

New targeted therapies in pancreatic cancer

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Abstract

Patients with pancreatic cancer have a poor prognosis with a median survival of 4-6 mo and a 5-year survival of less than 5%. Despite therapy with gemcitabine, patient survival does not exceed 6 mo, likely due to natural resistance to gemcitabine. Therefore, it is hoped that more favorable results can be obtained by using guided immunotherapy against molecular targets. This review summarizes the new leading targeted therapies in pancreatic cancers, focusing on passive and specific immunotherapies. Passive immunotherapy

may have a role for treatment in combination with radiochemotherapy, which otherwise destroys the immune system along with tumor cells. It includes mainly therapies targeting against kinases, including epidermal growth factor receptor, Ras/Raf/mitogen-activated protein kinase cascade, human epidermal growth factor receptor 2, insulin growth factor-1 receptor, phosphoinositide 3-kinase/Akt/mTOR and hepatocyte growth factor receptor. Therapies against DNA repair genes, histone deacetylases, microRNA, and pancreatic tumor tissue stromal elements (stromal extracellular matrix and stromal pathways) are also discussed. Specific immunotherapies, such as vaccines (whole cell recombinant, peptide, and dendritic cell vaccines), adoptive cell therapy and immunotherapy targeting tumor stem cells, have the role of activating antitumor immune responses. In the future, treatments will likely include personalized medicine, tailored for numerous molecular therapeutic targets of multiple pathogenetic pathways.

Key words: Immunotherapy; Pancreas neoplasm; Vaccines

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Core tip: Adjuvant therapy in pancreatic cancer has limited efficiency, and low survival rates are related to resistance to gemcitabine. New targeted therapies, such as passive immunotherapy, may have a role in combination with radiochemotherapy by targeting various protein kinases, as well as specific immunotherapies, such as vaccines, adoptive cell therapy and immunotherapy targeting tumor stem cells. In the future, treatments will likely include personalized medicine, tailored for numerous molecular therapeutic targets of multiple pathogenetic pathways.

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INTRODUCTION

Patients with pancreatic cancer (PC) have a poor prognosis with a median survival of 4-6 mo and a < 5% five-year survival rate^[1]. Over 80% of patients have advanced disease at presentation (metastasis or invasion of the superior mesenteric artery or celiac trunk in case of locally advanced tumors), which does not allow for surgical resection of the tumor^[2]. Even if resection can be achieved, the median survival is still only 18 mo^[3]. Despite therapy with gemcitabine (GEM), which represents the first-line therapy for advanced tumors, patient survival typically does not exceed 6 mo for metastatic disease and 9-12 mo for locally advanced disease, likely due to natural resistance to GEM^[4,5]. FOLFIRINOX represents an alternative to gemcitabine in first line settings, with better survival, but it is suitable only for good performance status patients. As second line treatment, GEM-platinum-based combination provide the best results^[6]. Therefore, it is hoped that more favorable results can be obtained by using passive and specific immunotherapies against molecular targets.

PASSIVE IMMUNOTHERAPY

Passive immunotherapy involves *in vivo* infusion of monoclonal antibodies or *in vitro*-activated T cells. Monoclonal antibodies have been created to act on molecules at the cell surface of the tumor and on stromal tissue in connection with PC oncogenesis, tumor growth, and chemotherapy-resistant or immune-response regulation. Currently developed therapies target pre-transcriptional kinases, post-transcriptional level (DNA repair genes, histone deacetylases, microRNAs), antipancreatic tumor tissue stromal elements and antiangiogenic factors (Figure 1).

Anti-kinase therapies

Tyrosine kinases are important in the proliferation, migration, invasion, and resistance to apoptosis of tumor cells, and involve activation of mitogen-activated protein kinase (MAPK; which is responsible for the malignant transformation of pancreatic cells^[7]), phosphoinositide 3-kinase (PI3K; which stimulates cell proliferation and chemotherapy resistance^[8]), and protein kinase B [Akt; the overexpression of which promotes invasion and expression of insulin growth factor receptor (IGF-1R)^[9,10]]. In addition, K-ras is involved in the pathogenesis of PC *via* tyrosine kinase pathways^[11,12]. The expression of two tyrosine kinase receptors, epidermal growth factor receptors (EGFRs) B-1 and B-2, has been found in 90% and 21% of PCs, respectively^[13,14]. Increased coexpression of EGFR

and its ligand in PC is associated with greater liver metastasis and poorer prognosis^[15-17].

Anti-EGFR: Therapies involving anti-EGFR (epidermal growth factor receptor or HER1) monoclonal antibodies include cetuximab, a chimeric IgG1-type, and panitumumab, a humanized IgG2-type antibody. These antibodies reversibly inhibit the tyrosine kinase domain of EGFR by competitive binding of ATP. As a result of antibody binding, the receptor internalizes, complement-mediated cytotoxicity appears, and cell division is stopped. However, the anti-EGFR mechanism may not be effective if there are mutations in the *KRAS* gene. Cetuximab seems to be more effective than panitumumab, as IgG1 receptors are more effective than IgG2^[18]. However, its efficiency was not proved in clinical trials (Table 1).

Erlotinib is a small inhibitor of EGFR that increases survival by two weeks vs GEM monotherapy^[28,52]. However, resistance to erlotinib after an initial response can occur due to EGFR mutations, compensation through hepatocyte growth factor receptor (c-Met), human epidermal growth factor receptor (HER2) or K-ras amplification, EGFR-mediated pathway impairment, and histologic transformation with the addition of a mesenchymal component^[53]. Combined with GEM or capecitabine, erlotinib can increase survival approximately one month over conventional monotherapy^[54,55], proving its positive role in overall survival and progression disease free^[28]. Long survival was proved in association with radiotherapy and capecitabine, followed by association with GEM^[26]. The dose escalated to rash does not improve the survival rate in gemcitabine refractory patients^[56]. As second-line therapy, the erlotinib based-therapy failed to show significant improvement in overall survival compared to other regimens^[6]. A phase III study found that the wild-type *KRAS* genotype is associated with an improved overall survival (OS) in erlotinib-treated PC^[57], but it is more of a prognostic than a predictive factor^[58]. Other drugs in this class, such as gefitinib, have not been shown to be effective in PC^[59]. Lapatinib caused reduction of cell growth and proliferation, but it has only been tested in PC cell lines^[60]. Vatalanib is an oral poly-tyrosine kinase inhibitor with strong affinity for platelet-derived growth factor and vascular endothelial growth factor (VEGF) receptors (VEGFRs). In metastatic disease it provided limited survival gain compared to historic controls^[61].

