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Evaluation of an inflammation-based prognostic score in patients with advanced ovarian cancer

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ABSTRACT

Background: There is increasing evidence that the presence of an ongoing systemic inflammatory response is associated with poor outcome in patients with advanced cancer. The aim of this study was to validate whether an inflammation-based prognostic score (Glasgow Prognostic Score, GPS) is associated with survival in patients with advanced stage (stage III/IV) ovarian cancer.

Patients and methods: An audit was conducted of patients with a new diagnosis of stage III or IV ovarian cancer presenting to the West London Gynae-Oncology Centre between October 2003 and June 2006 ($n = 154$). The GPS was constructed as follows: Patients with both an elevated C-reactive protein (>10 mg/l) and hypoalbuminaemia (<35 g/l) were allocated a score of 2. Patients in whom only one or none of these biochemical abnormalities was present were allocated a score of 1 or 0, respectively.

Results: On univariate analysis GPS, histological type, ALP, performance status, primary surgery and ascites were predictors of overall survival. On multivariate a high GPS score, non-serous histology, high ALP and no initial surgery were independent predictors of worse overall survival in this population.

Conclusions: The presence of a systemic inflammatory response, as measured by the GPS, is an independent predictor of poor overall survival in patients with advanced ovarian cancer independent of treatment received.

1. Introduction

Ovarian cancer is the most common cause of gynaecological cancer-related death in the Western world (GLOBCAN).[1] Whilst the prognosis for early stage disease is good, approximately 80% of all newly diagnosed ovarian cancer patients have advanced stage disease at the time of presentation, having a 5-year overall survival of 25%.[2,3] The optimal management of stage III and IV disease is primary debulking surgery followed by adjuvant chemotherapy. However, despite advances in the management of ovarian cancer, the prognosis is variable. For the majority of patients, despite initial radical treatment, the disease will ultimately recur, and although life prolongation is a worthwhile aim, treatment is nevertheless palliative, aiming to improve or maintain quality of life and controlling symptoms. Specific subgroups of patients exist for which survival may range from a few months to several years. Whilst there are well-established prognostic factors for early stage disease, predicting survival in the advanced setting is more problematic. As a result, clinicians often overestimate survival.[4,5]

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There is increasing evidence that the presence of a systemic inflammatory response, as indicated by an elevated circulating C-reactive protein (CRP) concentration, is associated with poor survival in patients with malignancy, including ovarian cancer.[6–9] Furthermore, the presence of an inflammatory response is proposed to be pathogenic in the development of cancer-associated malnutrition.[10,11] Nutritional impairment in turn is correlated with poor performance status, shorter survival and increased mortality in patients with cancer.[12–15]

Recently, the combination of CRP and albumin has been used to develop the Glasgow Prognostic score (GPS).[16] Using the GPS, it has been shown that the combination of elevated CRP and hypoalbuminaemia is an adverse prognostic marker, independent of stage and performance status in advanced breast, non-small lung, pancreatic, renal cell and inoperable gastro-oesophageal cancer.[6,17–19] However, there is no information on the prognostic value of this combination in patients with advanced stage ovarian cancer.

The aim of the present study is to examine the relationship between the GPS and survival in patients with advanced stage ovarian cancer.

2. Patients and methods

An audit was performed of all patients with a new diagnosis of advanced stage ovarian cancer presenting to the West London Gynaecological Cancer Centre between October 2003 and June 2006. All patients had to have a diagnosis of stage III or IV disease on the basis of imaging or surgical findings. Patients with a history of inflammatory disease or infection were excluded from the study. Clinical information was obtained from a central database and after case note review. Data collected included demographic details, CRP, albumin, grade and stage of tumour, performance status, CA125, alkaline phosphatase (ALP), surgical debulk status and chemotherapy received. Individual readings of CRP, albumin, CA125 and ALP were collected at baseline prior to surgery or the administration of chemotherapy for advanced stage disease.

