REVIEW ARTICLE

Systematic review of peri-operative prognostic biomarkers in pancreatic ductal adenocarcinoma

Wilson Petrushnko[1], Justin S. Gundara[1], Philip R. De Reuver[1], Greg O'Grady[2], Jaswinder S. Samra[1] & Anubhav Mittal[1]

[1]Upper Gastrointestinal Surgical Unit, Royal North Shore Hospital, North Shore Private Hospital, University of Sydney, St Leonards, NSW 2065, Australia, and [2]Department of Surgery, University of Auckland, New Zealand

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) continues to be associated with a poor prognosis. This systematic review aimed to summarize the literature regarding potential prognostic biomarkers to facilitate validation studies and clinical application.

Methods: A systematic review was performed (2004–2014) according to PRISMA guidelines. Studies were ranked using REMARK criteria and the following outcomes were examined: overall/disease free survival, nodal involvement, tumour characteristics, metastasis, recurrence and resectability.

Results: 256 biomarkers were identified in 158 studies. 171 biomarkers were assessed with respect to overall survival: urokinase-type plasminogen activator receptor, atypical protein kinase C and HSP27 ranked the highest. 33 biomarkers were assessed for disease free survival: CD24 and S100A4 were the highest ranking. 17 biomarkers were identified for lymph node involvement: Smad4/Dpc4 and FOXC1 ranked highest. 13 biomarkers were examined for tumour grade: mesothelin and EGFR were the highest ranking biomarkers. 10 biomarkers were identified for metastasis: p16 and sCD40L were the highest ranking. 4 biomarkers were assessed resectability: sCD40L, s100a2, Ca 19-9, CEA.

Conclusion: This review has identified and ranked specific biomarkers that should be a primary focus of ongoing validation and clinical translational work in PDAC.

Received 27 April 2016; accepted 9 May 2016

Correspondence

Anubhav Mittal, Upper GI Surgical Unit, Royal North Shore Hospital, St Leonards, NSW 2065, Australia. Tel: +61 2 9463 2899. Fax: +61 2 9463 2080. E-mails: anubhav.mittal@sydney.edu.au, mittal.surgery@gmail.com

Introduction

Pancreatic ductal adenocarcinoma (PDAC) continues to convey a poor prognosis despite increasingly aggressive surgical resection and newer chemotherapeutic options.[1]

Current selection paradigms for surgical resection in PDAC are based on the anatomical relationship of the tumour to adjacent vessels, overall disease burden, and the patient's performance status.[3] Whilst clinically applicable, such existing paradigms lack any objective reference to tumour biology. This is no longer appropriate in the current era of molecular discovery and translational oncology. Tumour biology, which may be reflected through the use of validated biomarkers, represents the fourth and arguably most important arm of treatment selection paradigms for PDAC.[4,5] Prognostic PDAC biomarkers therefore may play an important role in identifying patients with favourable tumour biology and help in selection for resection to maximize survival advantage and reduce morbidity and mortality.[2]

Recently, there has been an explosion in the number of available biomarkers for PDAC,[6,7] with many of these being identified as having possible clinical significance for early diagnosis and/or prognosis. These biomarkers have been identified based on a variety of tissues and by applying a multitude of scientific and diagnostic methodologies. Despite numerous PDAC biomarker studies, Ca 19-9 remains the only clinically validated marker in routine practice,[8] efforts should be directed at reviewing the literature to identify additional markers with greatest potential for clinical application.

It is hypothesized that PDAC biomarkers, which are readily available in blood or tissue, will come to play a central role in optimizing patient selection for resection by predicting outcomes

based on tumour biology. The aims of this review were to therefore: i) systematically review all available biomarkers for PDAC that have been shown to be related to prognosis; and ii) rank these biomarkers by using a validated scoring system specifically designed for evaluating biomarker research.

Methods

Literature search

A systematic and comprehensive search of databases (PubMed, Embase and Medline) was performed. The search was restricted to the last ten years (2004–2014) and human studies only with no restrictions placed on language. The following search string was used "exp Pancreatic Neoplasms, exp *Adenocarcinoma/, exp *Biological Markers/ an, bl, ch, du, ge, me (Analysis, Blood, Chemistry, Diagnostic Use, Genetic, Metabolism)". The reference lists of all studies were individually reviewed to include relevant publications.