Anti-HER2: Trastuzumab, a humanized direct antibody against HER2 (human epidermal growth factor 2) kinase, was used in combination with GEM, but there was no survival benefit in phase II studies^[29,30]. As the presence of HER2 is relatively low in PC specimens^[62,63], anti-HER2 and anti-EGFR therapies can be combined, producing a synergistic effect in animal models that is independent of EGFR density^[64]. The mechanism of this combined action

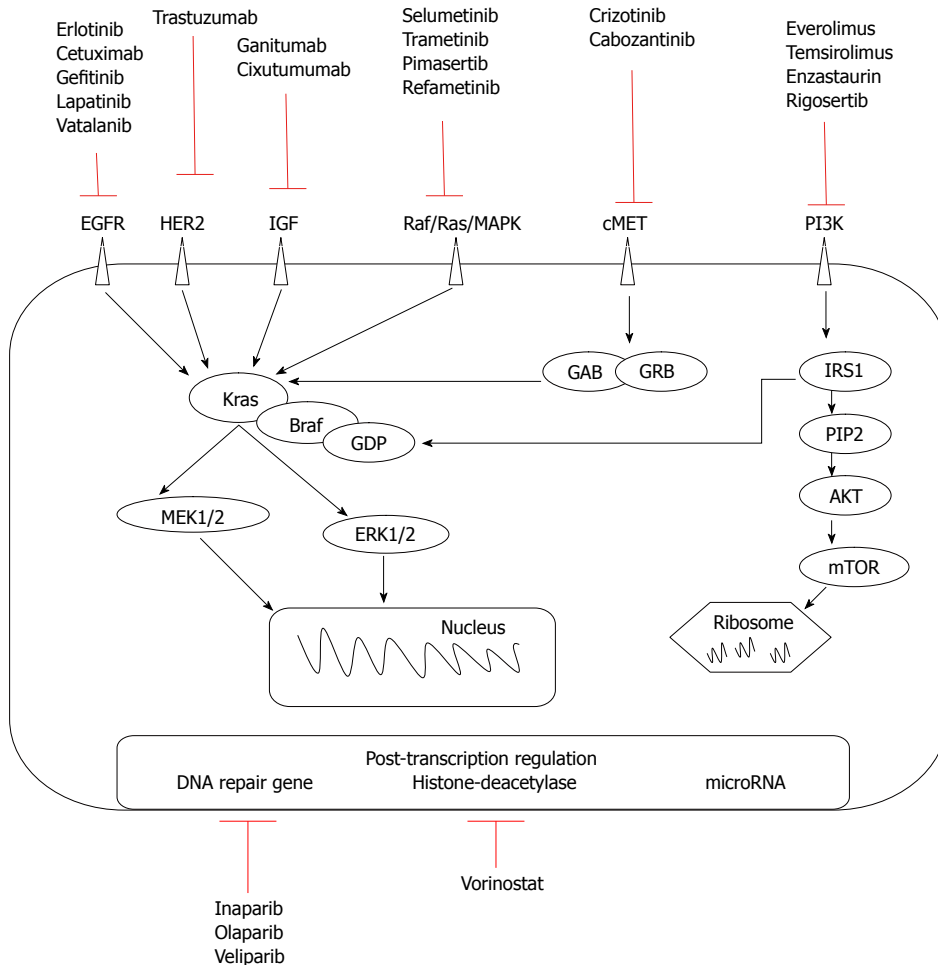


Figure 1 New targeted therapy at the cell surface of the tumor.

is based either on decreased Akt phosphorylation or on disturbance of EGFR/HER2 heterodimerization^[65]. The same mechanism of action occurs with vitamin E isoforms, such as tocotrienols, which inhibit cell proliferation and cell survival in studies on PC cell lines^[66].

Anti-MAPK: Inhibitors of the Ras/Raf/MAPK cascade, which represents the effect of K-ras activation, are being tested in clinical trials. In GEM failure therapy, selumetinib had the same efficacy as capecitabine^[31], though it seems promising in association with erlotinib^[67]. Trametinib inhibits the proliferation of PC cell lines with increased efficiency if EGFR/HER2 inhibitors are added, likely because inhibition of the MAPK pathway leads to activation of the tyrosine kinase pathway through feedback mechanisms^[68]. Trials with trametinib and other MAPK cascade inhibitors (pimasertib ClinicalTrial.gov NCT01668017, NCT01390818 and refametinib ClinicalTrial.gov NCT01764828, NCT01392521) are still ongoing.

Anti-IGF-1R: IGF-1R is potentially a predictive marker of resectability in PC. A phase II study for treatment of metastatic PC with monoclonal antibodies against

IGF-1R showed that ganitumab resulted in a 10-mo survival benefit^[34]. However, a phase III study showed no survival improvement^[33]. Experimental studies that have associated anti-EGFR therapy with anti-IGF-1R monoclonal antibodies have shown promising results^[69], but addition of cixutumumab to erlotinib and GEM did not lead to longer survival in metastatic PC^[24].

Anti-c-Met: c-Met and its ligand are overexpressed in PC, but are not sufficient for tumorigenesis in the absence of other pro-oncogenes. Crizotinib is an inhibitor of c-Met that has a role in reducing tumor progression and metastasis, showing efficacy in stimulating apoptosis in combination with GEM^[70-73]. Cabozantinib is another inhibitor of c-Met and tumor stem cell markers. Treatment in association with IGF-1R inhibitors may represent a future therapy^[74].

Anti-PI3K/Akt/mTOR: The PI3K/Akt/mTOR pathway is one of the major signaling pathways mediating the effect of K-ras. Akt stimulates the phosphorylation of mTOR kinase *via* activation of cyclin D1 and VEGF. mTOR inhibitors, such as everolimus and temsirolimus, have been tested in a phase II trial in patients with GEM-refractory PC, but with negative results^[75,76].