The GPS was constructed as described previously.[16] Patients with both an elevated CRP (>10 mg/L) and hypoalbuminaemia (<35 g/L) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities was present were allocated a score of 1. Patients in whom neither abnormality was present were allocated a score of 0. The study was approved by the Research Ethics Committee at Hammersmith Hospital, London.

3. Statistics

Survival (cancer-specific) analysis was carried out using the Cox proportional hazard model. Multivariate survival analysis was performed using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the model, the corresponding *P*-value had to be greater than 0.10. Deaths up to the 30th June 2006 have been included. Fisher's exact tests were used to test the effects of GPS on clinicopathological factors. Analysis was performed using SPSS software version 11.5 (SPSS Inc., Chicago, IL, USA).

4. Results

One hundred and fifty four patients were identified and their baseline clinicopathological characteristics are shown in Table 1. The average age of the patients at the time of diagnosis was 63.3 years (range 30–93). The majority of patients had a diagnosis of stage III, serous papillary carcinoma (79 of 147, 54%). Prior to receiving systemic therapy, CRP and albumin were measured in 142 and 154 patients, respectively. CRP was elevated (⩾10 mg/dL) in 65% (92 of 142), and 70% of the patients had an albumin less than 35 mg/dL (108 of 154). The majority of patients had an abnormal GPS (78%).

The minimum follow-up was 6 months or until date of death; the median follow-up of survivors was 21 months. At the time of analysis, 57 (37%) patients had died. Median survival was 39.9 months (27.93–51.94). The majority of patients underwent primary debulking surgery (78%), with optimal debulking (<1 cm) reported in 54% (60/112) of patients. Platinum based chemotherapy was prescribed for 99% of patients. The most common regimen administered was single agent carboplatin (50%). Other regimens administered included carboplatin/paclitaxel (42%), cisplatin/doxorubicin (2%), chlorambucil (2%), epirubicin/cisplatin/5-fluorouracil (1%), single agent cisplatin (1%), cisplatin/paclitaxel (1%), carboplatin/gemcitabine (1%).

Table 1 – Clinicopathological characteristics in patients with advanced ovarian cancer: univariate survival analysis

	Patients (*n* = 154)	Hazard ratio (95% CI)	*P*-value
GPS: 0/1/2	31/31/79	1.68 (1.16–2.45)	0.007
Tumour type: serous papillary/other	113/37	2.98 (1.70–5.21)	<0.001
Stage: III/IV	109/43	1.29 (0.73–2.29)	0.38
Grade: 1/2/3	6/38/80	1.64 (0.89–3.01)	0.108
Performance status: 0/1/2/3	18/61/27/12	1.75 (1.19–2.56)	0.004
Ascites: present/absent	87/45	2.97 (1.38–6.36)	0.005
Primary debulking surgery: yes/no	34/116	0.34 (0.19–0.59)	<0.001
Residual disease: <2/2–5/>5 cm	55/32/18	0.75 (0.46–1.22)	0.24
Alkaline phosphatase: ⩽130/>130 U/L	126/25	0.29 (0.12– 0.66)	0.003
C-reactive protein: ⩽10/>10 mg/L	50/92	1.88 (1.06–3.34)	0.031
Albumin: ⩾35/<35 g/L	46/108	1.71 (0.92–3.18)	0.091

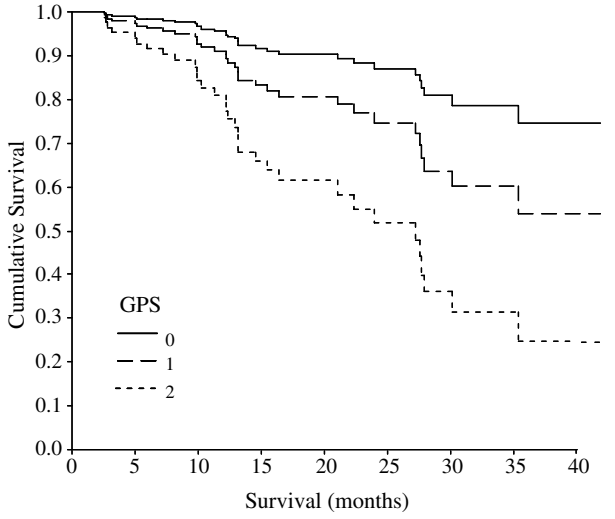

Fig. 1 – The relationship between GPS and overall survival in patients with a new diagnosis of advanced stage (stage III/IV) ovarian cancer.

