Mini Review

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A review on biomarker based therapeutics in pancreatic ductal adenocarcinoma

Abstract

In recent years, most cancers in various organs were suppressed due to the development of advanced biomarkers and novel therapeutics. In contrast, outcomes remain challenging in patients with pancreatic ductal adenocarcinoma (PDAC). Due to the lack of validated biomarkers to treat patients, therapeutic development for PDAC is accompanied by certain additional bioassays to evaluate the immune response and study mechanism of actions with respect to a corresponding increase in the number of trials in the beginning middle and the final stage with the integrated biomarkers. In this manuscript, we review the potential biomarkers for approved therapies as well as emerging biomarkers for therapeutics.

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Introduction

The role of biomarkers in the diagnosis and treatment of various cancers is the current requirement in the recent research of Cancer Genomics.[1] Most of the major cancers in various organs have seen improvements in survival over the last decade because of the development of therapeutic biomarkers to predict treatment efficacy and optimization of treatment in various patients.[2,3] For example, the BRAF V600 mutations in melanoma predict the response to MEK and BRAF inhibitor in lung cancer.[4] Similarly, ROS1, ALK, EGFR and BRAF mutations predict the level of sensitivity to their respective inhibitors. In pancreatic ductal adenocarcinoma (PDAC), biomarkers are lacking in treatment due to the observation of abnormal conditions in various stages of the disease and the usage of cytotoxic agents,[5] specifically, the usage of leucovorin, oxaliplatin, irinotecan, gemcitabine/nab-paclitaxel, OLFIRINOX [5-fluorouracil (5-FU) and liposomal irinotecan/5-FU combinations in treatment.[3] To date, Erlotinib is the only approved "targeted" agent, which was approved in a past era.[6] In the recent era, Bioassays are being incorporated into the therapeutic development of PDAC to evaluate the response and to study various mechanisms of action in pathophysiology.[7,8] On the basis of known facts, the era of biomarker-based therapy in PDAC is still emerging and this review gives an insight for the development of potential biomarkers for approved therapies as well as emerging biomarkers for bioagents under development.

Biology and pathophysiology of PDAC

Biomarkers reflect the mechanism of pathophysiology in PDAC and the transformation is driven by characteristic mutations and epigenetic modifications to initiate the expression of surface antigens, aberrant signaling pathways, altered metabolism, and remodeling of the microenvironment of tumor.[9] Nearly, 95% of tumors in PDAC have an oncogenic mutation in KRAS gene along with frequent mutations in SMAD4 (22%), CDKN2A/B and TP53 (75%),[10] the process of downstream signaling from these genetic alterations, studied on the basis of gene expression profiling has identified 12 aberrant and core signaling pathways to drive tumorigenesis in PDAC. Among these pathways, most notably hedgehog signaling, KRAS signaling, Wnt/Notch signaling, G1–S checkpoint regulation, and TGFb signaling were targeted by various therapeutics and contain numerous markers in the process of signaling.[11] As per the recent case studies on Biomarkers association with PDAC, Carcinoembryonic antigen (CEA) were overexpressed in present 94% of patients, Cell-surface carbohydrate antigen 19-9 (Ca 19-9) and EGFR is overexpressed in 70% of patients.[7–9] In the microenvironment of PDAC, cancer-associated fibroblasts secrete the increased amounts of hyaluronic acid (HA) to increase the interstitial pressure for decreasing blood flow to impair the process of drug delivery by creating a nutrient- and oxygen-deprived microenvironment.[13] Multiple metabolic changes in cells affected by PDAC rely on extracellular proteins, autophagy, and nonoxidative energy production for metabolism.[14,15] Therapeutic development of a biologic requires the exploitation of most of the above-mentioned characteristics, and in most cases, the assays were used to study the therapeutics at the basic level to initiate the incorporation of a biologic as a potential biomarker with clinical validation.

