Critical Reviews in Oncology/Hematology 116 (2017) 134–146

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: Systematic review and *meta*-analysis

Ross D Dolan*, Stephen T McSorley, Paul G Horgan, Barry Laird, Donald C McMillan

Academic Unit of Surgery, School of Medicine, University of Glasgow, Glasgow Royal Infirmary, Glasgow, United Kingdom

Contents

ARTICLE INFO

Article history:
Received 24 March 2017
Received in revised form 4 June 2017
Accepted 6 June 2017

Keywords:
Systemic inflammation
Advanced cancer
C-reactive protein
Albumin
White cell count
Neutrophil count
Lymphocyte count
Monocyte count
Platelet count
Glasgow prognostic score
Neutrophil lymphocyte ratio

ABSTRACT

Introduction: Cancer remains a leading cause of death worldwide. While a curative intent is the aim of any surgical treatment many patients either present with or go onto develop disseminated disease requiring systemic anti-cancer therapy with a palliative intent. Given their limited life expectancy appropriate allocation of treatment is vital. It is recognised that systemic chemoradiotherapy may shorten the quality/quantity of life in patients with advanced cancer. It is against this background that the present systematic review and *meta*-analysis of the prognostic value of markers of the systemic inflammatory response in patients with advanced cancer was conducted.

Methods: An extensive literature review using targeted medical subject headings was carried out in the MEDLINE, EMBASE, and CDSR databases until the end of 2016. Titles were examined for relevance and studies relating to duplicate datasets, that were not published in English and that did not have full text availability were excluded. Full texts of relevant articles were obtained and were then examined to identify any further relevant articles.

Results: The majority of studies were retrospective. The systemic inflammatory response, as evidenced by a number of markers at clinical thresholds, was reported to have independent prognostic value, across tumour types and geographical locations. In particular, C-reactive protein (CRP, 63 studies), albumin

* Corresponding author at: Clinical Research Fellow, Academic Unit of Surgery, University of Glasgow, New Lister Building, Glasgow Royal Infirmary, Glasgow, G4 0SF, United Kingdom.
E-mail address: Ross.Dolan@glasgow.ac.uk (R.D. Dolan).

http://dx.doi.org/10.1016/j.critrevonc.2017.06.002

Platelet lymphocyte ratio
Disease specific survival
Overall survival

(33 studies) the Glasgow Prognostic Score (GPS, 44 studies) and the Neutrophil Lymphocyte Ratio (NLR, 59 articles) were consistently validated across tumour types and geographical locations. There was considerable variation in the thresholds reported to have prognostic value when CRP and albumin were examined. There was less variation in the thresholds reported for NLR and still less for the GPS.
Discussion: The systemic inflammatory response, especially as evidenced by the GPS and NLR, has reliable prognostic value in patients with advanced cancer. Further prospective studies of their clinical utility in randomised clinical trials and in treatment allocation are warranted.

1. Introduction

Cancer remains one of the leading cause of death worldwide and is responsible for 7.6 million deaths per year. Therefore, while a curative intent is the aim of any surgical treatment many patients either present with or go onto develop disseminated disease requiring systemic anti-cancer therapy with a palliative intent. Given that patients with advanced cancer have a limited life expectancy appropriate treatment selection becomes vital. Indeed, the paradigm of precision medicine (right treatment, right patient, right time) is in the vanguard of oncology treatment, and if applied outcomes for all patients would improve irrespective of new treatment availability (Garraway et al., 2013).

