tumor antigen, and subsequently inducing maturation and activation through a combination of cytokines (typically TNF, IL1b, IL6, and PGE2) and Toll-like receptor (TLR) agonists. The tumor antigen loaded onto DCs may consist of TSAs, TAAs, or whole-tumor cell lysates, particularly advantageous when the cancer type features unknown antigens.[94]

The source of DCs for vaccine engineering encompasses four distinct subtypes, including plasmacytoid DCs (pDCs), conventional DCs

(cDCs) further categorized into type 1 (cDC1) and type 2 (cDC2), and monocyte-derived DCs (MoDCs).[95] The majority of clinical trials predominantly employ MoDCs, easily obtained from $CD14^+$ monocytes in peripheral blood and treated with granulocyte-macrophage stimulating factor and IL-4 to generate DCs.[96] This subset can be extracted in larger quantities from peripheral blood, ensuring practicality and has demonstrated safety in various studies.[95]

The evolution of DC vaccines reflects the transition from first-generation to second-generation formulations. The initial DC vaccines, utilizing monocyte-derived natural DCs without activation, demonstrated limited efficacy with only a 7.1% tumor regression rate.[97] Subsequent second-generation DC vaccines employed an activation cocktail to stimulate DC maturation, resulting in an upgraded performance with an overall response rate of 8%–15% and an almost 20% increase in overall survival.[98] This improvement signifies the importance of enhancing DC maturation for achieving greater efficacy in vaccine therapy.

The next generation of DC vaccines focuses on utilizing specific subsets of this cell population, as discussed previously. A phase I clinical trial demonstrated the feasibility of manufacturing a DC vaccines with a specific sub-population, achieving 82% conventional DC type I. This treatment was well-tolerated with minimal adverse events in patients with hormone-refractory prostate cancer.[99] Extensively tested in melanoma patients, DC vaccines have been administered to over 1,250 patients in various clinical trials, yielding an objective response of 8.5%. Prostate cancer, glioblastoma, and renal cell cancer are also among the cancers widely treated with DC vaccines, showing response rates ranging from 7.1% for prostate cancer to 15.6% in glioblastoma.[98] In a recent phase III randomized control trial investigating the efficacy of lysate-loaded dendritic cell vaccine (DCVax-L) as an adjunct to standard-of-care therapy (temozolomide) in glioblastoma patients; those receiving the DC vaccine had a better median overall survival than those on standard therapy alone (19.3 vs. 16.5 months).[100]

However, the efficacy of DC vaccines in PDAC is yet to be substantiated by large controlled randomized trials. Ongoing trials for PDAC primarily fall within phases I and II, with limited benefits reported so far and no clearly reported objective responses. In one of the earliest phase I/II clinical trials testing DC vaccination in PDAC patients, autologous DC transfected with cDNA of the human tumor antigen mucin (MUC1) elicited an immunologic response in 40% of the cohort, demonstrating an increase in the frequency of mucin-specific IFN-γ-secreting $CD8^+$ T cells. However, no objective responses or improvements in survival were observed.[101] Another study employing MUC1-peptide-pulsed dendritic cells in seven patients with advanced pancreatic cancer showed increased IFN-γ and granzyme B levels, but all patients experienced disease progression.[102] Yet, a combination therapy using DC vaccines pulsed with a mixture of three types of WT1 peptide in conjunction with chemotherapy demonstrated a survival benefit in a phase I clinical trial for stage IV PDAC.[103] This therapy was also tested with MUC1-peptide as an adjuvant treatment in 12 patients with pancreatic and biliary cancer after resection, resulting in a 100% survival rate after the first year and a 33% 5-year overall survival in this cohort.[104] Similarly, the experimental design was tested with WT1-DC vaccine in resected patients with pancreatic cancer, achieving an overall survival at 2 years of 62.5%.[105]

Similarly to PDAC, DC vaccines in CCA have not yielded promising results compared with other cancer types. In a retrospective study involving 65 patients receiving a DC-based vaccine targeting various peptides, including WT1 and Mucin 1 for biliary tract cancer, the overall response rate was notably low, at only 6%.[106] However, combining DC vaccine therapy with adoptive T cell transfer has demonstrated more encouraging outcomes in the treatment of CCA. A cohort of 36 patients with intrahepatic CCA underwent autologous tumor lysate-pulsed dendritic cells, coupled with *ex vivo* activated T cell transfer as an adjuvant treatment following curative surgery. Significantly improved overall survival was observed in the group receiving DC cell vaccine and T cell transfer therapy compared with the surgery-alone group (31.9 vs. 17.4 months).[107] Ongoing clinical trials are exploring combinations of DC vaccines with existing treatments, such as radiotherapy (NCT03942328) and pembrolizumab, an anti-PD-L1 antibody (NCT03546361, NCT04201873).