Inclusion and exclusion

Articles for inclusion were reviewed by two authors (WP and AL) and any differences were resolved by the senior author (AM). Studies that investigated biomarkers and their correlation with PDAC prognosis were included for review. Randomized control trials (RCT) and cohort studies were included. Articles were excluded if they were review articles or did not investigate biomarker(s) and their correlation with PDAC.

Data extraction and REMARK scoring

Four authors were involved in the data extraction process (WP, AL, AP and RC). Data were extracted in duplicate into a predefined database. Differences in data collection were referred to the senior author (AM) for resolution. Biomarkers were ranked based on the quality of the available evidence presented in the literature, and the Reporting Recommendation for tumour Marker Prognostic Studies (REMARK) scoring system was used to assign a score to each biomarker from the study.[9] The REMARK checklist was published in 2005 and consists of twenty items for reporting of published tumour markers. The REMARK is a well-established scoring system for evaluating the quality and appropriateness of study design, methods and analysis of published biomarkers along with addressing their deficiencies (Supplementary Table 3). The REMARK scoring system aims to identify articles who have conducted an adequate assessment of the reported biomarker. The rigorous criteria are used to ensure consistency in the reporting of biomarkers at a high standard that encourages transparency for readers to make informed decisions about the data presented. Therefore, a higher REMARK score identifies biomarkers with a strong and reliable evidence base.

Biomarker definition

Biomarkers are defined by the World Health Organisation (WHO) 1993, as almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction.

Results

Data overview

The initial literature search revealed a total of 3324 potential articles, of which 141 studies met the inclusion criteria (Fig. 1). Another seventeen studies were obtained by hand searching reference lists, such that a total of 158 studies with 256 unique individual biomarkers were identified in this systematic review. Publications were found in the following types of journals: basic science (n = 17 publications), medical (n = 24), oncology (60), pathology (n = 31) and surgical (n = 29).

Of the total 158 studies examined, 133 of the studies were retrospective and 25 were prospective. Primary endpoints of the studies included: overall survival (n = 171 out of 240 biomarkers), disease free survival (n = 33), lymph node involvement (n = 17), tumour grade/size/differentiation (n = 13), metastasis (n = 10), resectability (n = 5) and recurrence (n = 4). Seventy-one studies included follow-up details with a median follow-up of 26.8 (range: 6–84) months.

Biomarker overview

The tissue types upon which biomarker assays were performed included resected pancreatic tissue (n = 221 biomarkers; 74%), serum (n = 66; 22%), pre-operative pancreatic tissue (n = 9; 3%) and pre-operative pancreatic fluid (n = 2; 0.6%). Biomarkers were most often detected by immunohistochemistry (n = 182 biomarkers; 60%), followed by RT-PCR (n = 47; 15%) and radioimmunoassay (n = 28; 9%; Fig. 2).

Biomarkers were classified into biologic subtypes (generic protein, antibodies, antigens, miRNA, RNA and DNA) and functional groups or pathways. The most common biomarker category was generic protein (n = 201; 67%) followed by antigen (n = 41; 14%) and miRNA (n = 29; 10%; Fig. 3). The most common functional group was cell proliferation (n = 50; 26.3%), followed by immune system (n = 27; 14.2%) and transcription factors (n = 24; 12.6%) (Fig. 4, Supplementary Table 1).

Biomarker association with specific outcomes

Total biomarker REMARK scores were collated and a mean REMARK score for each individual biomarker calculated. The endpoints identified in the studies included overall survival (n = 171 biomarkers), disease free survival (n = 33), lymph node involvement (n = 17), tumour grade/size/differentiation (n = 13), metastasis (n = 11), resectability (n = 6) and recurrence (n = 4). Biomarkers were grouped as per these pre-defined prognostic endpoints. All biomarkers listed in Table 1 reached statistical significance in their respective studies (further details