Editorial

Clinical impact of cachexia biomarkers in advanced cancer

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The appeal of the work by Kim *et al.* is its simplicity (1). In this study, a quick and easy physical measurement, using mid-upper arm circumference (MUAC), is compared to established inflammatory markers as a potential prognostic tool. Entry into the study was determined by the treating oncologist. It included unselected patients with a diagnosis of advanced cancer with an estimated survival of less than a year. The commonest diagnosis was lung cancer (33.5%) and two thirds (65.5%) of patients were receiving palliative chemotherapy. The median follow-up of this cohort was 33 weeks and the median survival was 32.4 weeks [95% confidence interval (CI): 5.6–142.7 weeks].

The study compared: Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS), Prognostic Nutritional Index (PNI), neutrophil/lymphocyte ratio (NLR) and C-reactive protein/albumin ratio (CAR) with MUAC. Of these markers GPS and mGPS are the most established (2). MUAC was highly specific (86%) and GPS was highly sensitive (81.1%) for 12-week survival.

By comparing levels of inflammation with muscle mass, Kim *et al.* were investigating the proposed mechanism of inflammation with MUAC as an assessment of muscle loss, as an end organ effect of cachexia (1). Although several definitions of cachexia exist, they have common features including elevated systemic inflammation, functional decline, unintended weight loss and muscle loss (3-5). Cachexia may be measured in many ways, but could include assessment of muscle mass, weight loss or inflammatory status. It is common in advanced cancer, particularly lung cancer, upper gastrointestinal and pancreatic cancer. Kim *et al.*'s study is part of a growing body of work that show associated measures of cachexia have a prognostic role in patients with cancer (1,2,6-9).

Despite the evolving evidence for biomarkers of systemic inflammation and cachexia to be prognostic in this setting, they are not yet routinely incorporated into clinical trials or routine practice. One of the major challenges in developing a biomarker for cancer outcomes, is the increasing complexity of oncological diagnosis and management. Specific biomarkers from homogeneous populations are necessary, to allow accurate application of population outcomes to an individual patient.

As an example, a recent meta-analysis in more than 7,000 patients demonstrated that high GPS is associated with poor prognosis in patients with non-small cell lung cancer (NSCLC) (9). The study benefited from a standardised score with consistent thresholds allowing comparison of multiple studies. However, the study included patients with NSCLC across all disease stages and treatment modalities. Thus, although it provides generic prognostication for patients with lung cancer, it remains challenging to apply this data in specific clinical circumstances. Furthermore, as Kim *et al.* allude to, many biomarkers of systemic inflammation and cachexia have been developed in selected cohorts, often dictated by treatment status, but are applied more generally to broader populations without the same level of rigour.

Using NSCLC as an example, there is increased understanding of the molecular characteristics of individual cancers, leading to increasing stratification into NSCLC subgroups with different treatment pathways and outcomes. Oncogene (i.e., EGFR, ALK, ROS1) driven NSCLC is now considered a distinct entity to non-oncogene driven NSCLC, affecting different populations, with higher

response rates to treatment and more favourable survival (10-12). It is therefore important that biomarkers of systemic inflammation and cachexia are validated in specific cohorts of well-defined patients, ideally to address clinically relevant questions.

Our group have shown that a novel inflammatory score, the Scottish Inflammatory Prognostic Score (SIPS), predicts survival in patients with NSCLC with PDL-1 expression >50% receiving first-line pembrolizumab monotherapy as per its licensing. In those with the highest levels of inflammation (SIPS2, albumin <35 mg/L and neutrophil count >7.5×10^9/L) median overall survival was 5.1 months, with no patients demonstrating evidence of long term response (13). Conversely, the median survival of the low inflammation group (SIPS0, albumin ≥35 g/L, neutrophils ≤7.5×10^9/L) was 28.7 months, with 42% continuing treatment at 1 year. By investigating the prognostic value of this biomarker in a well-defined clinical setting we increase the relevance of these findings for routine clinical practice. This tool is in the process of being validated, but gives clinicians a framework to talk about outcomes associated with pembrolizumab monotherapy. Although the same tool may be useful in other clinical settings, such as chemoimmunotherapy for NSCLC expressing programmed death ligand-1 (PD-L1) <50%, we advocate further investigation.

Kim *et al*. highlight the usefulness of biomarkers of systemic inflammation and cachexia in advanced care planning discussions with patients. We agree that this is a primary role for these tools, used alongside routine clinical assessments where they may provide additional objective information. In patients presenting with malignancy of undefined primary origin (MUO) the mGPS stratifies survival from the time of first clinical or radiological finding of cancer; mGPS2: 2.3 months, mGPS1: 5.0 months, mGPS0: 13.6 months (14). This validated score is now routinely used in UK clinical practice in discussions with patients about the appropriateness of further investigations and intervention. For example, in a patient with radiological evidence of metastatic malignancy who has poor performance status, a high inflammatory status supports a decision for not performing comprehensive investigations as the patient is unlikely to live long enough to benefit from treatment.

However, this represents a rare success story for biomarkers of systemic inflammation and cachexia in the clinic. Although retrospective studies such as that described by Kim *et al.* can provide useful information, a key issue for cancer clinicians is the lack of prospective data supporting their use. We advocate for their inclusion in prospective studies, including in clinical trials of investigational agents where many of the biomarkers of systemic inflammation described are already routinely collected. Measures such as MUAC could be easily incorporated at key data collection points. Dedicated prospective clinical trials using biomarkers of systemic inflammation and cachexia as stratification factors are also required. This will potentially help understand who benefits from specific treatments in standard oncology intervention trials. It will also help to evaluate the effect of strategies aimed at treating cachexia, specifically maintaining or improving systemic inflammation, muscle or weight loss and functional status.

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