On univariate analysis GPS ($p < 0.05$, Fig. 1), histological subtype ($p < 0.001$), ascites ($p < 0.05$), performance status ($p < 0.05$), ALP ($p < 0.05$), CRP ($p < 0.05$) and primary debulking surgery ($p < 0.05$) were significant predictors of cancer specific survival (Table 1). A trend was observed between overall survival and albumin ($p = 0.09$). On multivariate analysis GPS ($p < 0.05$), primary debulking surgery ($p < 0.05$), ALP ($p < 0.05$) and histological subtype ($p < 0.05$) remained as significant independent predictors of cancer specific survival.

The relationship between clinicopathological characteristics and an inflammation-based prognostic score (GPS) in patients with advanced stage ovarian cancer is shown in Table 2. A significant association was observed between GPS 2 and grade 3 disease (73%, 43 of 73) ($p < 0.05$). Patients with GPS 2 were also more likely to have ascites (80%, 57 of 82) ($p < 0.05$) and worse PS (17%, 10 of 12)($p < 0.05$). The median survival in these patients was 41, 28 and 22 months for a GPS of 0, 1 and 2, respectively. No other associations were observed.

5. Discussion

In the present study, a simple inflammation-based prognostic score (GPS) was shown to be an independent predictor of survival in patients with advanced stage ovarian cancer. This measure of inflammation is based on standard laboratory measurements of CRP and albumin, which are routinely measured in the clinical setting. These results are consistent with a number of previous studies in inoperable gastro-oesophageal cancer, lung cancer and metastatic breast cancer and improves on the prediction of survival using elevated CRP alone.[6,17,19]

Previous studies have investigated a number of possible predictive factors in advanced ovarian cancer.[21,22] In particular the effect of age, stage, histology, performance status, ALP, CA125 and amount of residual disease remaining after debulking surgery have been identified as possible prognostic factors.[23,24] In the present study, we found that GPS was superior to ECOG-PS in predicting overall survival, consistent with previous studies.[17] This is an important consideration as conventionally treatment decisions are often based on PS.[25] However, the reporting of PS is subjective, with oncologists being the most optimistic in their assessment.[26] CA125 was not significant in this study, and it is widely accepted that baseline measures of CA125 do not predict long-term survival of patients with advanced disease states.[27] Consistent with previous studies we identified non-serous histology, ALP > 135U/L and delayed primary surgery as negative prognostic factors.[21] The presence of ascites was not significant on multivariate analysis and this may be due to the small sample size of the patients studied. The use of prognostic models in ovarian cancer is not new and many validated prognostic factors have been identified.[21,28,29] This study does not aim to replace the known prognostic models for ovarian cancer, rather to refine and to add information that can then be validated in larger population sets. In particular, there is increasing evidence of a negative influence of inflammation on prognosis the molecular basis of which requires further elucidations. Therefore this information is of importance both to clinicians wishing to further validate this data and to scientists interested in the potential biological basis of these observations.

Only one study has previously investigated the effect of CRP on overall survival in ovarian cancer. This study was conducted in 120 patients with epithelial ovarian cancer and did not find a significant relationship between raised levels of CRP and overall survival on multivariate analysis.[20] Differences between this study and our results may pertain to the definition of raised CRP. In the study by Kodama and colleagues, a

Table 2 – The relationship between clinicopathological characteristics and an inflammation-based prognostic score (GPS) in patients with advanced stage ovarian cancer