Table 1 Results of different studies concerning new targeted therapy

Ref.	Patients no./disease stage	Study type	Drugs	OS	PFS	Benefit
Burtness <i>et al</i> ^[19] , 2014	87/metastatic	II RCT	Docetaxel + Irinotecan ± Cetuximab	6.5 vs 5.4	3.9 vs 4.5	Negative
Fensterer <i>et al</i> ^[20] , 2014	73/resected	II	GEM + Cetuximab	22.4	NA	Negative
Philip <i>et al</i> ^[21] , 2010	743/locally advanced or metastatic	III RCT	GEM ± Cetuximab	5.9 vs 6.3	3 vs 3.5	Negative
Munter <i>et al</i> ^[22] , 2008	66/locally advanced	II RCT	RT + GEM ± Cetuximab	15	-	Negative
Lim <i>et al</i> ^[23] , 2014	127/locally advanced	Retrospective	GEM + Capecitabine vs GEM + Erlotinib vs GEM	21 vs 12 vs 15	8.9 vs 5.2 vs 3.9	Negative for Erlotinib
Philip <i>et al</i> ^[24] , 2014	10/metastatic	I RCT	GEM + Erlotinib + Cixutumumab vs GEM + Erlotinib	7 vs 6.7	3.6 vs 3.6	Negative
Watkins <i>et al</i> ^[25] , 2014	44/advanced	II	GEM + Capecitabine + Erlotinib + Bevacizumab	12.6	8.4	
Herman <i>et al</i> ^[26] , 2013	48/metastatic	II	Capecitabine + Erlotinib + RT followed by GEM + Erlotinib	24.4	15.6	
Feliu <i>et al</i> ^[27] , 2011	42/advanced	II RCT	GEM + Erlotinib	8	5	Negative
Moore <i>et al</i> ^[28] , 2007	569/advanced	III RCT	Gem + Erlotinib vs GEM	6.2 vs 5.9	3.7 vs 3.5	Positive
	17/metastatic HER2+	II	Capecitabine + Trastuzumab	6.9	12.5	Negative
Harder <i>et al</i> ^[29] , 2012						
Safran <i>et al</i> ^[30] , 2004	34/metastatic	II	Gemcitabine + Trastuzumab	7		Negative
Bodoky <i>et al</i> ^[31] , 2012	70/advanced	II	Capecitabine vs Selumetinib	5 vs 5.4	88% vs 84%	Negative
Infante <i>et al</i> ^[32] , 2014	160/metastatic	II RCT	GEM + Trametinib vs GEM	8.4 vs 6.7	-	Negative
Fuchs <i>et al</i> ^[33] , 2015	322/metastatic	III RCT	GEM + Ganitumab vs GEM	7.2 vs 7	3.7 vs 3.6	Negative
McCaffery <i>et al</i> ^[34] , 2013	84/metastatic	II RCT	GEM+Ganitumab vs GEM	16 vs 5.9		Positive
Kindler <i>et al</i> ^[35] , 2012	125/metastatic	II RCT	GEM + Ganitumab vs GEM + Conatumumab vs GEM	8.7 vs 7.5 vs 5.9	5.1 vs 4 vs 2	Positive
Bramhall <i>et al</i> ^[36] , 2002	239/advanced	RCT	GEM + Marimastat vs GEM	165.5 d	92.5 d	Negative
De Jesus-Acosta <i>et al</i> ^[37] , 2014	17/metastatic second line therapy	I	GEM+ inhibitor γ secretase	4	1.5	Positive
Goldstein <i>et al</i> ^[38] , 2015	861/metastatic	III RCT	GEM + Nab-paclitaxel vs GEM	8.7 vs 6.6	-	Positive
Hosein <i>et al</i> ^[39] , 2013	19/advanced second line therapy	II	GEM + Nab-paclitaxel	7.3	-	Positive
Pant <i>et al</i> ^[40] , 2014	30/advanced locally	II	GEM + Capecitabine Bevacizumab	10.4		Negative
Kindler <i>et al</i> ^[41] , 2010	535/advanced	III RCT	GEM + Bevacizumab vs GEM	5.8 vs 5.9	3.8 vs 2.9	Negative
Crane <i>et al</i> ^[42] , 2009	82/advanced	II	RT + capecitabine+bevacizumab, followed by GEM + bevacizumab	11.9		Negative
Ko <i>et al</i> ^[43] , 2010	36/metastatic GEM refractory	II	Bevacizumab + Erlotinib	102 d		Negative
Van Cutsem <i>et al</i> ^[44] , 2009	607/metastatic	III RCT	GEM + erlotinib + bevacizumab vs GEM + erlotinib	7.1 vs 6	4.6 vs 3.6	Negative
IokaT <i>et al</i> ^[45] , 2015	632/advanced	III RCT	GEM + axitinib vs GEM	5.1 vs 5.4	-	Negative
Spano <i>et al</i> ^[46] , 2008	103/advanced and metastatic	II RCT	GEM + axitinib vs GEM	6.9 vs 5.6	-	Negative
Kindler <i>et al</i> ^[47] , 2011	632/advanced or metastatic	III RCT	GEM + axitinib vs GEM	8.5 vs 8.3	-	Negative
Rougier <i>et al</i> ^[48] , 2013	427/metastatic	III RCT	GEM + Aflibercept vs GEM	6.5 vs 7.8	3.7 vs 3.7	Negative
Chiorean <i>et al</i> ^[49] , 2014	27/advanced		GEM + Sorafenib followed by RT + GEM	12.6	10.6	Negative
Cascinu <i>et al</i> ^[50] , 2014	144/advanced	II RCT	GEM + Cisplatin + Sorafenib vs GEM + Cisplatin	7.5 vs 8.3	4.3 vs 4.5	Negative
Gonçalves <i>et al</i> ^[51] , 2012	104/advanced or metastatic	III RCT	GEM + Sorafenib vs GEM	5.7 vs 3.8	9.2 vs 8	Negative

OS: Overall survival; PFS: Progression free survival; RCT: Randomized control trial; Advanced diseases: Locally advanced and metastatic; RT: Radiotherapy; GEM: Gemcitabine.

Rapamycin, another mTOR inhibitor, has also failed to demonstrate efficacy in the treatment of PC in humans^[76]. Everolimus and enzastaurin had no effect on GEM-resistant tumor therapy or on advanced tumors^[75,77]. Rigosertib, a small molecular inhibitor of PI3K, added no survival benefit in a phase III trial^[78]. Early phase clinical trials of other inhibitors of the P13K/Akt/mTOR pathway or combining these inhibitors

with chemotherapy in PC are ongoing parentheses ClinicalTrials.gov; NCT02294006, NCT01087554, NCT01537107 parentheses.

