Biomarker predicts treatment resistance in prostate cancer

A marker detectable through a simple blood test can predict resistance to abiraterone and enzalutamide in men with advanced prostate cancer, a prospective US study shows.

In patients with a shortened version of the androgen receptor—AR-V7—which could be identified from circulating tumour cells, the drugs appeared to have no effect.

Of 31 men treated with abiraterone, six (19%) had detectable AR-V7 which is defective and lacks the necessary ligand-binding domain.

None responded to treatment as measured by prostate-specific antigen, clinical, or radiographic progression compared with 17 (68%) of 25 who did not carry the marker.

In the enzalutamide group, none of 12 patients whose blood samples tested positive for AR-V7 responded to the drug, compared with ten (53%) of 19 men who had no AR-V7 detected.

For both abiraterone and enzalutamide, median survival was significantly shorter for those who were AR-V7 positive (10·6 months *vs* not reached, HR 12·7 [95% CI 1·3–125·3], p=0·006; and 5·5 months *vs* not reached, HR 6·9 [1·7–28·1], p=0·002, respectively).

The researchers are now planning an international multicentre trial to test its clinical potential for selecting treatment options.

"The remarkable thing was that every single patient who had AR-V7 had no response whatsoever to the drug, and their cancer progressed at a faster rate than we would have expected," said study leader Emmanuel Antonarakis (John Hopkins University School of Medicine, Baltimore, USA).

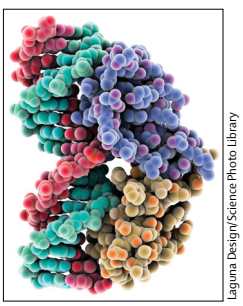
"We envisage a scenario where the clinician can order that test and if that patient was found to have AR-V7 in their cancer cells they should probably not have abiraterone or enzalutamide."

Gerhardt Attard, clinician scientist at the Institute of Cancer Research, London, UK, said the data were "compelling" and the test might be useful in those already treated with abiraterone or enzalutamide and now considering the other—something currently restricted in the UK due to funding.

"This abnormality is present in one in ten who have not had either drug but in 50–70% of those who have had and not responded."

He added studies were being done on other tests which would eventually give a more accurate picture.

Emma Wilkinson



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Published **Online** September 19, 2014 http://dx.doi.org/10.1016/S1470-2045(14)70468-1

For the **study by Antonarakis and colleagues** see *N Engl J Med* 2014; **371:** 1028–38

Pleuropulmonary blastoma early detection improves survival

New research suggests that pleuropulmonary blastoma—the most common primary malignancy of the lungs in childhood—shows better outcomes in its purely cystic stage (type I), compared with other advanced and aggressive stages (type II or III). Yoav Messinger and colleagues also show that surveillance of the carriers of *DICER1*—the gene that shows a germline mutation in most pleuropulmonary blastoma cases—might allow the earlier detection of type I pleuropulmonary blastoma before its progression to type II or III and thereby improve outcomes.

Pleuropulmonary blastoma has three pathological types: type I (purely cystic), type II (cystic/solid), and type III (completely solid). However, not all cystic type I pleuropulmonary blastomas progress to more aggressive stages: these nonprogressed or regressed cases are called type I regressed (type Ir). The researchers presented data from 350 confirmed cases of pleuropulmonary blastoma by the International Pleuropulmonary Blastoma Registry, which allowed a statistically robust analysis of survival and prognostic factors for pleuropulmonary blastoma.

Analysing the data, Messinger and colleagues found that 33% (115/350) of pleuropulmonary blastoma cases were type I or type Ir, 35% (124/350) were type II, and 32% (111/350) were type III or type II/III. For type I/Ir patients, the 5-year overall survival was 91% (95% CI 83–99). Overall survival was substantially better for type II versus type III (71% [95% CI 62–81] *vs* 53% [43–65], p=0·0061). According to the researchers, 5-year disease-free survival was also better for type II versus type III (59% [95% CI 50–70] *vs* 37% [28–48], p=0·0002). 97 patients with pleuropulmonary blastoma were assessed for germline *DICER1* mutations, and 64 (66%) had a heterozygous, deleterious *DICER1* mutation.

Julian Martinez-Agosto (David Geffen School of Medicine at UCLA, CA, USA) says, "This study reinforces the emerging view that identifying the type of pleuropulmonary blastoma early on is prognostically important, as the presence of metastasis is associated with poor survival." Apiwat Mutirangura (Chulalongkorn University, Bangkok, Thailand) comments, "[The researchers] describe the roles of germline *DICER1* mutations in the clinical course of pleuropulmonary blastoma. Also, surveillance of *DICER1* carriers might allow the earlier detection of type I pleuropulmonary blastoma. This is important in improving outcomes because earlier detection can prevent the disease from progression to type II or III."

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Published **Online** September 19, 2014 http://dx.doi.org/10.1016/S1470-2045(14)70469-3

For the **study by Messinger and colleagues** see *Cancer* 2014; published online Sept 10. DOI:10.1002/cncr.29032