Acute Phase Reactant Proteins as Prognostic Indicators in Cancer

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Raised levels of APRPs in a patient with cancer at presentation are generally an unfavourable factor for the patient's survival. The APRPs can be prognostic indicators alone but are more effective when used in combination with powerful indices such as stage and clinical performance status. The pre-treatment APRPs tend to reflect shorter term survival risks up to 18 months and are often raised during the last 6 months of life in patients with disseminated cancer, as well as acute events such as sepsis.

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The acute phase reaction in clinical oncology has been the subject of very many investigations. More than 500 papers have been published on this topic since 1975, see Cooper and Stone (3) for the earlier references. The measurements of the serum levels of key proteins such as CRP, α1 acid glycoprotein (AGP) and haptoglobin involve simple technology and are attractive to many clinical investigators. Despite all this work there is still uncertainty as to the value of these measurements in clinical practice. This paper will briefly review some examples of the measurements of acute phase reactant proteins (APRPs) in oncology as aids to assessing prognosis.

There is firm evidence that the prognosis of cancer of a given type and site will depend on many features, the most powerful usually being stage, and performance status and differentiation. Many biochemical indices when considered alone may have the property of being prognostic indices but often fail to add information to what is already known to the clinician. Acute phase protein levels in cancer can raise suspicion, for example a CRP > 30 mg/l in a patient with Hodgkin's disease whose previous values were < 10 mg/l suggests recurrence, a CRP > 100 mg/l in a patient with leukaemia suggests septicaemia. In other situations they can help to stratify patients so that they add weight to the many clinical factors that have to be kept in mind when making a clinical decision about a patient.

LUNG CANCER

Bradwell et al. (1) demonstrated in patients undergoing surgery for lung cancer there was a strong correlation between tumour mass and the pre-operative levels of several APRPs. Linder et al. (7), in an extensive study of ceruloplasmin in lung cancer, observed pre-treatment levels rose with increasing tumour burden. High levels before surgery were associated with a poor prognosis. Long remissions were accompanied by serum ceruloplasmin levels returning to normal. Müller et al. (10) observing 290 patients with lung cancer referred for possible surgery, found that the level of APRPs could not discriminate those patients with resectable lesions and inoperable cases. The pre-operative level of C3 complement had a prognostic significance in the operable group and AGP in the inoperable patients. Caspers et al. (2) observed that a combination of stage, clinical status and CRP or AGP level produced the optimum stratification for survival probability in 98 cases of squamous cell lung cancer referred for radiotherapy. Similarly Marshall et
al. (9) observed in squamous cell lung cancer, the survival probability to six months was a reflection of the clinicians' assessment of the patients' suitability for radical or palliative treatment and "biochemical status" of which the most important factor is the CRP level but a raised CEA or AGP or a low albumin also had an adverse effect on prognosis.

GASTROINTESTINAL CANCER

In gastric cancer, which tends to present as an advanced disease in the UK, a study was made of 104 patients, 46 patients with a normal ACT at presentation had a median survival of 53 weeks, compared to 59 patients with a raised ACT (>0.8 g/l) and a median survival of 9 weeks. Further pre-operative stratification in terms of survival risk could be achieved by adding the CEA level using an arbitrary cut off of >5 ng/ml as the discriminant. This gave 3 stratifications ACT normal + CEA normal, ACT or CEA raised, ACT + CEA raised. There was a striking difference in the median survival of the 32 patients with both variates normal (median survival 64 weeks) and the 24 patients in whom both variates were raised (median survival 5 weeks) (12). In a second study of stomach cancer De Mello et al. (4) demonstrated that the CRP level prior to surgery tended to reflect the probability of the surgery being ineffective (non-resectable, no by-pass) or only a palliative operation was possible compared to those that were able to be treated by radical resection. CRP was demonstrated to be the analyte with the greatest discriminating power. Using a 20 mg/l cut off then 22/44 (50%) of the non-resectable and inoperable cases were identified and whilst only 6/50 (12%) of the resectable cases had a CRP>20 mg/l (only 2 of whom survived >6 months.

The Dukes staging of colorectal cancer is well recognised as a powerful guide to the patients' prognosis. De Mello et al. (4) examined the contribution of several variates, including APRPs that might potentially enhance the predictive power of the Dukes classification. Step wise analysis showed that once sex, age and Dukes stage are included the addition of the pre-operative ACT concentration gave information not in the clinical terms in the model. Furthermore once ACT was included other biochemical tests failed to contribute more information.