Therapy against DNA repair genes

PC may induce expression of DNA repair genes at post-transcriptional level from BRCA category 1 or 2 in 7%-10% of sporadic tumors^[79]. We believe that such

Table 2 Potential therapeutic targets using miRNA

Ref.	miRNA	Oncogene/tumor suppressor	Target genes	Cellular process affected
Moriyama <i>et al.</i> ^[99] , 2009	miR-21	Oncogene	<i>CDK6, PDCD4, CDKN1A, FAS, IL6R, SOCS5, APAF1, NFIB, TPM1</i>	Apoptosis, cell proliferation, cell invasion
Park <i>et al.</i> ^[94] , 2009	miR-221	Oncogene	<i>CDKN1B, CDKN1C, KIT</i>	Cell migration, proliferation
Habbe <i>et al.</i> ^[100] , 2009	miR-155	Oncogene	<i>AGTR1, APC, ARID2, BACH1, CEBPB, CYR61, DET1, EDN1, ETS1, FADD, FGF7, FOXO3</i>	Cell migration
Chen <i>et al.</i> ^[101] , 2011	miR-196a	Oncogene	<i>NRAS, HOXB8, HMGA2, ANXA1</i>	Cell growth and differentiation
Cai <i>et al.</i> ^[95] , 2013	miR-181b	Oncogene	<i>BCL2</i>	Sensitization to gemcitabine
Yan <i>et al.</i> ^[96] , 2010	miR-20a	Oncogene	<i>STAT3, CDH1</i>	Proliferation and invasion
Torrisani <i>et al.</i> ^[102] , 2009	Let-7	Tumor suppressor	<i>KRAS, HMGA2, TRIM71, NF2</i>	Cell proliferation
Ji <i>et al.</i> ^[98] , 2009	miR-34a	Tumor suppressor	<i>NOTCH1, BCL2, E2F3, VEGFA, SIRT1, CCND1, CDK6</i>	Apoptosis, cell proliferation
Zhao <i>et al.</i> ^[103] , 2010	miR-217	Tumor suppressor	<i>KRAS, SIRT1, PTEN</i>	Cell proliferation, invasion
Yu <i>et al.</i> ^[97] , 2010	miR-96	Tumor suppressor	<i>KRAS</i>	Invasion, cell migration, apoptosis
Li <i>et al.</i> ^[104] , 2010	miR-146a	Tumor suppressor	<i>EGFR</i>	Invasion
Hou <i>et al.</i> ^[105] , 2012	miR-216a	Tumor suppressor	<i>PTEN, CDC42, CD44, SIRT1</i>	Tumorigenicity

tumors are more sensitive to the administration of polymerase inhibitors (iniparib), as verified *in vitro*^[80] and *in vivo* in a patient who achieved pathologic complete response^[81]. Treatments with olaparib or veliparib, in combination with GEM or alone, are currently being assessed in ongoing trials (ClinicalTrials.gov; NCT00515866 and NCT01908478)^[82].

Therapy against histone deacetylases

Chromatin is formed by the wrapping of DNA around histones, a process that is regulated by histone acetylation status. Epigenetic regulation of tumor suppressor genes *via* deacetylation of histones is involved in the apoptosis, differentiation and growth of cells, which influence tumor cell survival. Suberoylanilide hydroxamic acid (vorinostat) administered in combination with GEM and bortezomib, a 26S proteasome antagonist, confers a strong apoptotic, especially in association with bortezomib and GEM and radiosensitizing effect through the nuclear factor- κ B pathway, which is not activated in normal tissue^[83-86]. Phase I and II trials using such substances in association with radiotherapy are ongoing (e.g., Clinical Trial.gov. NCT00983268, NCT00243100 and NCT00948688 for nonmetastatic disease).

Therapy against microRNAs

miRNAs are single-stranded chains of non-coding RNA of 18-24 nucleotides that inhibit gene expression at the post-transcriptional level *via* triggering complete degradation of the proteins or halting translation. miRNAs can influence the proliferation, apoptosis, and susceptibility of tumors to chemotherapeutic agents. miR-21 regulates the expression of the tumor suppressors *CDKN1A*, *PTEN* and *PDCD4*, and can be stimulated by taking medications that interfere with tyrosine kinase pathways^[87]. This miRNA is overexpressed in 79% of evaluated PCs, and represents an unfavorable prognostic factor^[88]. miR-21 is also frequently found in chemoresistant pancreatic cells^[88-90], and a lower level was associated with better

response to GEM^[91]. In addition, miR-21 upregulates Bcl-2 and reduces chemosensitivity to GEM, thus increasing cell proliferation^[92].

Inhibition of miR-221 in PC cells suppresses proliferation and upregulates the tumor suppressors *PTEN*, and p27, p57 and PUMA^[93]. Introducing anti-sense oligonucleotides targeting miR-221 or miR-21 induces apoptosis and increases cell sensitivity to GEM^[94]. Furthermore, miR-181b increases the response of animals and chemoresistant cell lines to chemotherapy^[95]. miR-20a targets tumor suppressor gene *CDH1* and reduces proliferation and metastasis^[96]. miR-96 regulates the expression of *KRAS*, and shows low expression in PC compared to normal tissues^[97]. Administration of a synthetic precursor of this miRNA also decreases cell proliferation and invasion^[97]. Therapeutic overexpression of miR-34, which targets the tumor suppressor p53, decreases cell growth, arrests the cell cycle in G1 and G2/M phases, and sensitizes cells to chemotherapy^[98]. A summary of cancer-related target genes is presented in Table 2^[94-105].

Therapy against stromal compartments

A number of studies have targeted stromal elements of PC, including the extracellular matrix, various intracellular signaling pathways, and immune cells (Figure 2, Table 3)^[36,106-114].

Therapies against stromal extracellular matrix: In the past few years, scientists have begun to appreciate the importance of the microenvironment in sustaining pancreatic tumor growth. The microenvironment of PC is characterized by an extensive deposition of extracellular matrix components and hypovascularity. These desmoplastic features are believed to prevent drug delivery and contribute to primary resistance of drug therapy. When targeting the stromal tissue, the difference between local tumor and metastasis microenvironments should be considered. Metastasis is characterized by the ability of tumor cells to escape

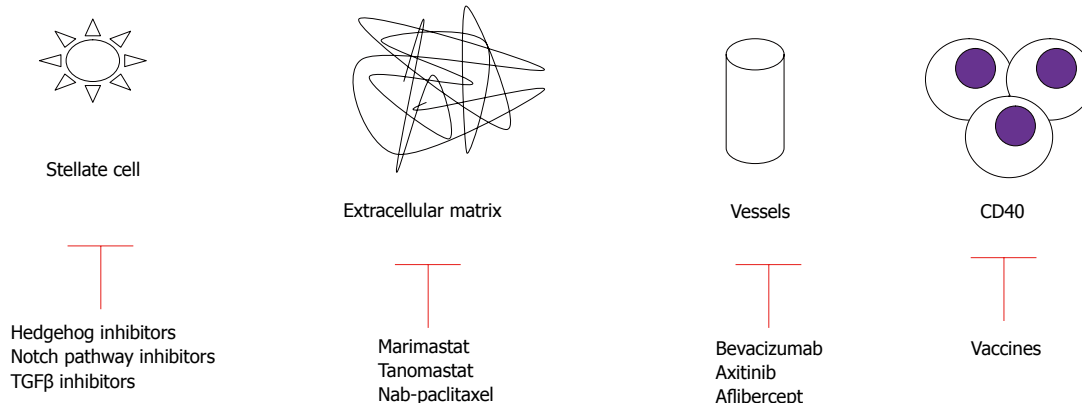


Figure 2 New targeted therapy directed against stromal compartments.