	GPS 0, $n = 31$	GPS 1, $n = 31$	GPS 2, $n = 79$	P-value
Tumour type: serous papillary/other	25/6	20/11	58/17	0.26
Stage: III/IV	22/9	22/9	55/22	0.99
Performance status: 0/1/2/3	5/17/3/1	3/16/4/1	9/21/19/10	0.036
Primary debulking surgery: yes/no	3/26	7/23	22/56	0.15
Grade: 1/2/3	4/9/16	0/13/14	2/14/43	0.03
Ascites: present/absent	7/16	18/9	57/14	<0.001
Residual disease: <2/2–5/>5 cm	12/6/3	14/6/3	2/14/43	0.087
Alkaline phosphatase: ⩽130/>130	0/28/3	1/24/6	1/63/15	0.59
Survival (months)	40.9 (29.9–51.9)	27.5 (23.3–31.8)	22.4 (12.1–32.6)	0.02

CRP greater than 50 mg/L was considered elevated, whilst we considered any value greater than 10 mg/L as being elevated, in keeping with other published studies. The mechanism by which systemic inflammation may impact on survival is not well understood. Levels of circulating CRP are regulated by pro-inflammatory cytokines, in particularly IL-6.[30,31] IL-6 has been shown to increase the anti-apoptotic and oncogenic potential of tumour cells, as well as inducing drug resistance *in vitro*.[32,33] Furthermore, it has been proposed that elevated CRP identifies those patients with T-lymphocyte impairment, which is associated with poor outcome in malignancy.[34,35] Moreover, a raised CRP may reflect a pro-angiogenic environment, as circulating concentrations of vascular endothelial growth factor are directly associated with CRP, allowing unrestrained tumour growth and dissemination.[36,37] What still remains unclear are the cytokines that contribute to the pro-inflammatory state associated with malignancy. A number of individual cytokines have been investigated including VEGF with variable conclusions.[38–41] Identification of the pathogenic cytokines could be useful in designing anti-inflammatory strategies for this common clinical situation.

Hypoalbuminaemia has previously been established as a negative prognostic marker in ovarian cancer, and an indicator of progressive nutritional decline in patients.[42–45] The development of hypoalbuminaemia and cancer cachexia has been attributed to the presence of raised levels of circulating pro-inflammatory cytokines, in particular IL-6.[46] Moreover, it is well recognised that progressive weight loss is associated with poor tolerance to, and worse toxicity from, standard doses of chemotherapy which may account for the poor overall survival seen in patients with GPS of 2.[47–50] It is well recognised that levels of serum albumin declines in response to inflammation.[51] A number of authors suggest that a serial reduction in prealbumin levels in the face of stable measures CRP is an accurate measure of nutritional decline but this is yet to be validated in the cancer setting and remains an area of investigation.[52]

More recently, the presence of a systemic inflammatory response has been shown to impair the activity of cytochrome 3A (CYP3A4) in patients with advanced cancer patients.[50,53] As CYP3A4 is the principal drug metabolising enzyme for over 60% of all prescribed medications, including paclitaxel, changes in the activity of CYP3A4 may result in impaired drug response or increased toxicity, and this research is part of an ongoing research project.[50] It is further hypothesised that high protein catabolism, and stimulation of the acute phase response, may induce perturbations of the cellular response to chemotherapy-induced DNA damage in normal tissues and result in increased toxicity. Moreover, nutrition may alter the pharmacokinetics of many anticancer agents through altered protein binding and P450 activity.[53,54] GPS therefore, may not only be a valuable tool in prognostication but may also be used to predict those patients at risk of developing toxicity. Dose adjustments before the initiation of treatment in this patient group may improve the tolerability of anticancer agents and help maintain dose intensity. However, this concept requires further evaluation in a prospectively designed trial.

Irrespective of the mechanisms involved, the results of the present study suggest that the presence of a systemic inflammatory response, as indicated by GPS, is a useful tool in the assessment of survival in patients with advanced stage ovarian cancer. As described, GPS is simple to construct from laboratory measures that are routinely assessed in patients prior to treatment. GPS therefore should be further evaluated as a prognostic marker in patients with advanced ovarian cancer at diagnosis, and in the stratification of patients entering clinical trials.

Conflict of interest statement

None declared.

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