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Review article

Host systemic inflammatory response influences outcome in pancreatic cancer☆

Clem W. Imrie

Glasgow Royal Infirmary, G31 2ER, UK

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ABSTRACT

This review of the influence of host systemic inflammatory response(SIR) on the outcome of pancreatic ductal adenocarcinoma (PDAC)was the kernel of the 2014 George E Palade Memorial Prize Lecture at the Combined IAP-EPC Meeting held June 25-8 in Southampton,UK. The ability of the modified Glasgow Prognostic Score(mGPS) to stratify cancer outcomes has been demonstrated in >50 studies including >25000 patients from many countries. Other markers of SIR such as Prognostic Index and neutrophil/lymphocyte ratio(NLR) may also be used emphasising the non homogeneity of the PDAC patients. The mGPS score 0 is associated with better outcome,while scores of 1 & 2 are linked to poor performance status, greater weight loss, comorbidity and earlier death. Two papers show in resectable PDAC that longer life (27-37 months) occurs with mGPS 0, and < 18 months for mGPS 1 and 2, such that alternative therapy employing RFA may well be better than resection in those patients. In the greater number of PDAC patients unsuitable for resection the JAK-STAT inhibitor, ruxolitinib, has been found only to favourably modify PDAC in those with mGPS 1 or 2. Likewise the possible benefits of older anti inflammatory agents may be confined to these patients. An urgent reappraisal of the prognostic and therapeutic implications is now required in PDAC.

Local inflammatory responses(LIR) are beneficial in PDAC and other cancers. Four grade stratification systems using Klintrup histology, T cell subtype analysis and Galon immune scores are accurate prognosticators.

Introduction

Over 2 decades a body of consistent and cohesive literature has shown that all common cancers have their outcome greatly influenced by host systemic inflammatory response (SIR) illustrating that cancer sufferers are not a homogeneous population. The time has come for greater recognition of this and corresponding action by our medical and allied professions.

Initial interest in SIR in cancer patients arose from questions as to the mechanism of cachexia in those with advanced lung or gastrointestinal cancers. This subject is well reviewed [1] and the relationship between the markers of the SIR and both signs and symptoms of cancer cachexia is increasingly well recognised [2].

Major studies of SIR in patients with cancer

In the 1990s several reports of poorer cancer outcomes associated with elevated C reactive protein (CRP) blood levels > 10 mg/L appeared. In 1994 a remarkable prospective randomised study of 135 advanced cancer patients showed both improved survival and quality of life for the treatment cohorts each of 45 patients receiving either 10 mg prednisolone x 2 daily or 50 mg indomethacin x2 daily (Table 1). This Gothenburg paper reported the placebo group had a 274 days median survival versus 325 days for

☆ This paper is based on the 2014 George E Palade Memorial Lecture awarded by the International Association of Pancreatology (IAP) to honour the 1974 Nobel Laureate's pancreatic research work. It was delivered at the Combined Meeting of the European Pancreatic Club and the IAP held from June 25-28, 2014 in Southampton, UK. The prize was awarded by Professor Jeremy Wilson of Sydney on behalf of the committee of the IAP.
The previous recipients of this prize are:
2010 Professor James D Jamieson (Yale University)
2011 Professor Fred Gorelick (Yale University)
2012 Professor John Williams (NIH, UCSF & Michigan University)
2013 Professor Ashok Saluja (Harvard & Minnesota Universities).

E-mail address: clemimrie@gmail.com.

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Table 1
Results from prospective randomised study of anti inflammatory drugs in 135 patients with advanced carcinomas.

	Placebo	Prednisolone	Indomethacin	ANOVA
Patients (n)	45	45	45	(p value)
CRP (mg/l)	54	48	49	NS
WBC	10.0	10.3	8.2	0.0003
Karnofsky score	66	73	75	0.003
Median survival (days)	274	325	530	0.07

The daily dose of prednisolone was 20 mg and indomethacin 100 mg (Lundholm et al., 1994) Ref [1].
The CRP, WBC and Karnofsky scores are mean values in the follow up period.

the steroid group and 530 days for those receiving the anti-inflammatory drug indomethacin [3]. Kent Lundholm, the lead author, subsequently published a further prospective study of 335 patients with irresectable cancers investigating the possibility that intravenous amino acid therapy would improve survival and quality of life. All of these patients were treated with indomethacin 50 mg x 2 daily plus omeprazole with the approval of the local ethical committee. There was no significant advantage found from the amino acid treatment [4].

In 2001 a retrospective analysis of 772 patients with a variety of solid cancers demonstrated strikingly better survival curves (Fig. 1) for those with normal CRP (<10 mg/l) compared to intermediate (11–100 mg/l), and very high (>100 mg/l) levels of CRP. Those differences were significant ($P < 0.001$) between the groups and were not linked to histological TNM grading [5].