Table 3 Studies with monoclonal antibodies that target the tumor stromal component			
Ref.	Stromal component	Therapeutic target	Treatment
Strimpakos <i>et al</i> ^[106] , 2013	Extracellular matrix	Hyaluronan	PEGPH20
Bramhall <i>et al</i> ^[36] , 2002	Extracellular matrix	Metalloproteinase	Marimastat
Stephenson <i>et al</i> ^[107] , 2011	Signaling pathways	Hedgehog	Vismodegib (GDC-0449)
Oettle <i>et al</i> ^[108] , 2009	Signaling pathways	Transforming growth factor β receptor	Trabectedin
Yabuuchi <i>et al</i> ^[109] , 2013	Signaling pathways	Notch	PF-03084014
Brahmer <i>et al</i> ^[106] , 2012	Immune cells	Receptor for programmed cell death	BMS-936559
Le <i>et al</i> ^[111] , 2013	Immune cells	Cytotoxic T-lymphocyte antigen 4	Ipilimumab
Beatty <i>et al</i> ^[112] , 2013	Immune cells	CD40	CP-870893
Lutz <i>et al</i> ^[113] , 2011	Immune cells	CB8	GVAX
Laheru <i>et al</i> ^[114] , 2008	Immune cells	CB8	GVAX

GVAX: Granulocyte-macrophage colony-stimulating factor vaccine.

from the primary tumor, survive in circulation, and invade and establish colonies in distant sites, thus warranting special consideration in the design of clinical studies^[115].

Matrix metalloproteinases are a family of proteolytic enzymes responsible for the breakdown of connective tissue proteins. These enzymes are crucial in maintaining the growth, differentiation and repair of normal healthy tissue, but aberrant expression is associated with invasive activities of solid tumors^[116]. However, inhibition of matrix metalloproteinases by marimastat and tanomastat showed no clinical activity in combination with GEM^[36,117]. The extracellular matrix also contains hyaluronan (a nonsulfated glycosaminoglycan), is highly abundant in pancreatic tumors, and has been implicated in angiogenesis, epithelial mesenchymal transition, and chemoresistance^[118]. A phase Ib study combining GEM with hyaluronidase demonstrated partial response in 64% of PC patients with high levels of hyaluronan^[106]. A phase II study of this combination is currently underway ClinicalTrials.gov; NCT01453153.

Therapies against intracellular signaling pathways:

Transforming growth factor (TGF)-β signaling has been implicated in cancer cell proliferation, tumor angiogenesis, metastasis, and suppression of antitumor immunity^[119,120]. Its overexpression is

associated with disease stage, clinical prognosis, and the immunodeficient state of the patients. TGF-β signaling is mediated by SMAD4, for which 50% of human PCs show allelic deletion^[121]. The complex TGFβ-SMAD4 translocate to the nucleus, where they interact at the promoter with other transcription factors at DNA sequence-specific binding sites or with transcriptional coactivators. Thus, aberration of TGFβ-SMAD4 signaling is believed to be an important step in pathogenesis of this cancer^[122]. SMAD4 mutation leads to feedback overexpression of TGF-β1. Development of anti-TGF treatment in advanced PC is still in the early clinical stage (ClinicalTrials.gov NCT00844064).

The hedgehog pathway has been shown to be an important signaling system in the microenvironment of PC. The sonic hedgehog ligands are present in the fibroblasts of the PC, but not in the normal pancreatic fibroblasts^[123]. Binding of the sonic hedgehog ligand to its patched receptor activates the smoothed and zinc finger proteins, driving the expression of several target genes responsible for desmoplastic reactions and inhibition of pancreatic cell autophagy^[124]. Sonic hedgehog is expressed in cancer stem cells (CSCs), rare tumor cells with abilities of self-renewal which are responsible for tumor recurrence and metastasis, as well as resistance to current therapies^[125]; thus, this factor represents an attractive target for therapeutic intervention. Saridegib IPI-926 is an inhibitor of this

pathway that elevates intratumoral concentrations of GEM, reduces the dense fibrotic reaction, and increases tumor neo-vascularization in an animal model^[126]. However, in a double-blind randomized placebo-controlled phase II study, the combination of GEM with Saridegib was associated with shorter survival in PC patients, and the trial was terminated prematurely^[127].

The dense fibro-inflammatory microenvironment of PC results in hypoxia, which activates hypoxia-inducible factor-1 α and promotes tumor cell secretion of sonic hedgehog. As a result, the epithelial to mesenchymal transition is activated, CSCs are maintained, and resistance to therapy occurs. Moreover, hypoxia-inducible factor-1 α activates leptin receptors and influences metastasis and survival^[128], and activates actin-related mechanisms as well^[129]. Myo-inositol trispyrophosphate can reverse hypoxia and decrease desmoplasia in an animal model, with improved susceptibility to GEM treatment^[130,131]. Gene expression of hypoxia-inducible factor 1 α was reduced in an animal model by administration of a novel synthetic compound^[132], which is currently being tested in an ongoing trial (ClinicalTrials.gov; NCT01248637).

Hypoxic conditions can also trigger Notch signaling, which plays a critical role in organ development and cell differentiation. Notch signaling mediates PC stem cell function, which contributes to chemotherapy resistance, tumor recurrence, and metastasis. Upon receptor activation, Notch is cleaved by a cascade of proteolytic enzymes, including metalloproteinases, tumor necrosis factor- α -converting enzyme, and γ -secretase^[133]. The oral γ -secretase inhibitor RO4929097 has completed a phase I trial for treatment of metastatic cancer, and results are promising. Recently, preliminary results from two phase I clinical trials testing anti-Notch antibodies (OMP-59R5 and demcizumab) have been presented^[134,135]. A phase I study of an oral Notch inhibitor (MK-0752) in combination with GEM is now ongoing (ClinicalTrials.gov; NCT010983440).