However, optimal allocation of treatment remains elusive. There is increasing evidence that inappropriate anti-cancer treatment does not improve quality of life or survival (Prigerson et al., 2015; Garrido et al., 2016; Mayor, 2008; Temel et al., 2010). A National Clinical Enquiry into Patient Outcome and Death (NCEPOD) reported that chemotherapy hastened or directly caused the death of over 25% of patients who died within 30 days of receiving treatment (Mayor, 2008). This need for caution has been further illustrated by a randomised control trial comparing early palliative and standard oncological care in patients with metastatic non-small cell lung cancer conducted by Temel et al. (2010). In this randomised trial patients who received palliative care early not only maintained better quality of life scores but also had a significantly longer median survival (Temel et al., 2010). These reports provide a persuasive argument for optimising the stratification of anti-cancer therapy in patients with advanced cancer. Therefore, it is important to examine the criteria that may be used to effectively stratify patients as to their likely survival prior to the allocation of treatment in patients with advanced cancer.

In the setting of patients with advanced cancer, Tumour, Node, Metastasis (TNM) staging has little discriminatory prognostic value and other patient related measures such as weight loss, performance status and quality of life have superior prognostic value. Therefore, the decision to proceed with systemic therapy is frequently based on these parameters by an oncologist and primarily on the basis of subjective clinical observation. More recently, measurement of skeletal muscle mass made from CT scans has been proposed to be useful in this context (Martin et al., 2013). Nevertheless, it is clear that the potential for sub-optimal allocation of anti-cancer therapy is considerable.

Recently, in a systematic review of prognostic tools in patients with advanced cancer, it was reported that a number of prognostic tools had been validated in different centres (Simmons et al., 2017). It was striking that the majority of these validated tools were based on subjective criteria, in particular the assessment of physical function. Only one validated prognostic tool the GPS (Glasgow Prognostic Score), assessing the magnitude of the systemic inflammatory response, was based exclusively on objective criteria. Indeed, there is now strong evidence that the chronic systemic inflammatory response results in classical features of cancer cachexia, including the preferential loss of lean muscle mass (McMillan, 2009; Diakos et al., 2014; Johns et al., 2014). Indeed, studies have shown a direct relationship between systemic inflammation measured by the GPS and NLR (Neutrophil Lymphocyte Ratio) and elevation of inflammatory cytokines, adipokines and other biochemical disturbances associated with loss of lean muscle mass and reduced performance status (McMillan, 2009; Kerem et al., 2008; Guthrie et al., 2013; McMillan, 2008; McMillan, 2013a). Recently, Laird and co-workers showed that in a large cohort study in two international bio banks, the combination of performance status and the systemic inflammatory response (SIR) as measured by the mGPS (modified Glasgow Prognostic Score) improved the prediction of outcomes of patients with advanced cancer (Laird et al., 2013a). Furthermore, they showed that quality of life was independently associated with both performance and the GPS (Laird et al., 2016).

Therefore, from the above and with the introduction of immunotherapeutic agents for advanced inoperable cancer it is timely to review the role of the markers of systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer.

2. Methods

The present systematic review and *meta*-analysis of published literature was undertaken according to a pre-defined protocol described in the PRISMA-P statement. The primary outcome was to assess the prognostic value of the SIR in patients with advanced inoperable cancer treated with chemotherapy, immunotherapy, radiotherapy, best supportive care or a combination of these treatment strategies.

This was carried out by a wide-ranging literature search to identify studies. Medical subject heading (MeSH) terms (Advanced Cancer, CRP, C-Reactive Protein, Albumin, White Cell Count, Neutrophil Count, Lymphocyte Count, Monocyte Count, Platelet Count, Red Blood Cell Count), were used in the US National Library of Medicine (MEDLINE), the Excerpta Medica database (EMBASE) and the Cochrane Database of Systematic Reviews (CDSR) to identify articles.

On completion of the online search, the title and abstract of each identified study was examined for relevance. Studies relating to duplicate datasets, studies not available in English and those published in abstract form only were excluded. Full texts were obtained for all studies deemed potentially relevant. Once further exclusions outlined below were carried out the bibliographies of all included articles were subsequently hand searched to identify any additional studies.

Only articles that reported survival analysis and gave hazard ratios or odds ratios with associated confidence intervals were included in the review. Studies with patients who had failed resections and patients who underwent palliative symptom control procedures were also included.