

by Dr Charles Appleton & Dr Kerry DeVoss

Serum Tumour Markers

Salient Points

- Malignancy and cardiovascular disease are Australia's leading causes of death, with each accounting for over 25% of our nation's mortality.
- Non-selective screening of individuals without clinical evidence of malignancy offers low benefit for the cost and is fraught with hazard.

Tumour markers, those materials whose presence qualitatively or quantitatively signal the presence of malignancy, offer some hope in the fight against cancer. Some well defined clinical applications include:

- The detection of malignancy
- The establishment of prognosis
- As an aid in differentiation, and
- The monitoring of treatment and the detection of a recurrence

Detection of Malignancy

With few exceptions, the non-selective screening of individuals without any clinical evidence of malignancy offers little benefit/cost. More importantly it is fraught with the hazard of initiating expensive and anxiety provoking investigations in large numbers of patients to exclude the possibility of malignant disease.

In contrast, the selective screening of high risk groups is well established and is cost-effective. Such groups and their associated tumour markers include:

- Males with prostatomegaly – prostate specific antigen
- Hypercalcaemia – PTH and myeloma protein
- Hypertension – urinary catecholamines for phaeochromocytoma
- Haemochromatosis – alpha fetoprotein for hepatoma
- Pituitary lesion – prolactin and other pituitary hormones for pituitary adenoma

Differentiation, establishment of prognosis and detection of recurrence

Use of a tumour marker in the monitoring role depends on finding one which is directly associated with the tumour mass. Note that with therapy, particularly chemotherapy, the malignant cell line may change such that it may cease secreting one marker.

Conversely, a given tumour may commence secreting another marker during its natural history. Aspects of this are illustrated with the case study (over page).

Future Clinical Applications

Clinical Trials are currently investigating the use of tumour-directed antibodies in several areas:

- In radio-immune-scintigraphy, labelled antibodies directed against cell surface markers are injected to locate primary tumours or metastases within the body.
- Cancer 'vaccines' stimulate production of antibodies against markers such as CEA and so destroy tumours or recurrences at the site of development.
- Radio-or-chemo-immuno targeting where specific marker antibodies carrying cell destructive labels are injected to seek and destroy neoplastic cells.

Continued inside...

Cancer site	Incidence/100,000		Mortality/100,000	
	Males	Females	Males	Females
Colorectal	41	45	22	15
Lung	54	13	46	12
Breast		56		21
Melanoma	18	18	5	3
Prostate	38		17	
Bladder	18	6	5	2
Gastric	13	6	9	4
NH Lymphoma	10	7	6	4
Pancreas	8	4	7	4
Kidney	8	4	3	2
All Cancer	289	218	164	102

With the fall in coronary mortality, malignancy is now Australia's leading cause of death (MJA 1992, 156:587)

Inside: Blood group and antibody screening during pregnancy

Guidelines for blood grouping and antibody screening during pregnancy

ABO and Rh(D) grouping and antibody screening should be performed on all pregnant women to detect antibodies that may cause Haemolytic Disease of the Newborn (HDN).

To ensure optimal management of alloimmunised pregnant women there should be close serological follow-up. This assists clinicians identify patients that will require further assessment of the fetus. Communications between laboratories and clinicians enables appropriate diagnosis and management.

Routine antenatal testing is performed:

- To determine the blood group – this is particularly to identify Rh(D) negative women that may require the administration of prophylactic Rh (D) immunoglobulin
- To determine the presence of red cell antibodies in particular those that have the potential to cause HDN
- To monitor the level of clinically significant antibodies

These tests should be requested as Group and Antibodies and clinical notes should specify the weeks gestation.

Antenatal testing protocols:

During first trimester, all pregnant women, should be tested for blood group and red cell antibodies.

When no clinically significant antibodies are detected in the first trimester testing:

All pregnant women should have a repeat blood group and antibody screen performed between 26-32 weeks.

Rh(D) negative women should also have repeat testing again at 34-38 weeks.

When clinically significant antibodies are detected in the first trimester testing:

The antibodies should be identified and the potential to cause HDN assessed. Antibodies that cause HDN are reactive at 37°C and are IgG.