Enhanced drug delivery to microenvironment:

Inefficient drug delivery might explain the lack of efficacy of systemic treatments. Novel drug delivery vehicles have reformed the clinical use of traditional cytotoxic agents. Nab-paclitaxel is an albumin-bound formulation that increases tumor accumulation of paclitaxel *via* binding of albumin to the surrounding stroma that is enriched in secreted protein acidic and rich in cysteine (SPARC). Nab-paclitaxel was developed to exploit the ability of SPARC to bind to albumin as a means of increasing drug delivery to the tumor^[136]. In an animal model, intratumoral concentration of GEM was increased 2.8-fold in mice receiving nab-paclitaxel in combination with GEM, and treatment of patients with nab-paclitaxel alone was also more effective than GEM alone (aggregate tumor regression rates of 55%, 36% and 24% for nab-paclitaxel plus GEM,

nab-paclitaxel alone and GEM alone, respectively)^[137]. These findings suggest that nab-paclitaxel is able to destroy or alter the characteristics of the tumor stroma and increase vascularization in order to achieve enhanced delivery of cytotoxic chemotherapy to the tumor. Indeed, in two GEM-resistant xenografts, a profuse desmoplastic stroma remained after treatment with vehicle or GEM alone, whereas the administration of nab-paclitaxel resulted in a significant reduction in stromal content^[108]. In another study using the GEM-resistant mouse model, treatment with nab-paclitaxel and GEM also resulted in an increase in intratumoral GEM concentration and a reduction in tumor size compared with treatment with either agent alone^[138].

In a recently published phase III study comparing nab-paclitaxel plus GEM vs GEM alone, the addition of nab-paclitaxel significantly prolonged median OS from 6.7 to 8.5 mo, with a corresponding increase in response rate from 7% to 23%^[139], and after one year from 22% to 35%^[137,140]. The nab-paclitaxel/GEM combination has become the second regimen shown to be superior to GEM alone and has been approved by the FDA for treatment of advanced PC. In a second-line setting, nab-paclitaxel monotherapy demonstrated clinical activity in GEM-refractory advanced PC patients in a phase II trial^[39]. In this trial, high expression of stromal protein was used to specifically enrich the concentration of a cytotoxic agent in the tumor. Additionally, Alvarez *et al.*^[141] demonstrated that nab-paclitaxel reduces the stiffness and the number of cancer-associated fibroblasts in human tumors treated with nab-paclitaxel. Its combination with different agents is now one of the most popular areas of clinical research in advanced PC. Another innovative approach to improve drug delivery that is under development is the use of nanotechnology and cancer-specific liposomes^[142].

Antiangiogenic therapies

Antiangiogenesis is clinically ineffective in treating PC patients. Although most preclinical models of PC have suggested potential activity of many antiangiogenic agents, they failed to simulate human tumor microenvironments where dense stromal tissue with decreased vascular density is now known to be the main obstacle for effective drug delivery. Moreover, the withdrawal of antiangiogenic agents after therapy may be associated with increased tumor aggressiveness and invasion, offsetting the potential therapeutic benefits offered by antiangiogenic agents. It has also been said that angiogenesis inhibition might alter the natural history of tumors by increasing tumor invasion and metastasis^[143].

Overexpression of VEGF in PC has been associated with tumor progression and a worse prognosis. Therefore, similar to other cancer therapies, angiogenesis is considered to be a therapeutic target^[144,145]. Humanized monoclonal antibodies such as bevacizumab have affinity for circulating VEGF-A, but phase II and III studies

showed no survival advantage when bevacizumab was combined with GEM and erlotinib^[41-44]. A meta-analysis found that therapy with bevacizumab-GEM was associated with a modest response rate, without survival modifications^[52]. Associations of two chemotherapeutic agents (GEM, capecitabine) with two biologic therapies (erlotinib, bevacizumab) provided an additional ten months of survival in metastatic disease^[25]. The proposed mechanism for this effect involves the overexpression of platelet-derived growth factor and fibroblast growth factor^[146]. The development of bevacizumab-related hypertension is also associated with better survival^[147]. Other VEGF inhibitors, such as axitinib and aflibercept, provide no survival advantage^[46-48,148]. In addition, sorafenib (an inhibitor of VEGFR and Ras/Raf/MAPK signaling) had no supplementary value for patient survival over GEM^[51].

SPECIFIC IMMUNOTHERAPY

In pancreatic adenocarcinoma, interactions between tumor and host cells are mediated by inflammatory cells, fibroblasts and vascular endothelial cells. Intratumoral desmoplastic tissue is less vascularized, and cytotoxic substances cannot easily penetrate the connective matrix. Therefore, inflammatory cells and macrophages represent potential therapeutic targets. These cells can acquire antitumor properties, which is the main purpose for specific immunotherapies, including vaccines and adoptive cell therapy.

Antitumor vaccines are biologic preparations that involve administering an antigen that is specific for a particular tumor type and stimulating the body's natural ability to protect itself. There are a number of ways to deliver these vaccines: whole-cell recombinant vaccines, dendritic cell (DC) vaccines that combine antigen with DCs to present to white cells, DNA vaccines (by inserting viral or bacterial DNA into human or animal cells), or T-cell receptor peptide vaccines (by inserting peptides to modulate cell-mediated immunity).

Whole-cell recombinant vaccines

The advantage of using whole-cell recombinant vaccines is that tumor cells express a wide range of tumor-associated antigens. This rich source of antigens contains epitopes of the two types of T cells (CD8+ and CD4+), compared with peptide-based vaccines that contain only one epitope. Autologous tumor cells are the best source of protein for immunization, but only 10%-15% of patients diagnosed with pancreatic tumors are candidates for surgical treatment. In addition, it is difficult to prepare a sufficient quantity of tumor cells required to achieve the vaccine due to prolonged culture periods and possible contamination with bacteria and fungus. To avoid these difficulties, allogeneic tumor cells can be used, which can be

produced in larger quantities and do not require determination of the patient's human leukocyte antigen and cell types. Furthermore, multiple allogeneic tumor antigens can be processed using the mechanism of cross-presentation and simultaneous induction of CD4+ and CD8+ cells^[149].

Algenpantucel-L: Algenpantucel-L contains cell lines expressing α -galactosyl epitopes on the surface of proteins and glycolipids. In humans, these epitopes are missing, but there are natural anti- α -gal antibodies that stimulate the immune response, including against tumor cells^[150,151]. In a phase II study with this type of immunotherapy in combination with GEM and 5-FU/irradiation, algenpantucel-L was injected intradermally (up to 14 vaccinations)^[152]. The adverse reactions were local response and peripheral hypereosinophilia. Survival at 1 year was 86%, better than the 81% reported in the RTOG-9704 trial using the same chemoradiotherapy scheme^[153]. Interestingly, the patients who received a higher dose of vaccine in the study (300 vs 100 million cells/dose) had an increase in 12-mo disease-free (81% vs 51%) and overall (96% vs 79%) survivals. Additionally, patients in this trial had a higher percentage of lymph node positivity (stage II b) in comparison with the RTOG-9704 trial (81% vs 68%)^[152]. Phase III studies are ongoing and the results are expected (ClinicalTrials.gov; NCT 01836432).

