

Tumour markers

SUMMARY

Doctors are faced with an increasing multitude of tumour markers, biomarkers, tissue markers and genetic markers.

Some markers will make it through years of development and evaluation to clinical trial and eventual clinical use. The majority, however, will never proceed beyond the development stage.

Doctors need to be aware of the clinical use of tumour markers, but at the same time realise their limitations and the implications of inappropriate use.

Introduction

Tumour markers have been defined as 'substances, usually proteins, that are produced by the body in response to cancer growth or by the cancer tissue itself'.¹ In fact, a tumour may not generate elevated markers, particularly in its early stages. Conversely, markers may increase due to benign conditions, as is the case with cancer antigen 125 in endometriosis, cirrhosis and diabetes.

Screening for cancer with tumour markers has only very limited applications. In patients with vague symptoms, or when the likelihood of cancer in the population is low, tumour markers should not be used in the initial diagnostic pathway. In this setting, tumour markers are rarely diagnostic due to low sensitivity and specificity.

Most established tumour markers have roles in prognosis and post-treatment monitoring. They should only be measured where knowledge of the tumour marker will benefit the patient, while bearing in mind that results can be falsely reassuring or unduly alarming.

Screening asymptomatic populations

A screening test that detects disease in an asymptomatic population has long been the goal of scientists and physicians worldwide. In reality, this goal has met with very limited success. For example, a recent European-based prostate specific antigen screening trial reported no mortality benefit,² while a US-based trial concluded that to prevent one death over a 10-year period, 1410 men would have to be screened and 48 treated.³

Bowel (colorectal) cancer screening is recommended by the Cancer Council of Australia. The National Bowel Cancer Screening Program sends an immunochemical-based faecal occult blood test to people based on their age. However there is insufficient evidence to support any other tumour-based screening program.⁴

Newly developed tumour marker tests are marketed to patients and health professionals. Physicians should realise that while their well-informed patients may actively seek a particular test, it is not likely to have been validated in prospective clinical trials and is probably not available at their local pathology laboratory.

Tumour markers in diagnosis, prognosis and monitoring

There are many different methods used to measure tumour markers, and samples analysed at different laboratories may yield different results. These discrepancies can be minimised by using the same laboratory.

The National Academy of Clinical Biochemistry (NACB) in the USA has published guidelines for the use of tumour markers in several malignancies (Table 1).^{5,6} Despite the numbers of proposed tumour markers under development, only the 'traditional' markers are used in diagnosis, prognosis and monitoring. For example in bladder cancer there are at least six urine tumour marker kits available that have been approved by the US Food and Drug Administration, yet there are no prospective clinical trial data establishing increased survival time, improved quality of life or decreased cost of treatment for any of the tests. However for testicular cancer, the measurement of beta-human chorionic gonadotrophin hormone and alpha-fetoprotein has been validated and is well established for diagnosis, prognosis and monitoring. Similarly cancer antigen 15-3 in breast cancer, cancer antigen 125 in ovarian cancer and carcinoembryonic antigen in colorectal cancer are recommended for prognosis and monitoring. Prostate specific antigen is used to monitor men treated for prostate cancer (Aust Prescr 2011;34:186-8).

The patient suspected of having multiple myeloma should have serum and urine electrophoresis screening tests along with routine biochemistry and haematology tests. If paraprotein is detected, skeletal X-ray, bone marrow and other specialised tests are needed. The serum free light chain test is a fairly new

David Faulkner

Scientist in Charge
Biochemistry and Specimen
Reception

Cliff Meldrum

Head
Diagnostic Molecular
Pathology

Peter MacCallum Cancer
Centre
Melbourne

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tumour marker which may become useful in multiple myeloma screening as an adjunct to serum and urine electrophoresis.⁷ In the rare case of non-secretory multiple myeloma, testing can detect small increases in free light chains. Currently however, there are no guidelines for its use in this role, but it is accepted for monitoring previously diagnosed patients.

Less frequently requested tumour markers and their roles

Many other tumour markers exist and are used in specific clinical circumstances. However, it is doubtful if any of the following markers would be ordered outside of a specialist's office:

- beta-human chorionic gonadotrophin for diagnosing and monitoring gestational trophoblastic neoplasia
- thyroglobulin for monitoring follicular or papillary thyroid cancer
- calcitonin for monitoring medullary thyroid cancer

- cancer antigen 19-9 for monitoring pancreatic cancer
- chromogranin-A for monitoring carcinoid tumour and phaeochromocytoma
- beta-2 microglobulin for monitoring multiple myeloma
- neurone specific enolase for monitoring neuroendocrine secreting tumours
- 24-hour urinary and plasma catecholamines and metanephrine for detecting phaeochromocytoma
- 24-hour urinary 5-HIAA (5-hydroxyindoleacetic acid) for detecting carcinoid tumour
- parathyroid hormone for parathyroid adenoma.

