The direction of travel to better outcomes for patients with oesophago-gastric cancer

Globally, oesophago-gastric cancers account for 10% of cancer incidence and approximately 14% of cancer deaths, with a preponderance in males, and in low and middle income countries (1). The traditional histological classifications, squamous versus adenocarcinoma, and intestinal versus diffuse, as well as the anatomical delineators (oesophageal, junctional and gastric), are being superseded by molecular-based classifications (2,3). The aim is to identify patients whose outcomes can be improved by the judicious use of standard chemotherapeutic agents and/or novel targeted therapies.

The Cancer Genome Atlas (TCGA) analysis of gastric cancers identified 4 potential groupings or molecular subsets: 1) Epstein-Barr virus (EBV) associated tumors 2) tumors characterized by microsatellite instability (MSI) (genetic hypermutability resulting from impaired DNA mismatch repair) 3) a group characterized by chromosomal instability (CIN) and, 4) tumors with stable genomes with mainly diffuse histology (2). Given the ongoing debate around the causes for the divergence in incidence and clinical outcomes for oesophago-gastric cancers by geographic region, it might have been expected that the different molecular phenotypes would correlate with the regional differences. Yet, a recent analysis by Schumacher *et al.* of somatic copy-number profiles in 657 gastric adenocarcinomas from a mixed population of Eastern and Western patients, with ancestry delineated by germline single nucleotide polymorphisms, showed no definite regional delineation by the TGCA subgroups (4).

The molecular phenotype of oesophageal cancers has also been explored identifying clear genetic differences between squamous cell cancers and adenocarcinomas, confirming the current practice of considering these as 2 distinct clinical entities. Although the squamous cell cancers demonstrated features in common with squamous cancers at other anatomical sites they showed no evidence of human papilloma virus (HPV) infection challenging the idea that they should be included in the HPV-

associated group of malignancies. Oesophageal adenocarcinomas resembled the CIN variant of gastric cancers, suggesting that together they might be considered a single disease entity (3).

In a recent paper, Janajigian and colleagues (5) present an analysis, using targeted next generation sequencing, of a large (n=295) prospectively collected series of biological samples (mainly endoscopic biopsies of the primary tumour) accompanied by clinical data from patients with metastatic oesophago-gastric adenocarcinoma from a single centre in the US (Memorial Sloan Kettering (MSK)). Platinum based chemotherapy remains the central tenant of therapy for metastatic oesophago-gastric cancer, though as this paper demonstrates identifying the subset of patients most likely to benefit from chemotherapy remains elusive with putative biomarkers of platinum sensitivity e.g mutations in DNA repair genes, or defects in homologous recombination deficiency not correlating with response.

Trastuzumab (a monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER-2/*ERBB2*) was the first molecularly-directed therapy to enter standard practice in this field based on the result of the ToGA study where median survival for metastatic HER-2 positive gastric and junctional tumours was 13·8 months (95% Confidence Interval (CI) 12–16 months) for those assigned to receive trastuzumab plus chemotherapy compared to 11·1 months (95% CI 10–13 months) from chemotherapy alone (hazard ratio 0·74; 95% CI 0·60–0·91; p=0·0046) (6). In the MSK cohort overall, twenty three percent (68/295) of patients were reported as having HER-2 positive tumours – a higher percentage than previously seen but includes patients who had serial biopsies. There was a strong correlation between ERB2 copy number and HER-2 positivity but beyond this there was significant heterogeneity in co-mutational events potentially explaining the modest increase in response rates 35% to 47% with the addition of trastuzamab to chemotherapy in the ToGA trial (6).

A limitation of the Janajigian paper is the mixed population of gastric and oesophageal tumours making comparisons with other datasets difficult to tease out, and the retrospective analysis of the

treatment given. Its strengths include the detailed clinical data, and does undoubtedly represent the direction of travel. The median overall survival of 26 months for metastatic HER-2 negative tumours is encouraging and though the authors point out that this cohort was predominantly younger and of better performance status than the general population with this disease, the baseline clinical demographics are not inconsistent with the ToGA study where 90% were ECOG 0-1 with a median age of 59 years and median overall survival was clearly shorter. 14% of the MSK cohort received immune checkpoint inhibitors, as in other tumour types these agents are not a panacea, but initial results from heavily pre-treated patients are encouraging (7,8). Across tumour types, high mutational load and viral aetiology appear to correlate with response to immune checkpoint inhibition (9) providing a strong rationale for further evaluation in oesphago-gastric cancer.

The proportion of microsatellite instability high (MSI-H) or mismatch repair deficient tumours in the MSK cohort is low (3%) compared to the TCGA dataset of 16%. The authors postulate that this is because all of the patients in their study had metastatic disease. In colorectal cancer MSI-H tumours have a better prognosis (10), and this has also been shown for gastro-oesophageal cancer in the MAGIC trial (11). Interestingly the proportion of patients with MSI-H tumours in the MAGIC trial, where patients had locally advanced disease was 7%, with a prognosis midway between the other 2 cohorts in keeping with the prior hypothesis.

The ultimate goal of precision medicine – tailored treatment to maximise benefit – has inherent challenges. Primary tumours, subsequent metastases and the host micro-environment are molecularly unique, as well as heterogeneous, with new mutations acquired over time necessitating repeated biopsies to assess the best potential therapy at a given time point, as elegantly demonstrated by Pectasides and colleagues (12). They suggest that the lack of success for molecularly targeted therapies in metastatic oesophago-gastric cancer is predominantly related to intrapatient tumor heterogeneity, and highlight the potential role of cell free DNA profiling to aid the selection of targeted therapies for metastatic disease. The OCCAMS (oesophageal cancer clinical

and molecular stratification) consortium, using whole genome sequencing have identified 3 broad but distinct mutational signatures for oesophageal adenocarcinoma, validated in an independent cohort, and suggest potential therapeutic strategies for each group (13).

Less talked about is the challenge of incorporating this rapidly evolving molecular knowledge into confirmatory molecularly directed, practice changing phase III platform trials. Examples include the FOCUS4 trial in metastatic colorectal cancer (14), and the PLATFORM trial in metastatic oesophago-gastric cancer (15). The aim of these, and similar studies, is to harness the evolving knowledge and define biomarker-enriched cohorts where new agents can be assessed. The targeted nature of this approach should ensure that a more modest sample size is required, and new agents and combinations can be efficiently assessed. For such designs to be successful, several key considerations need to be addressed. Firstly, can the biomarker of interest be reliably measured using a validated assay on clinically available samples and what is the prevalence in the population? Secondly, is the biomarker also a prognostic factor? – in which case a separate control arm to distinguish prognostic from predictive effects will be required, and finally what is the strength of evidence for the predictive effect e.g. the specificity of the new agent? (16). The design iterations of the trials mentioned above are a testament to these challenges, and not least, the availability (or not) of new agents and combinations for such projects, as well as access to the technology that allows molecular stratification. In the quest to find the best drug to treat the cancer there are 3 key stages, biomarker identification linked to companion diagnostic and targeted agent, evaluating these combinations in confirmatory clinical trials, and finally ensuring access to these advances to those mostly likely to benefit. For a disease that is prevalent in low and middle income countries the latter may be the greatest challenge.

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