Antibodies are often arranged into the following groups according to the probability of causing HDN.

• **Anti-D, -c, -E, -e, -C, -K, -k**

These antibodies are commonly associated with some degree of HDN. Anti-D, anti-c and anti-K are most often associated with moderate to severe HDN.

• **Anti-Cw, -Fya, -Fyb, -Jka, -Jkb, -Lua, -Lub, -S, -s, -M**

These antibodies are not usually associated with HDN but occasionally can cause HDN if the IgG component is of a high titre.



Next month: Guideline recommendations for the use of Rh(D) Immunoglobulin (anti-D) in pregnant patients.

- **Anti-P1, -N, -H, -Lea, -Leb, -Lea+b, -Sda, -Bga, -Bgb and other HLA antibodies**

These antibodies do not cause HDN.

If the antibody has potential to cause HDN, titre and/or quantitation is determined by a standardised technique.

Antibody investigation and titre/quantitation should be repeated every four weeks until 36 weeks gestation, then every two weeks until delivery.

A clinically significant rise in titre/quantitation may aid the clinician in determining fetal monitoring such as ultrasound, amniocentesis or cordocentesis.

When clinically significant antibodies are present in the first trimester:

All women, including those who have had a previous infant with HDN, should be referred to specialist care as soon as possible and preferably before 20 weeks gestation irrespective of the antibody titre.

Reference:

ANZSBT "Guidelines For Blood Grouping And Antibody Screening in the Antenatal and Perinatal Setting" 2nd edition, 2004

Safety first for QML Pen Holders



QML Pathology's Pen Holder range has recently been updated as part of the new Workplace Health and Safety requirements throughout Queensland.

The QML Pen Holder now features a detachable or 'break away' cord for ease of removal in an emergency situation (see illustration).

Please order your new Pen Holder through your local Medical Liaison Officer, or alternately Brisbane Liaison on (07) 3840 4539.

Serum Tumour Markers

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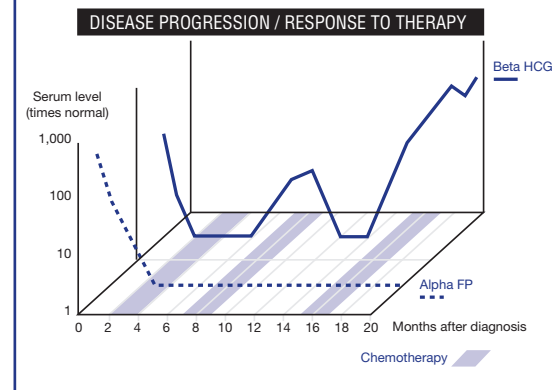
The view of HIC

HIC's view is that the payment of Medicare benefits for health screening and for "clinically relevant" services is described in Sections 13.3 and 1.1.4 of the Medicare Benefits Schedule Book. In addition certain restrictions are placed in the descriptions of some item numbers eg. Item 66650, 66655, 66656 and 66659.

CASE STUDY

A 17 year-old female presented with a pelvic mass. At surgery, a large poorly differentiated tumour arising within the pelvis was incompletely resected. Analysis of her pre-operative serum revealed high-levels of beta HCG and alpha fetoprotein, suggesting with the histological and clinical features, a primary germ neoplasm.

Chemotherapy proved effective in reducing the residual tumour bulk and in controlling the first recurrence. However the second recurrence was refractory to treatment and the patient died 20 months after diagnosis. The behaviour of the tumour markers over the course of her illness is illustrated below.