Based on the current research literature, the use of DC vaccine as a standalone therapy in PDAC and CCA does not appear to yield significant results. DC vaccines may have limitations as single-agent therapies but show promise when integrated as adjuvant treatments after surgery or in combination with chemotherapy and ICIs. Consistent with previous discussions, the trials demonstrating the efficacy of DC vaccine therapy have necessitated a combination approach. The clinical application of DC vaccines has exhibited superior efficacy in an adjuvant setting, particularly following the reduction of tumor burden through surgery or chemotherapy.[94]

Cellular vaccines

This category of vaccine employs a whole-tumor approach to provide antigenic stimuli to the immune system.[108] Selecting the appropriate tumor antigen for vaccine therapy poses a challenge, and cellular vaccines have emerged as a strategy employing a diverse array of antigens, thereby enhancing efficacy against the tumor. One widely utilized type is GVAX, derived from allogeneic or autologous PDAC cell lines. These cells are genetically modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF) and are irradiated to prevent further division.[49]

GVAX was initially tested as an adjuvant treatment after resection in PDAC patients, yielding a noteworthy outcome with three out of 14 patients remaining disease-free for almost 2 years.[109] Combining GVAX with CRS-207, a live-attenuated *Listeria monocytogenes* expressing mesothelin, along with low-dose cyclophosphamide in patients with metastatic pancreatic cancer resulted in improved overall survival compared with chemotherapy alone (6.1 vs. 3.9 months).[110] In the context of resected pancreatic cancer, a clinical trial involving

87 patients demonstrated that those who received GVAX in the neoadjuvant and adjuvant settings had superior overall survival compared with those receiving it solely as an adjuvant treatment (35.0 vs. 24.8 months).[111] Neoadjuvant GVAX therapy was associated with the formation of vaccine-induced intratumoral tertiary lymphoid aggregates (TLA) in 85% of the cohort,[112] and patients with a higher TLA density exhibited better overall survival.[111] However, the efficacy of GVAX in the metastatic setting is limited, as evidenced by a phase II clinical trial where GVAX combined with ipilimumab was inferior to FOLFIRINOX as a maintenance treatment, with a median overall survival of 9.38 vs. 14.7 months, leading to trial discontinuation.[113] Several ongoing phase II clinical trials are exploring the combination of GVAX with radiotherapy or ICIs (NCT02648282, NCT03190265). Notably, GVAX is also under investigation in the neoadjuvant treatment of borderline resectable PDAC and as an adjuvant therapy for resected cancers.

In the realm of CCA, the utilization of whole-cell vaccines is still in a preclinical stage with limited available data. Limited *in vivo* studies, primarily focused on hepatocellular carcinoma, demonstrated the effectiveness of an irradiated whole-cell vaccine from hepatocellular carcinoma cells in suppressing tumor growth in a mouse model.[114]

The field of cellular vaccines is rapidly evolving, particularly with the prominent use of GVAX in PDAC tumors. The efficacy of this therapy appears more pronounced as an adjunct to surgical resection, as evidenced by successful trials in this context. While more phase III clinical trials are warranted in PDAC, additional phase I studies should be conducted to explore the potential of whole-tumor vaccines in CCA tumors.

Next-generation cancer vaccines

As previously discussed, the prevailing approach in vaccine therapy for cancer predominantly employs TAAs, often overexpressed in tumor cells but also present in normal cells. However, this characteristic poses a significant limitation, as TAAs can trigger autoreactive T cell responses, leading to organ toxicity and restricting vaccine efficacy. The negative selection process, inherent in immune responses to high-affinity T cells, further diminishes the effectiveness of the vaccine as a natural safeguard against autoimmunity.