Granulocyte-macrophage colony-stimulating factor vaccine:

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a potent cytokine that is able to mobilize monocytes, eosinophils and lymphocytes to the tumor sites. GM-CSF vaccine (GVAX) showed tumor-free survival and also caused regression of tumors in mice^[154]. In a phase I study, 14 patients were vaccinated with a GVAX made from irradiated cancer cell lines (PANC 6.03 and PANC 10.05) that were engineered to express GM-CSF, with an interval of 8 wk after resection of the pancreas and chemoradiotherapy^[155]. Patients who developed delayed hypersensitivity reaction were disease-free at 25 mo from diagnosis. Another phase II study vaccinated 60 patients with surgical treatment of adenocarcinoma and with radiochemotherapy (5-FU-based regimen) with an allogeneic GVAX^[113,114]. A total of five immunotherapy treatments were delivered intradermally and the first treatment was given 8-10 wk after surgical resection resulting in an 85% 1-year survival; the effect was attributed to the induction of CD8+ mesothelin-specific T cells. GVAX immunotherapy induces expression of anti-thyroglobulin antibodies that recognize a unique antigenic repertoire associated with prolonged survival^[156]. All these trials demonstrate post-vaccination induction of CD8+ T cells to multiple mesothelin-specific epitopes, which correlates with improved survival^[113,114,155]. Mesothelin is a tumor-

associated antigen that is overexpressed in most ductal adenocarcinomas of the pancreas and is thought to be involved in cell adhesion, and, therefore, to play a role in metastasis^[157].

Peptide vaccines

Peptide-based anti-tumor vaccines are prepared from fragments of antigenic proteins, which are the minimal immunogenic region of tumor-associated antigens that are simple, safe, stable and economical for this purpose. Multiple peptides related to major histocompatibility complex class I have been identified and considered as candidates, and vaccination with synthetic peptides has been studied in clinical trials in combination with chemotherapy sessions in order to produce cytotoxic T lymphocytes^[158]. The use of peptide vaccines has some limitations: the existence of a limited number of known antigenic peptides; the presence of suppressive immune cells in tumoral microenvironments; the fact that DCs may have poor functionality in patients with advanced pancreatic tumors; the observation that CD8+ cytotoxic T cells are sometimes ineffective in the reaction with pancreatic tumor cells, which is mediated by production of immunosuppressive cytokines such as interleukin-10 and tumor growth factor.

K-ras vaccine: K-ras is thought to be recognized by helper and cytotoxic T cells, and almost 90% of pancreatic tumors involve mutations in the *KRAS* oncogene. Peptide vaccines against mutated K-ras are safe for administration to humans^[159-161], but only one of the nine patients had a cytotoxic T lymphocyte immune response^[161]. A study of synthetic vaccine for a K-ras mutation and GM-CSF showed an immune response in 25/48 of the enrolled patients^[162]. For these patients, survival was 148 d compared to 61 d for the non-responders. Twenty patients in this study, and another group of 23 patients, have been followed-up for a long time and have shown a median 5-year survival rate of 20% (four patients), while a 29% survival rate was observed in another group of patients with immune response; adverse effects to the vaccine were minimal^[163]. Using synthetic K-ras vaccines based on long peptides to induce antigen-specific polyclonal CD8+ and CD4+ T, Weden *et al.*^[163] reported a 10-year survival rate of 20% in a group of patients after pancreatic tumor resection. Another recent study showed no effect of a 21-mer peptide vaccine based on a *KRAS* mutation in 24 patients vaccinated monthly for 3 mo^[164]. Administration of Reolysin, an oncolytic virus that replicates and kill cells with a *KRAS* mutation, was well tolerated by patients with breast tumors^[165], but further studies are expected.

Immunotherapy in the form of vaccination against mutant K-ras has been developed as an adjunct to surgical resection and appears as a promising principle of adjuvant therapy. Taking into account that K-ras vaccination is virtually free of side effects, the results

should encourage much larger controlled studies.

Telomerase peptide vaccine: Telomerase is a ribonucleotide enzyme that maintains cellular stability and is expressed by almost all cancer cells (85%-90%)^[166], including PC^[167]. Activation of reverse transcriptase from human telomerase increases cell viability, and is thus an attractive target for an immunotherapy antigen. In a phase I - II study, the administration of a telomerase peptide vaccine (GV1001) and immunogenic response was found to be correlated with prolonged survival (25% at 1 year) and good tolerability^[168]. However, a phase III study in unresectable and metastatic pancreatic ductal adenocarcinoma that compared PrimoVax (GV1001 and GVAX) administered sequentially with GEM against GEM alone was closed due to lack of survival (median OS: 5.9 mo vs 7.3 mo)^[169,170]. A second GV1001 phase III trial (TeloVac) in unresectable and metastatic PC compared the association between the vaccination and subsequent or concurrent chemotherapy (GEM and capecitabine) vs chemotherapy alone; there were no significant survival differences (median OS: 6.94 and 8.36 mo vs 7.89 mo, respectively)^[171]. Furthermore, patients in the sequential arm received only 2 mo of chemotherapy before being taken off an active therapy that has a historical median progression-free survival of 4.3 mo^[172]. Despite the disappointing phase III results, the findings have identified biomarkers that may predict response to this vaccine and new research may indicate benefit in a subgroup of patients^[173]. In addition, there is another ongoing study in patients with advanced disease that includes radiochemotherapy (ClinicalTrials.gov; NCT01342224).

Survivin-based vaccine: Survivin is an inhibitor of apoptosis and is found in PC. There have been isolated cases of complete remission with a survivin-based vaccine in patients with metastatic disease^[158]. This effect was confirmed only in combination with GEM in an experimental study using a modified vaccinia Ankara in a murine pancreatic model, which showed enhanced survivin-specific CD8 interferon- γ immune responses in the vaccinated mice^[174].

Mucin 1 vaccine: Mucin (MUC)1 is highly expressed in PC^[175], and phase I and II studies of MUC1 antigen-pulsed DC vaccines showed hopeful results in advanced PC^[176,177]. A phase I study in advanced PC showed that the vaccinia virus expressing carcinoembryonic antigen (CEA) and MUC1 and co-stimulatory molecules was well tolerated and provided an OS advantage in immune-responsive patients^[178]. However, a phase III trial using fowlpox viruses expressing these same molecules failed to show improvement in OS in PC patients when compared to chemotherapy or best supportive care in a palliative setting^[179]. Administration of a pox virus-based vaccine targeting

MUC-1 and CEA induced a favorable immune response on T cells, but has not been confirmed as beneficial in a phase III study^[176,178]. Intratumoral administration of the recombinant fowlpox PANVAC plus subcutaneous recombinant vaccinia and recombinant GM-CSF is currently underway in a phase I study. In another study, 16 patients with advanced PC who were vaccinated with DCs pulsed with MUC1 showed an increase in CD8+ cells in peripheral blood; 2/15 patients with resected PC were alive and disease free at 32 and 61 mo^[176].