Approved biomarkers of PDAC

Serum CA19-9 is the only approved biomarker for PDAC with an indication to monitor the status of the disease.[16] CA19-9 has many limitations because it is not sufficiently sensitive or specific to be used for the detection of disease in the asymptomatic populations and may be elevated in the biliary obstruction in PDAC.[17] CA19-9 has shown a prognostic value after performing a surgical resection the initiation of chemotherapy to leading to its approval for monitoring disease.[18] Similarly, CEA is a tumor antigen that is elevated in the serum from certain patients with PDAC and has shown a prognostic value. It is used along with CA19-9 for some applications.[19] Despite their use for disease monitoring, CA19-9 and CEA are mainly utilized as adjuncts to radiographic imaging and are rarely used in isolation for treatment.[20]

Pathway biomarkers of PDAC

PDAC tumor metabolic pathways are actively being targeted by multiple agents. The amino acid L-asparaginase in Eryaspase, a red blood cell–encapsulated formulation of L-asparaginase that was being developed to treat tumors with a low level of asparagine synthetase. Asparagine was synthesized by the enzyme asparagines synthetase (ASNS) and in some PDACs, there is a good correlation. It was predicted that the depletion of asparagine by L-asparaginase in tumors with impaired asparagine synthesis will deplete the pool of asparagine by impairing the process of apoptosis and protein synthesis.[21] In a

randomized study of phase II trials, the patients subjected to the study were set to receive the standard second-line chemotherapy of FOLFOX or gemcitabine. The primary improvement in the endpoint of survival in patients with ASNS was met and interestingly, among the entire population, 30% contain the upregulated ASNS and it had both improved OS and PFS. The application of ASNS as a biomarker is being further investigated.[22] The inhibitor of autophagy, hydroxychloroquine is being studied with gemcitabine in phase I and phase II trial with a robust correlative design. In the mere future, there are more possibilities to evaluate JNK1 as a potential biomarker of autophagy.[23]

Targeted biomarkers of PDAC

Based on the evidence of the strong preclinical data, targeted therapy met significant challenges in PDAC. Numerous agents targeting the core signaling pathways in PDAC were studied and it includes AKT, hedgehog, Janus kinase, and mitogen-activated protein kinase. The molecule Erlotinib is the only targeted agent that has been approved for PDAC. It's approved in combination with gemcitabine and it was based on a modest survival benefit in an unselected population. In the case of the retrospective analysis of the PA.3 trial, it was found that 49% of patients had an increased expression of EGFR. However, there is a lack of correlation between the expression of EGFR and OS.[24] Patients with wild-type KRAS had an improved OS but the subsequent study of patients treated with the second-line therapy of erlotinib did not identify expression of EGFR. The developments of targeted therapeutics are studied in the selected population to screen biomarkers. For example, cabozantinib with erlotinib was being studied in patients with tumors expressing EGFR- and c-MET. The Targeted monoclonal antibodies were also being studied in the selected populations with the increased expression of the biomarker.

Impact of immunotherapy in PDAC

The first trial of immunotherapy associated with the biomarker of PDAC was the usage of pembrolizumab and it was recently approved for patients with a high level of instability in microsatellite (MSI-H).[25] Approval was based on collected data from five different studies with 149 patients with multiple malignancies. The published data of PDAC have included four patients with dMMR tumors, among four two, who have demonstrated a partial response.[26] Nine patients with PDAC and MSI-H tumors were included in the study of KEYNOTE158, which demonstrated an overall response rate of 37.7%. Initial studies on monotherapy failed due to the differential expression signaling molecules and immunosuppressive cytokines in inhibiting the migration of T-cell.[27] Combinations of agents to inhibit the process of tumor immunogenicity were being analyzed. The molecule, Cergutuzumab amunaleukin is a hybrid targeted immunotherapeutic combination because it consists of a CEA-specific antibody fused to an IL2 variant. In Patients, Cergutuzumab is being studied in combination with atezolizumab. Chimeric antigen receptor T cells (CART) are designed to capture the tumor-specific antigens.[28]

Conclusion

Multiple biomarkers are emerging as potential candidates to treat PDAC in the future. In the clinic, the malignancies of MSI-H and dMMR are the first approved target to establish a biomarker-based therapeutic for PDAC, though the overall indication is the presence of the disease agnostic mechanism. Deleterious mutations found in BRCA and the homologous repair genes appear to predict the benefits of the biomarker-based studies. The importance of biomarker-based therapeutic selection is a well-established research objective in cancer research. Hence, Novel trial platforms to integrate the biomarker-based therapies were being designed. Recent case studies on biomarkers of PDAC established a good level of clinical significance. Future research in PDAC requires the identification of validated and reproducible biomarkers to predict the therapeutic response in patients.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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