I report grants from Genentech and Sellas, and personal fees from Orbis Health Solutions, Heat Biologics, Pelican Therapeutics, and Abexxa, outside the submitted work. In addition, I have a patent for a breast cancer vaccine with royalties paid.

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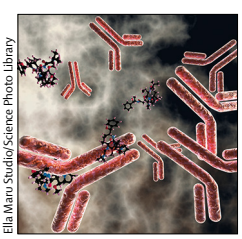
Targeting tissue factor in advanced solid tumours



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Despite the development of more effective therapies that modulate antitumour immune responses, target oncogenic mutations, and block key hormonal and cell cycle pathways, outcomes remain poor in many patients with metastatic cancers. Antibody–drug conjugates—which are therapeutics composed of an antibody that targets receptors overexpressed on cancer cells, a cytotoxic agent or payload, and a linker molecule—are an intriguing approach in these settings. Antibody–drug conjugates might offer advantages over both conventional chemotherapy (by permitting delivery of the cytotoxic molecule to the tumour microenvironment, while limiting systemic absorption) and classical antibody-directed therapy (by the addition of a cytotoxic payload). So far, four antibody–drug conjugates have been approved by the US Drug and Food Administration for cancer treatment.[1] Gemtuzumab ozogamicin, an anti-CD33 antibody linked to calicheamicin, is approved for acute myeloid leukaemia. Inotuzumab ozogamicin, an anti-CD22 antibody linked to calicheamicin, is approved for acute lymphoblastic leukaemia. Brentuximab vedotin, an anti-CD30 antibody linked to monomethyl auristatin E (MMAE), is approved for Hodgkin lymphoma (both relapsed refractory and untreated disease in combination with chemotherapy), both systemic and cutaneous anaplastic large cell lymphomas, and CD30-expressing mycosis fungoides. In 2013, ado-traztuzumab emtansine, which is a human epidermal growth factor receptor 2-targeted antibody linked to DM1 (a microtubule inhibitor), was approved for human epidermal growth factor receptor 2-positive metastatic breast cancer, becoming the first antibody–drug conjugate approved for treatment of solid tumours. The success of these antibody–drug conjugates has spurred further interest in evaluating different antibodies and cytotoxic molecules, with more than 60 of these therapeutics currently under investigation.[2]

Tissue factor is a 47-kDa transmembrane glycoprotein that activates the extrinsic coagulation pathway, and is overexpressed in numerous cancers as a result of hypoxia, loss of tumour suppressor genes (such as *TP53* and *PTEN*), and overactivity of MAPK signaling.[3] Tissue factor is of interest as an anticancer therapy because of its overexpression in various cancers, its perceived role in oncogenesis, and its association with inferior clinical outcomes.[4,5] The targeting of tissue factor with tisotumab vedotin and other agents had only minimal effects on coagulant and bleeding parameters in pre-clinical models, providing some reassurance that this approach could be feasible in patients.[6]

In *The Lancet Oncology*, Johann S de Bono and colleagues[7] report the outcomes of a phase 1–2, open-label, dose-escalation and dose-expansion study evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumour activity of tisotumab vedotin in patients with advanced cancer. Tisotumab vedotin is an antibody–drug conjugate that links a fully human monoclonal antibody targeting tissue factor with MMAE. Although the study was done in cancers with relatively high concentrations of tissue factor expression, patients were not selected for eligibility on the basis of this marker. The dose-escalation phase showed a maximum tolerated dose of 2·0 mg/kg given intravenously every 3 weeks. In the dose-expansion phase, some preliminary

evidence of activity was seen in heavily pretreated patients with several cancers, particularly bladder cancer (four responses in 15 patients) and cervical cancer (nine in 34). Most responses were relatively short-lived (median duration 5·7 months), although further follow-up will be needed to assess duration of responses. The most common treatment-emergent adverse events included fatigue, nausea, alopecia, decreased appetite, constipation, diarrhoea, and vomiting, which are common with other antibody–drug conjugates. However, other common adverse events in this study—such as epistaxis, conjunctivitis, and dry eye—have not often been described in other antibody–drug conjugates studies.

The incidence of epistaxis (69%) and ocular adverse events (60%) merits further exploration. Epistaxis was the most common treatment-emergent adverse event, although most events (98%) were grade 1 and thus did not require intervention. Ocular symptoms, particularly conjunctivitis, were noted early on in the study's enrolment, and a mitigation strategy was enacted. After this intervention, the incidence of conjunctivitis decreased from 56% to 29%. However, the incidence of other ocular toxicities increased, such as dry eye (from 17% to 27%), conjunctival ulcer (from 1% to 7%), and conjunctival hyperaemia (from 0% to 6%). Notably, high concentrations of tissue factor have been shown in the nasal mucosa,[8] and are hypothesised to be present in the eye as well, given that it is a highly vascular mucosal site.

Correlative studies are needed to determine the most appropriate patients for therapy. Although the tumour types studied by de Bono and colleagues are known to have tissue factor expression in at least some cases, it was not reported how many patients had tissue factor-expressing tumours in this study. Conceivably, only tumours with moderate or high expression of tissue factor would benefit from this agent. It also remains to be seen whether tisotumab vedotin will be tolerable in combination with other agents, given its toxicity profile.

In summary, de Bono and colleagues provide preliminary evidence of the activity of tisotumab vedotin in patients with advanced solid tumours. Tisotumab vedotin has a novel mechanism of action accompanied by somewhat unusual side-effects. Translational studies to define the most appropriate patients and understand the mechanisms of toxicities will be important next steps.

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Global elimination of cervical cancer as a public health problem

In May 2018, the WHO Director-General made a global call for action to eliminate cervical cancer as a public health problem.[1] Before embarking on the pathway to eliminate cervical cancer, which will require immense resources and a global concerted effort, an essential initial step is to understand whether

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