Anti-VEGFR vaccine: An anti-VEGFR vaccine was given in association with GEM to patients with unresectable or metastatic disease, and produced an OS rate of 8.7 mo; phase II study results are expected^[180].

Personalized peptide vaccination: Personalized peptide vaccination was attempted after preparation of pre-vaccination peripheral blood mononuclear cells and plasma as a first-line therapy in association with GEM in unresectable patients. This attempt showed a 1-year survival rate of 38%^[181]; however, further evaluations are needed.

Nanoparticles: Nanoparticles are non-specific and are taken-up in the spleen. They can be safely used as a vaccine platform without the risk of prolonged side effects. In animal models, nanoparticulate delivery of diphtheria toxin DNA effectively kills mesothelin-expressing PC cells^[182].

Heat shock proteins: Heat shock proteins also play a role in the stabilization and delivery of peptides, and in inducing immunity against autologous tumors^[183]. In one study, 3/10 patients treated with an autologous vaccine prepared from resected tumors showed no tumor recurrence at 2.6, 2.7 and 5.0 years of follow-up, though there was no correlation between stimulating immunity and survival^[184].

DC vaccines

DCs are the most potent antigen-presenting cells, and they can cause a high antigenic response *via* stimulation of T and B cells. DC vaccines combine tumor antigens with DCs for presentation to effector T cells. Viral or bacterial DNA is inserted into human cells to modulate cell-mediated immunity by the DNA vaccines. It has been shown that DC vaccine plus lymphokine-activated killer cell treatment and chemotherapy prolonged OS compared to effects observed in patients who received only DC vaccine or chemotherapy^[158,185]. In a multi-center study of 255 patients who received chemotherapy plus vaccine, the median survival was 16.5 mo, with erythema reaction after vaccination identified as a factor related to better survival^[186]. The effects were considered likely due

to the enhancement of tumor cell immunogenicity by treatment with GEM, which increases the efficacy of the vaccine^[187]. However, tumor-reactive T cells in peripheral blood were decreased and the cytotoxic T cell-mediated killing was normal^[188]. The combination of these vaccines with mRNA encoding CEA produced an effective immunization and survival benefit for three patients with resected pancreatic tumors receiving neoadjuvant therapy, each of who survived 30 mo after diagnosis^[189]. The combination of DC vaccines with DNA for MUC1 has been found to be beneficial in a small portion of resected patients^[176], and as ineffective in metastatic disease^[177]. The combination with telomerase reverse transcriptase mRNA demonstrated encouraging results when administered after radical surgical treatment^[190]. Targeting more than one checkpoint pathway at the same time might be another option for obtaining increased efficacy.

Administration of the anti-cytotoxic lymphocyte antibody (ipilimumab) and GVAX increased the survival of 15/30 previously treated patients with metastatic disease compared to GEM alone (5.5 mo vs 3.3 mo), supporting the approach of blocking cytotoxic lymphocytes by promoting the GM-CSF antitumor response^[111]. Survival was correlated with CD8+, mesothelin-specific T cell quantity. A phase II study of this protocol is under development due to this promising result. Despite the encouraging findings, however, clinical responses have been seen in only a minority of patients, presumably due to insufficient expansion of antigen-specific cytotoxic T lymphocytes capable of eradicating tumor cells. Interestingly, endoscopic ultrasound-guided fine-needle injection of OK432-pulsed DCs into a tumor followed by intravenous infusion of lymphokine-activated killer cells stimulated with anti-CD3 monoclonal antibody was synergistically effective in a phase I study^[191].

CD40 is a potential immunomodulatory target, because it is a co-stimulatory molecule for antigen-presenting cells. GEM with CD40 agonist-activated T cells reduces tumor burden in advanced PC patients in a phase I study^[192], by decreasing tumor stroma and increasing infiltration of activated macrophages^[112].

Adoptive cell therapy consists of re-transferring autologous cytotoxic T lymphocytes harvested from the patient after *in vitro* activation of K-ras, telomerase, or mesothelin. This method helps the immune system to recover more quickly after chemotherapy and improves responses to other immunotherapies. However, extensive studies have not been performed^[193-195].

IMMUNOTHERAPY TARGETING TUMOR STEM CELLS

Most patients with PC who initially respond to standard chemotherapy relapse because of small populations of tumor cells/tumor stem cells (*i.e.*, CSCs). CSCs are

better able than other tumor cells to multiply and to initiate new tumors and sustain tumor growth. It has been shown that pancreatic tumors that are resistant to chemoradiotherapy are rich in CSCs. These tumors are candidates for immunotherapy, and CSC-targeted therapy can be applied to prevent resistance to chemotherapy.

Targeted immunotherapy on tumor stem cells using $\gamma\delta$ T cells, natural killer cells, and anti-tumor vaccines based on DCs has been successfully used to activate responses of CSC-specific cytotoxic T lymphocytes, leading to the expression of high levels of interferon- γ and enhanced destruction of CSCs *in vitro*. Transfer of stem cells may have antitumor effects due to decreased activity of Wnt or Akt pathways^[196,197]. Antitumor action will be possible only if three conditions are met: direct tumor migration and intratumoral incorporation, release of the antitumor agent, and generation of a specific organ-vector^[197].

The use of immunotherapy for treatment of pancreatic ductal adenocarcinoma is promising, though its immunotolerant environment continues to be a major hurdle. Therapeutic vaccines have the ability to activate antitumor immune responses; however, these strategies need to be combined with immunomodulating agents, chemotherapies or radiation, depending on the patient disease status. There is also a great need to optimize vectors, antigens, and patient selection. Additionally, more preclinical and early-phase clinical trials need to be conducted to determine if and which chemotherapies would complement immunotherapies, and determine how to optimally sequence the administration of immunotherapy with chemotherapy and radiation. Combinations of active and passive immunologic treatments, targeted agents and conventional chemotherapies might be important strategies for increasing efficacy.

CONCLUSION

The goal of these new treatments is to obtain faster and more stable tumor response. Passive immunotherapy may have a role in combination with radio-chemotherapy. Furthermore, vaccines would allow restoration of specific immune responses after adjuvant or palliative treatment, and would continue the fight against residual tumor cells. Knowing the genetic implications in PC, the combination of two or more vaccines would be beneficial.

In the future, treatment will likely include personalized medicine to each patient, tailored for numerous molecular therapeutic targets of multiple pathogenetic pathways in PC, and is expected to occupy a central role in stem cell therapy.

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