Molecular tumour biomarkers

A number of molecular genetic markers have become available that predict a patient's response to targeted therapy. The most commonly used of these are mutations in the KRAS gene (Kirsten rat sarcoma-2 virus oncogene) which are indicative of lack of

Table 1 Recommendations for tumour marker testing in common malignancies^{5,6}

Malignancy*	Sample type	Tumour marker		
		Screening	Assisting diagnosis	Informing prognosis, monitoring and surveillance
Liver	Serum	Alpha-fetoprotein (in high risk groups only, e.g. patients with chronic viral hepatitis)	Alpha-fetoprotein	Alpha-fetoprotein
Bladder	Serum	None	None	None
Cervical	Serum	None	None	None
Gastric	Serum	None	None	None although CEA and CA19-9 may be useful but clinical trials lacking
Testicular	Serum	Alpha-fetoprotein, B-HCG, LDH**	Alpha-fetoprotein, B-HCG, LDH	Alpha-fetoprotein, B-HCG, LDH
Prostate	Serum	None	PSA	PSA
Colorectal	Faeces	FOBT	None	CEA
Breast	Serum	None	None	CA15-3 but the clinical value is unclear
Ovarian	Serum	None***	CA125 for differential diagnosis of suspicious pelvic masses	CA125
B cell proliferative e.g. multiple myeloma	Serum and urine	Serum and urine paraprotein	Serum and urine paraprotein	Serum and urine paraprotein, sFLC

* a tumour may not raise levels, at least not in the early stages, and levels may also be raised in benign disease

** elevations in LDH can also be due to confounding factors including haemolysis and liver, muscle or cardiac disease

*** CA125 together with transvaginal ultrasonography is recommended for early detection in women with hereditary syndromes

B-HCG beta-human chorionic gonadotrophin hormone
 CA cancer antigen
 LDH lactate dehydrogenase
 PSA prostate specific antigen
 FOBT faecal occult blood test
 CEA carcinoembryonic antigen
 sFLC serum free light chain

response to therapy with anti-epidermal growth factor receptor (EGFR) antibodies. Similarly, mutations in the EGFR gene predict sensitivity or resistance to EGFR tyrosine kinase inhibitors, and mutations in the BRAF gene (proto-oncogene B-Raf) predict response to BRAF inhibitors.

Lung cancer

A number of international consensus groups have recommended testing for EGFR mutations in non-small cell lung cancer as a prerequisite to treatment with EGFR tyrosine kinase inhibitors, such as gefitinib or erlotinib. More than 80% of these EGFR mutations are either a single nucleotide substitution in exon 21 (p.Leu858Arg:L858R) or small deletions in exon 19.⁸ These mutations are termed classical activating mutations because they both activate the receptor tyrosine kinase and respond to the EGFR inhibitors gefitinib and erlotinib.

Not all EGFR gene mutations predict sensitivity to treatment. Primary and secondary resistance has been observed in non-small cell lung carcinoma, and a single mutation in exon 20 of the EGFR gene (p.Thr790Met:T790M) accounts for approximately 50% of acquired resistance to anti-EGFR therapy.⁹ Amplification of the MET oncogene is another common mechanism of acquired resistance and is associated with a poor prognosis.¹⁰

Importantly, high response rates to gefitinib and erlotinib can be achieved in appropriate populations of non-small cell lung cancer based on stratification by EGFR gene mutation status compared to the treatment of unselected populations with these inhibitors.

Colorectal cancer

Anti-EGFR monoclonal antibodies are increasingly being used in both first- and second-line treatment of colorectal cancer.¹¹ However, mutations in genes downstream of EGFR in the mitogen-activated protein kinase (MAPK) pathway can predict non-response to these therapies. Anti-EGFR therapy with cetuximab or panitumumab is generally not indicated if the tumour carries a mutation in exon 2 of the KRAS gene. These mutations commonly occur at codons 12 and 13. However, recent data suggest that not all

KRAS mutations in these codons are equal in their prediction of response to cetuximab.¹²

Melanoma

Mutations in the BRAF gene have been identified in over 40% of melanomas, and specific inhibitors to a mutated form of the BRAF protein (BRAF V600E) have produced a clinical response in phase III trials (Aust Prescr 2012;35:134-5).¹³ The most prevalent mutation is a single nucleotide substitution (c.1799T>A) that results in an amino acid substitution of glutamic acid for valine in the BRAF protein. Similar to KRAS, other BRAF mutations may result in varying responses to treatment.