Addressing these challenges, a promising frontier in vaccine therapy involves the engineering of vaccines targeting neoantigens, which are exclusively expressed in tumor cells, eliminating the risk of autoimmunity associated with TAAs. The future of cancer vaccines lies in personalized approaches, where neoantigens are selected based on the specific mutations unique to each patient's tumor, made possible through next-generation sequencing to identify TSAs. The first clinical application of this concept involved a trial targeting melanoma patients with a messenger RNA (mRNA) vaccine directed against personal neoantigens. Each patient received a personalized vaccine designed to target mutations identified through exome and mRNA sequencing of tumor biopsies. Notably, this approach yielded two objective responses in a group of five patients with metastatic disease. The trial also demonstrated the preventive potential of neoantigen vaccines in melanoma recurrence.[115]

Further extending the application of personalized mRNA neoantigen vaccines, a recent phase I clinical trial in pancreatic cancer yielded promising results. mRNA extracted from tumors underwent whole-exome and RNA sequencing to identify patient-specific mutations. Bioinformatics predicted neoantigens, and the vaccine was engineered to encode up to 10 MHC I and MHC II neoantigens. Administered as an adjuvant treatment post-surgical resection, in combination with atezolizumab (anti-PDL-1) and FOLFIRINOX, the treatment generated neoantigen-specific T cells in 50% of patients, with responses persisting up to 2 years post-treatment. This enduring T cell response correlated with delayed PDAC recurrence, challenging the perception of PDAC's low mutational burden.[116]

The trial demonstrated the feasibility of developing targeted vaccines against PDAC within a relatively short time frame of 9 weeks, showcasing the potential for personalized treatments for challenging tumors. Ongoing research, in the form of a phase II clinical trial (NCT05968326), aims to evaluate the combination of the mRNA vaccine, atezolizumab, and FOLFIRINOX compared with FOLFIRINOX alone in patients with resected PDAC. Future investigations should extend this promising therapy to biliary tract cancer.

PERSPECTIVES AND FUTURE DIRECTIONS

Pancreaticobiliary tumors rank among the most lethal malignancies, demonstrating resistance to conventional treatment modalities. Despite extensive efforts, these aggressive cancers have proven refractory to various therapeutic interventions. Immunotherapy, while holding promise for these challenging neoplasms, has exhibited limited efficacy in clinical trials conducted thus far. Nevertheless, a ray of optimism emerges as immunological responses are scrutinized in afflicted patients. Numerous trials have observed discernible immunological reactions, although the correlation with enhanced survival is not universally evident. Immunotherapy presents a compelling avenue for modulating the immune system and approaching tumor eradication from diverse perspectives. This adaptable therapeutic approach necessitates personalized implementation to tailor interventions according to the specific mutations unique to individual patients—an accomplishment beyond the capabilities of standard chemotherapy. Noteworthy advancements have been witnessed, particularly in adoptive T cell therapy and vaccine therapy, wherein optimal outcomes manifest when treatments are meticulously designed to target the distinct tumor antigens present in each patient. The advancements in precision therapy also bring the emergence of novel prospects for crafting tailored treatments, unique to the tumors of individual patients. Current clinical trials are actively exploring precision therapies directed at distinct genetic mutations such as KRAS, concomitant with inhibitors of pathways such as STAT3 in pancreas ductal adenocarcinoma.[117]

In advancing precision medicine, the utilization of patient-derived organoids (PDOs) emerges as a promising strategy for evaluating novel

immunotherapies. These PDOs offer a valuable platform for assessing the efficacy of tumor-specific cytotoxic T cells generated in response to adoptive cell therapy products, such as TCR T cells or CAR-T cells.[118] A preclinical study employed organoids derived from colorectal and non-small cell lung carcinoma cancers in co-culture with autologous peripheral blood lymphocytes. This co-culture system demonstrated efficiency in enriching and evaluating the cytotoxic capabilities of these T cells against corresponding tumors.[119] Given the expandability of PDOs from tumor biopsies, the ability to cultivate tumor-reactive T cells through co-culture with PDOs presents a novel avenue for TIL therapy in patients with unresectable diseases. Testing such therapies on models like organoids facilitates the identification of the most effective treatments, expediting access to efficient modalities while avoiding unnecessary delays associated with ineffective treatments and their related adverse events. Notably, data on the quality of life of patients in clinical trials is often underreported. While overall survival and disease-free survival are commonly reported outcomes in new therapy assessments, the absence of comprehensive reporting on quality of life is a notable gap. Considering the increasing application of immunotherapy in pancreaticobiliary cancer, it is imperative to include quality of life data in these clinical trials. A retrospective study assessing quality of life in clinical trials revealed that 50% of trials reporting an improved quality of life were utilizing immunotherapy drugs.[120] Integrating such assessments in future clinical trials can provide a more holistic understanding of the impact of immunotherapies on patients' well-being.

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AUTHOR CONTRIBUTIONS

N.A. conceived the main ideas for this paper, taking the lead in manuscript writing, the literature search, and selection. L.-H.T. handled the editing and revision of the manuscript, with J.C. providing additional perspectives and revisions as a patient-partner. All authors contributed to the article and approved the submitted version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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