References

1. Giles, GG (1992) Cancer epidemiology in Australia: priorities or the 1990s and beyond, *The Medical Journal of Australia*, Vol. 156, May 4
2. Safi, F, Roscher, R, and Beger, HG (1990) The clinical relevance of the tumour marker CA 19-9 in the diagnosing and monitoring of pancreatic carcinoma, *Bull, Cancer*, 77:83-91
3. Beastall, GH, Cook B, Rustin, GJS and Jennings, J (1989) A review of the role of established tumour markers, *Ann Clin Biochem*, 26:379-387
4. Lange, Paul, H and Brawer, Michael, K (1989) Serum prostate-specific antigen: Its use in diagnosis and management of prostate cancer, *Supplement to Urology*, Volume XXXIII, number 6
5. Duffy, MJ, (1989) New cancer markers, *Ann Clin Biochem*, 26:379-387

THE MORE WIDELY USED SERUM MARKERS

MARKER	MAJOR TUMOUR SOURCE	LESSER TUMOUR SOURCE	FALSE POSITIVE
ACTH	pituitary basophil adenoma, oat cell carcinoma of lung	pulmonary carcinoma	
Alpha Fetoprotein	hepatoma, dysgerminoma (70%), teratoma, hepatoblastoma	gastrointestinal (10%) and bronchogenic ca. (10%)	non-neoplastic liver disease
Beta Human Chorionic Gonadotrophin (hCG)	choriocarcinoma (>80%) and dysgerminoma (40%)	seminoma (20%) and non-trophoblastic ca. (10%)	
Beta 2 Microglobulin	myeloma, plasmacytoma		renal or inflammatory disease
CA 125 (cervix, pancreas, stomach)	epithelial ovarian cancer (>80%) pancreatitis, peritonitis	endometrium, fallopian tube,	endometriosis, PID, CRF,
CA 15-3	metastatic breast ca. (70%)	localised breast ca. (10%), ovary	non-malignant liver disease
CA 19-9 (Fetoacinar Pancreatic Antigen)	pancreas (80%), gastric (50%), bile duct (65%), hepatoma (50%)	colorectal (25%)	cirrhosis, cholangitis and rarely pancreas & colorectal inflammation
Calcitonin	medullary thyroid carcinoma, carcinoma	liver, lung, renal, breast	
Carcinoembryonic Antigen CEA	colorectal, gastric, liver, pancreatic and breast ca. (all >60%)	lung, prostate, cervix, uterus, ovary	smoking, acute & chronic pancreatic, bowel & breast disease
Catecholamines, H1MMA (VMA)	phaeochromocytoma, neuroblastoma		non-specific illness, anti-hypertensive drugs, syncope
Human Chorionic Gonadotrophin	Refer Beta HCG		
Lactate Dehydrogenase (LD Isoenzymes	seminoma, lymphoma and epithelial carcinoma		benign disease of organs, haemolysis
Paraprotein, Bence Jones Protein	multiple myeloma (98%) and plasmacytoma	other lymphoid malignancies	autoimmune conditions
Placental Alkaline Phosphatase	seminoma (>80%), ovary, lung, uterus cancer		smoking
Prostatic Acid Phosphatase (ACP)	metastatic prostate (>70%)	intracapsular prostate (<30%)	prostatitis and prostatic massage
Prostate Specific Antigen (PSA)	prostatic adenocarcinoma intracapsular (65%), metast (90%)		benign prostatic hypertrophy (30%)
Serotonin, 5HT1AA	carcinoid tumour		diet, diarrhoea, coeliac disease
Thyroglobulin	differentiated thyroid ca.		
Vasoactive Intestinal Polypeptide (VIP)	bronchogenic lung, pancreatic islet, neuroblastoma, thyroid medullary, phaeochromocytoma		shock, cirrhosis, hepatic failure

GUIDE TO MARKERS BY SITE OF TUMOUR

Medullary Ca Thyroid:
CEA,
Calcitonin
Thyroid:
CEA,
Thyroglobulin

Breast:
CEA, CA 15-3

Liver:
 α FP
Biliary Ducts:
CA 19-9
Pancreas:
CEA, CA 19-9

Ovary (epithelial):
 α FP, CA 19-9,
CA 125, hCG
Cervix:
CEA
Trophoblast:
hCG

Oesophagus:
CEA
Stomach:
CEA, CA 19-9
Colon:
CEA, CA 19-9

Germ cell:
 α FP, hCG

Prostate:
PSA

TUMOUR	MARKER								
	aFP	CEA	CA 19-9	CA15-3	CA 125	hCG	Calcitonin	Thyroglobulin	PSA
Oesophagus		•							
Stomach		●	•						
Pancreas		•	●						
Colon		●	●						
Liver	●								
Biliary Ducts			•						
Breast		●		●					
Ovary	●		●		●	●			
Cervix		●							
Trophoblast						●			
Germ cell	●					●			
Prostate									●
Thyroid		•						●	
Medullary Ca Thyroid		•					●		

Upcoming Events...