This modified Dukes scheme allowed the probability of individual patients surviving for 1 to 2 years to be calculated. For example the estimated 1 year survival probabilities for a 67 year old male patient with a raised ACT (1.1 g/l) would be 0.7 for Dukes B, and 0.3 for Dukes C, in the same aged patients with normal ACT the probability rose to 0.85 to 0.65 respectively.

Durdey et al. (5) found that the combination of pre-operative CEA levels and APRPs were helpful in the pre-operative detection of fixation of colorectal tumours. In 89 colorectal carcinomas 32 (36%) were fixed, 18 by malignancy and 14 by inflammation. The levels of CEA, AGP and CRP were significantly higher in the serum of patients with fixed tumour (p <0.05), concentration of AGP >1.4 g/l or CRP <15 mg/l were accurate predictors of tumour fixation (specificity 87 and 90 percent) and both had a sensitivity of 78 percent. CEA appeared to be more accurate in determining the nature of the fixation, a CEA >50 ng/ml predicted 82% of malignant fixed tumours.

UROLOGICAL CANCER

An example is of invasive bladder cancer stages T3 (into the muscle wall) and T4 (beyond the muscle wall). In both these stages it was demonstrated that in patients referred for radiotherapy the finding of a CRP>12 mg/l before treatment was associated with a significant decrease in the probability of survival. This illustrates the additive effect of stage and acute phase reaction in the stratification of the patients (11). In renal carcinoma, the acute phase reactants are highly correlated, they do not tend to be raised in early localised tumours, but are often increased when there is renal vein involvement and distant metastases (3). Hence a raised acute phase would enhance the suspicion that the cancer is no longer localised but could not help in differentiating it from inflammatory disease of the kidney.

CRP MONITORING IN NEUTROPENIC PATIENTS

In leukaemia and lymphoma the risks from septicaemia are life threatening. The development of rapid quantitative measurements of CRP, especially nephelometry, has shown that this component of the acute phase response can be a useful test in monitoring pyrexia in leuco-
Bacterial infection is the commonest cause of pyrexia, but viral and fungal infections or blood products can also produce pyrexia. Antibiotics are given promptly, as it as unwise to delay for the results of microbiological tests which are often negative. Several studies have shown that bacterial infection often produces a very marked CRP response with the levels reaching >100 mg/l in 48–72 hours (8, 15, 17, 18). When an appropriate broad spectrum antibiotic is given the CRP falls, with a half life of about a day, in successfully treated patients. The pattern of the CRP response over the 7–10 days of the incident of infection and its treatment tends to reflect the disease control. All authors emphasise that the value of CRP measurements in acute infection lies in the rate of change rather than in isolated value. Viral and fungal infections tend to produce a lower CRP response than bacterial infections.

Generally serum amyloid A (SAA) protein closely follows a similar pattern to CRP, its level being amplified about 10 fold. Nevertheless, the general availability of commercial CRP assays makes it the test of choice in monitoring leukaemic patients during the high risk period associated with neutropenia.

The growing use of bone marrow grafts in the management of leukaemia places the patient at risk of infection, often viral and graft versus host disease (GVHD). The acute phase response to GVHD tends to be loss marked than bacterial infection (6). Riches et al. (14) reported that GVHD alone produced little CRP response, high levels were found when GVHD was complicated by infection or the grafted patient was infected. However, significant increases of SAA and ACT were seen in acute GVHD. There is considerable overlap between the acute phase responses in the different complications of bone marrow transplantation which limits the value of the test as a diagnostic aid.

In summary it can be seen that the acute phase reaction can provide prognostic information of various types in clinical oncology. In acute emergencies a high CRP provides a warning of sepsis, and a failure of the level to decline rapidly on treatment is a bad prognostic sign. In patients who have been monitored on a regular basis, a rising level of APRPs is a fairly late sign in metastatic or recurrent disease, tumour markers such as CEA, CG, AFP etc. tend to be more sensitive markers. The rising APRPs are usually a sign of disturbance of the host-tumour relationship, the survival probability tending to decrease as the levels of APRPs rise. Finally, and in a more academic context APRPs at presentation when taken into account with stage can help to improve the stratification of patients in those cancers where the survival probability is less than 50% at 2 years.

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364—E. H. COOPER