CHIEF SCIENTIST OFFICE

CODE: CAF/20/01

RESEARCH PROJECT BRIEFING

Identifying and validating predictive Biomarkers in advanced gastroesophageal cancer – a springboard to REAListic medicine (BE-REAL)

AIMS

Cancer of the food pipe (oesophagus) and stomach, termed gastroesophageal cancer, primarily affects older adults (defined as those aged 65 and older). It is associated with significant symptoms, for example pain and difficulty swallowing and a very poor prognosis – average survival is less than one year when surgery is not possible.

Older adults, who are more at risk from side effects of treatment, represent an increasing proportion of patients (currently ~70%), but have been underrepresented in clinical trials, leading to a lack of evidence on how to best treat this important patient group. Extrapolation of clinical research findings from younger adults is unsatisfactory and potentially leads to sub-optimal treatment. There is a need to improve the outcomes (length and quality of life) of older adults diagnosed with this cancer.

We aimed to use baseline patient information and samples of cancer from a completed clinical trial in older adults with stomach and oesophageal cancer to:

- Describe the population we see in clinic and use these details to find ways to predict who is most likely to develop side effects from chemotherapy
- Find markers (e.g levels of proteins) in the cancer tissue or patient that may allow us to predict who is likely to have a better outcome with chemotherapy

KEY FINDINGS

- Older adults with cancers of the oesophagus and stomach are not as fit as patients normally recruited to clinical trials – termed ‘frailty’.
- These patients have many symptoms at diagnosis, which are often severe. The severity of the symptoms can predict survival.
- A marker, in the tumour, called the DNA Damage Immune Response signature, can predict which tumours will shrink with chemotherapy.
- This marker also indicates how many immune cells are present and may therefore also predict outcome from immunotherapy.

WHAT DID THE STUDY INVOLVE?

This study used samples from a completed clinical trial – the GO2 trial, which recruited 559 older and/or frail patients with gastroesophageal cancer (median age 76) from UK centres between 2014-2017. This population was felt to represent real-world patients seen in clinic. The trial and the future planned studies (this study included) had input from patient and public representatives from the beginning to ensure the research questions being asked were relevant to older adults with cancer.

The trial database with anonymised data was analysed, including a description of patient characteristics, alongside individual patient side effects and cancer outcome (492 patients). In addition, the tumour samples from a selection of patients (252 patients) had genetic material removed and sequenced.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

In this unique study we provide a detailed analysis of the burden of symptoms (**Figure 1**) and frailty (**Figure 2**) within a real-world population of patients. This knowledge will help inform and design future services to better serve our older adults with cancer.

We then assessed the ability of several frailty screening tools to predict prognosis including the GO2 Frailty Score and the Geriatric-8 (G8) score. The GO2 frailty score is a continuous score based on nine domains of frailty. The G8 has eight components and a score of 14 or less suggests a thorough geriatric assessment would be beneficial. In GO2, both a low frailty score (defined as 0-1 or not frail) and a normal G8 score before treatment (defined as >14) indicated a significantly improved outcome. This could be used to aid decision making in clinic.

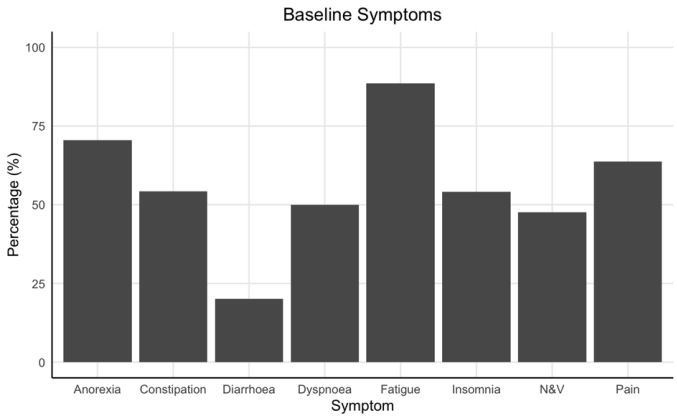

Figure 1. Percentage of patients within the GO2 trial who had individual symptoms.

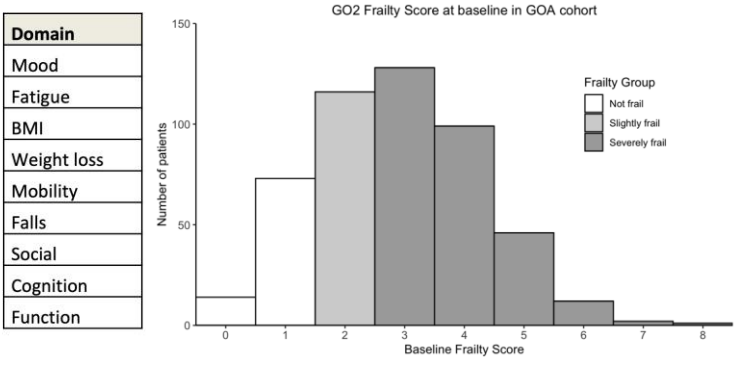

Figure 2. The domains of frailty recorded at baseline in GO2 and the number of domains affected for each individual patient represented as a frailty score.

Regarding the tumour, the DNA Damage Immune Response (DDIR) signature, a 44 gene score (classified as positive or negative), obtained by testing the tumour, was able to predict which patients were more likely to respond to chemotherapy (52% vs 28%) and also predict who was more likely to live longer.

This signature could also be used as a decision-making tool in the future.

WHAT IMPACT COULD THE FINDINGS HAVE?

Our findings could have implications for:

- Patients – improving shared decision-making regarding treatment decisions in a poor prognosis cancer, balancing the risk of treatment against likely benefit, especially in older and frailer patients who have been previously under-represented in clinical research.
- Policy – our work highlights the extent of frailty in this cohort of patients and the need for early frailty screening to guide targeted intervention in older adults with cancer
- Practice – our work highlights the need for early intervention to identify and improve a patient's symptoms e.g. early supportive or palliative care assessment

HOW WILL THE OUTCOMES BE DISSEMINATED?

Results from the project have already been presented at international conferences and published in several peer-reviewed manuscripts. We will also disseminate through our connections with local and national patient representative groups, including the Tayside Maggie's Centre gastroesophageal support groups, Ochre and Heartburn UK. Following on from the results, we have:

1. Established a local frailty screening clinic in NHS Tayside to enable early identification of symptoms and facilitate intervention in patients newly diagnosed with advanced cancer, referred to the Oncology department for treatment.
2. Obtained funding to explore the biology of the DDIR signature within the laboratory both in cell lines and organoids (a miniaturised and simplified 3D version of a tumour) with the hope of finding ways to improve both response and long-term survival to treatment.

CONCLUSION

- The real-world population of patients with oesophageal and stomach cancer have a high burden of frailty and symptoms, which can predict both survival and chances of side effects from treatment.
- Systematic early identification of frailty and symptoms could enable shared decision-making around treatment decisions, helping patients prioritise what matters to them – balancing quality of life and length of life. In addition, early intervention targeting frailty and/or symptoms may improve outcomes
- Features within the tumour may predict who is most likely to benefit from chemotherapy and provide a means to reverse treatment resistance.

RESEARCH TEAM & CONTACT

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Additional Information

The project was completed on 01/03/2024. Funding received was £258,601.88.