Capricornia Division of General Practice Conference 2004

Date: 24-26 April
Venue: Rydges Capricorn Resort
Contact: Suzanne Robertson on (07) 4927 3182

AMAQ Foundation Charity Fashion Parade

Date: 12th May
Venue: The Wintergarden Centre, Brisbane
Time: 6:00pm for 6:30pm
Details: Tickets \$50 including refreshments
RSVP: Neil Mackintosh, AMAQ, phone (07) 3872 2222, email n.mackintosh@amaq.com.au by 30 April

Women's Health Issues CPD – Brisbane South

Date: 20th April
Venue: Qld Sport & Athletics Centre, ANZ Stadium, Javelin Room, 4th Floor, Western Grandstand, Kessels Road, Nathan
Time: 6:30 for 7:00pm start
Speakers: Dr Claire Boothroyd MBBS (Hons) M.Med Sci. FRACP FRANZCOG CREI
Dr James Nicklin MBBS FRACOG CGO
RSVP: QML Marketing (07) 3840 4506

Women's Health Issues CPD – Brisbane North

Date: 27th April
Venue: Evan and Mary Thomson Auditorium, The Wesley Hospital, Auchenthaler
Time: 6:30 for 7:00pm start
Speakers: Dr Claire Boothroyd MBBS (Hons) M.Med Sci. FRACP FRANZCOG CREI
Dr James Nicklin MBBS FRACOG CGO
RSVP: QML Marketing (07) 3840 4506

St Andrew's CPD Evening

Date: 20th April
Venue: Royal on the Park, Brisbane
Time: 6:30pm for 7:00pm
Topics: Including: Upper Limb Conditions, Lower GIT Malignancies
Contact: (07) 3834 4210

RACGP Educational Weekend

Date: 1st - 3rd May
Venue: ANA, Gold Coast
Topics: Including: Respiratory Update, Urology, Physiotherapy, Management of Persistent Pain, Gastroenterology
RSVP: RACGP (07) 3878 9242 to register

St Andrew's CPD Evening

Date: 4th May
Venue: Royal on the Park, Brisbane
Time: 6:30pm for 7:00pm
Topics: Including: Skin Cancer Screening, Head and Neck Cancers
Contact: (07) 3834 4210



Doctors' Notice Board

Dr Brian Fredericks, Endocrinologist, would like to announce the opening of his rooms at the John Flynn Medical Centre, Level 2, Inland Drive, Tugun. Dr Fredericks' interests include diabetes, hypertension, osteoporosis, thyroidology, adrenocortical disorders & pituitary medicine. He is available for consultation on (07) 5571 0380.

Dr Christopher Schull, Thoracic and Sleep Physician, wishes to advise that his practice now deals exclusively with Sleep Disorders. For consultation please contact the Sleep Clinic, Ground Floor, Greenslopes Private Hospital, on telephone (07) 3397 1488 or facsimile (07) 3397 1499. Dr Schull also consults at Suite 8, 2nd Floor, Sunnybank Private Hospital on telephone (07) 3216 9511 or facsimile (07) 3344 5839.

COLLECTION CENTRE NEWS

For the convenience of our doctors and patients, we have listed the latest additions and changes to the QML network of clinics:

NEW LOCATION

Burpengary (07) 3888 6244

Shop 2, 184 Station Road

Mon-Fri 7.30am – 6.00pm
Sat 8.00am – 12.00noon
Pub. Hols. 8.00am – 12.00noon

Please contact your local branch or Brisbane Liaison for further information on (07) 3840 4539.

This newsletter has been prepared and published by QML Pathology for the information of referring doctors. Although every effort has been made to ensure that the newsletter is free from error or omission, readers are advised that the newsletter is not a substitute for detailed professional advice.

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