The Glasgow Prognostic Score (GPS) and neutrophil/lymphocyte ratio (NLR)

Combining data from blood albumin levels with CRP improved the accuracy of grading these cancer patients such that the Glasgow Prognostic Score (GPS) was introduced more than 10 years ago. Initially both an elevated CRP >10 mg/l and a low albumin <35 g/l scored a point such that the score range was 0–2. However, subsequent study revealed very few patients with a low albumin and normal CRP fared badly. Thus the modified GPS (mGPS) was soon introduced in which the additional point associated with low albumin <35 g/l was only valid in patients with CRP > 10 mg/l [6].

A much larger retrospective study of 6685 patients was published in 2011 (Table 2) showing that the mGPS separated 3 statistically different prognostic groups ($p < 0.001$) in 14 different forms of malignant disease [7]. Although the patterns of different survival curves were similar in comparing the 14 different disease

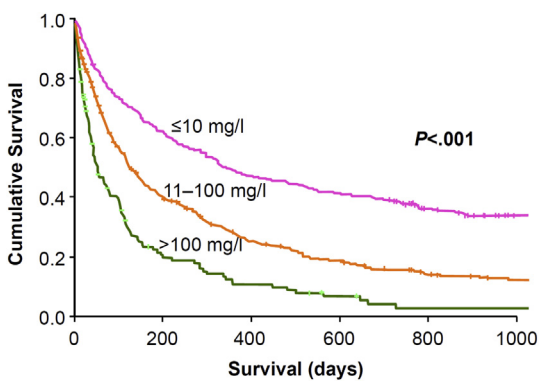

Fig. 1. Survival of 772 patients with a variety of solid cancers related to initial CRP levels(3).

Table 2
Tumour type and mGPS in 6685 patients.

Tumour type	Total	mGPS(%)			p
		0	1	2	
Breast	1199	950(79)	207(17)	42(4)	<0.001
Skin	1126	693(62)	310(27)	123(11)	<0.001
Bladder	296	174(59)	76(26)	46(15)	<0.001
Endocrine	145	84(58)	41(28)	20(14)	<0.001
Gynaecology	197	108(55)	60(30)	29(15)	<0.001
Prostate	267	143(54)	91(34)	31(12)	<0.001
Musculo skeletal	78	41(53)	15(19)	22(28)	<0.001
Gastro-esophageal	503	249(50)	162(32)	92(18)	<0.001
Haematological	499	245(49)	157(32)	97(19)	<0.001
Renal	294	132(45)	105(36)	57(19)	<0.001
Colorectal	784	342(44)	250(32)	192(24)	<0.001
Head & neck	156	67(43)	58(37)	31(20)	<0.001
Pancreato-biliary	321	122(38)	101(31)	98(31)	<0.001
Pulmonary	820	260(32)	387(47)	173(21)	<0.001

The list of 14 tumour types is sequentially arranged in column 2 according to the prevalence of patients with mGPS score 0, ranging from 79 to 32%.
P values indicate survival differences between mGPS groups.Proctor et al. (2011) Ref [5].

groups the proportion of patients without a SIR (mGPS = 0), and therefore a better prognosis, ranged from high in breast cancer (79%) to low in lung cancer(32%). Pancreato-biliary cancers had the 2nd lowest proportion of mGPS = 0 patients (38%). Multifactorial regression analysis showed that the Prognostic Index (employing CRP and white blood counts) had similar accuracy to mGPS, but the neutrophil/lymphocyte ratio (NLR > 5) was poorer than both [7].

Review of the considerable oncology literature on the use of mGPS has shown independent prognostic value in over 50 studies examining different malignant diseases comprising >25,000 patients from many countries [8]. The elevated mGPS scores of 1 and 2 are associated with raised levels of inflammatory cytokines, greater degrees of weight loss, poor performance status, increased co-morbidity, more treatment complications and shorter survival. This emphasises the non homogeneity of the various tumor populations based on host responses which greatly affect patient outcomes, yet rarely feature in therapeutic strategies.

The Hamburg study of 495 patients with esophageal cancer resections and no treatment with either radio/chemotherapy [9] is a very good example of the prognostic importance of host SIR which showed an impressive correlation between preoperative GPS scores and outcome. There were slightly more patients with squamous cell cancer than adenocarcinoma. Parallel findings occurred for the 2 histological types (squamous and adenocarcinoma) with the GPS proving not only a strong prognosticator of survival, but also of recurrent cancer in this fine study which had 5 year follow up in most patients. Indeed the probability of survival at 5 years in GPS = 0 group was 40%; GPS = 1 only 20%; and GPS = 2 zero. The differences between groups was highly significant ($p < 0.001$). GPS = 0 contained 54% of patients; GPS = 1 had 34% and GPS = 2 had 12% [7].

SIR in pancreatic cancer

When we examine outcomes for resectable pancreatic ductal adenocarcinoma (PDAC) we find similar results in 2 studies of 135 patients from Glasgow [10] and 102 patients from Rome [11] Table 3. Each group of surgeons reported much better survival for GPS = 0 ranging from 26.7 to 37.2 months and significantly poorer survivals for those with preoperative GPS of 1 (11.5–16.5 months) and GPS = 2 (only 7.3–13.1 months).

Two further studies of patients with resectable PDAC utilised the neutrophil/lymphocyte ratio as an index of host response (Table 4).

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