While cutaneous melanomas commonly harbour mutations in the BRAF gene, melanomas arising from acral and mucosal surfaces tend to harbour KIT gene mutations (8% of tumours) that predict response to another tyrosine kinase inhibitor, imatinib.

A role for BRAF mutations in the pathogenesis, diagnosis and targeted therapy of diseases beyond melanoma is also possible. In a recent report, all of 40 patients with hairy cell leukaemia carried the BRAF p.Val600Glu(V600E) mutation.¹⁴

Conclusion

Despite considerable scientific research into developing and validating tumour markers for screening asymptomatic patients, this goal is largely not met. However, a number of tumour markers are recommended in diagnostic, prognostic and monitoring roles. Tests for tumour markers should only be done if the result will benefit the patient. It is important to be aware that benign conditions can cause false elevations. To ensure continuity with results, the same pathology laboratory should be used each time.

Molecular biomarkers are increasingly being used to predict sensitivity to a specific therapy and can help identify patients who are more likely to respond. <

Conflict of interest: none declared



SELF-TEST QUESTIONS

True or false?

7. Cancer antigen 125 is recommended for monitoring testicular cancer.

8. Mutations in the KRAS gene can help to predict a patient's response to cetuximab therapy for colorectal cancer.

Answers on page 135

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ABNORMAL
LABORATORY RESULTS

Tumour markers

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FURTHER READING

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New drugs

Abiraterone acetate

Approved indication: metastatic prostate cancer

Zytiga (Janssen-Cilag)

250 mg tablets

Australian Medicines Handbook section 14.3.1

Androgens have an important role in the progression of prostate cancer. While castration can reduce progression, the cancer eventually becomes castration resistant and requires chemotherapy with drugs such as docetaxel. As androgen activity is increased at this late stage of the disease, anti-androgen treatments have been researched.

Abiraterone is an inhibitor of cytochrome P450 (CYP) C17. This enzyme is involved in androgen synthesis, so inhibiting it decreases the concentrations of testosterone and other androgens. When given alone abiraterone can cause secondary hyperaldosteronism. To reduce this problem it should be given with prednisone or prednisolone.

This combination was used in a phase II trial to treat 58 men with metastatic prostate cancer which had failed to respond to docetaxel. The response to therapy was assessed by changes in the men's concentrations of prostate specific antigen (PSA). This declined by at least half in 36% of the men. The median time to PSA progression was 169 days.¹

The same daily dose of abiraterone (1 g orally) was then used in a placebo-controlled phase III trial in 1195 men who had been previously treated with docetaxel. These patients also took prednisone 5 mg twice daily. The median follow-up was 12.8 months. There was a decrease of 50% or more in the PSA concentration in

29% of the men who took abiraterone and in 6% of the placebo group. The time to PSA progression was 10.2 months with abiraterone and 6.6 months with placebo. In the abiraterone group, 42% of the patients died compared with 55% of the placebo group. Overall survival was 14.8 months with abiraterone and 10.9 months with placebo.²

In the phase III trial the most common adverse events were fatigue, nausea and back pain, but they occurred at a similar frequency in the placebo group. Hypokalaemia, oedema and fluid retention were more frequent with abiraterone. Less frequent adverse events which occurred more often with abiraterone than placebo included urinary tract infections, hypertension and cardiac disorders, such as arrhythmias and heart failure. Patients with clinically significant heart disease or uncontrolled hypertension were excluded from the trial.²

Abiraterone can increase liver enzymes, so liver function must be monitored frequently. Treatment may need to be reduced or stopped depending on liver function. If prednisolone is stopped abruptly there is a risk of adrenocortical insufficiency. Abiraterone is metabolised by CYP3A4, but interactions with strong inducers and inhibitors of the enzyme have not been evaluated. CYP1A2 and CYP2D6 are inhibited by abiraterone so there is a potential for interactions with drugs which are metabolised by these enzymes. These include codeine, oxycodone and tramadol. Only 5% of the dose is excreted in the urine and there is no recommendation for a reduced dose in renal disease. Abiraterone must not be taken with meals because food alters absorption.



Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.