Cancer Biochemistry and Tumour Markers

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In this lecture

Cancer basics

Definition of Tumour Marker (TM)

What is the perfect TM?

History of TMs

Examples of TMs currently in use

Appropriate use of TMs

Analytical aspects of TM analysis

Cancer (tumour) - Introduction

- Malignant neoplasm – uncontrolled growth and invasion of healthy tissues (metastasis)
- Not all cancers all malignant
- Over 200 known cancers that affect humans
- Environmental and genetic factors

Cancer – Signs and symptoms

- Appear when the tumour starts growing and invading healthy tissues
- Local effects (specific)
  - Lung – blockage of bronchus – cough or pneumonia
  - Esophageal – narrowing of esophagus – painful / difficult to swallow
  - Colorectal – narrowing or blockage in the bowel – change in bowel habits
  - Bleeding (eg cough up blood, rectal bleeding, blood in the urine, vaginal bleeding)

Cancer – Signs and symptoms

- Systemic effects (general)
  - Unexplained weight loss
  - Unexplained fever
  - Fatigue
  - Back pain

What is a Tumour Marker?

'A Tumour Marker (TM) is any substance which can be related to the presence or the progress of a tumour'

A TM can be 'tumour specific' – only produced by the tumour - not normal tissue or

A TM can be produced in relatively larger amounts by malignant cells than non-malignant cells – usual scenario.

?Perfect Tumour Marker

- Total negativity in healthy subjects (ie 100% specific)
- Total positivity for a single tumour type (ie 100% sensitive)
- There is a close correlation between the blood TM concentration and the tumour size.
- THE PERFECT TM DOES NOT EXIST

Tumour Marker History

- **Urine Bence Jones Protein, 1847:** Patients with multiple myeloma. Monoclonal light chain.
- **1928 – 1968:** Study of hormones, enzymes, isoenzymes and proteins
- **1975**: monoclonal antibody techniques and use in oncofoetal antigens
- **1990s:** Molecular techniques, oncogenes, suppressor & DNA repair genes.

Types of Tumour Markers

Structural molecules – carbohydrate antigens: CEA, CA-19-9, CA15-3, CA 125

Secretion products, enzymes, hormones: AFP, hCG, PSA, catecholamines

Cell turnover markers

Metabolic Effects of Tumours

Hypercalcaemia - often seen, PTHrelated peptide.

Haematological - erthyrocytosis, anaemia.

Carbohydrate metabolism, hypoglycaemia, lactic acidosis.

Protein Metabolism - increased catabolism/decreased synthesis.

Hormone Production - can be appropriate to cell line or ectopic.

Classical Tumour Marker Use

Myeloma: Paraprotein band detection.

Phaeochromocytoma: Urine and serum catecholamines.

Carcinoid: 5HIAA, Chromogranin A

Colorectal Cancer & CEA

Carcinoembryonic antigen: Normally present in small concentrations. Elevated in cancer but also some benign conditions.

Primary use is in monitoring colorectal cancer to check for recurrence.

Other cancers that give CEA elevations: melanoma, lymphoma, breast, lung, pancreas, stomach, bladder, GI Tract.

Non cancer Conditions that give elevations: smoking, inflammatory bowel, liver disease.

AFP

- Alpha-foetal protein normally produced by developing foetus. 70 kDa glycoprotein
- Increase in hepatocellular carcinoma, germ cell cancer - ovary or testis, hepatoblastoma.
- Often normal in stage I testicular cancer.
- Elevated in non-cancer conditions include liver disease, pregnancy and first year of life.

Clinical Use

- With HCG to monitor non-seminomatous germ cell tumours.
- Diagnostic aid for hepatocellular carcinoma and hepatoblastoma
- Hepatocellular carcinoma screening in high risk population - China.

HCG

- Dimer composed of alpha and beta chains. Alpha chain almost identical to that of TSH, FSH, LH. Beta chain distinct but 75% homology with LH.
- Found in several forms in blood - intact, free and fragments.

Uses of HCG

- Monitor gestational trophoblastic disease.
- With AFP to monitor cancer of testis and ovary.
- Raised in pregnancy and marijuana use.

Ovarian Cancer & CA 125

Ovarian cancer 5th most common cancer in women with overall 5-year survival rate < 35%

Most women present with advanced disease having had symptoms for months before presentation

Additional delays often occur before specialist referral

Ovarian Cancer & CA 125

New NICE Guidelines (April 2011)

GPs should measure CA125 in women with **FREQUENT** symptoms that suggest ovarian cancer

- Persistent abdominal bloating or distention
- Feeling full and/or loss of appetite
- Pelvic or abdominal pain
- Increased urinary urgency and/or frequency
- Symptoms suggestive of IBS in women >50yrs

If CA125 >35kU/L, GP should arrange U/S of abdomen & pelvis

If U/S suggestive of cancer refer urgently to specialist team

Ovarian Cancer & CA 125

CA125 elevations in other cancers such as uterus, cervix, pancreas, liver, intestine.

Increased in non-cancer disease such as liver disease, pancreatitis, and any condition that inflames the pleura.

CA125 can also be increased in menstruation and pregnancy.

CA125 results within reference range DO NOT exclude ovarian or other malignancies

Other Routine Tumour Markers

CA 199: In pancreatic cancer higher levels associated with advanced disease. Originally found in colorectal cancer and also increased in hepatobiliary disease.

CA 153: Used in following breast cancer treatment. Rarely raised in early disease. Can also see elevated CA 153 in benign breast or ovarian disease and range of other diseases.

LDH: Ubiquitous enzyme. Can be useful in monitoring treatment, for example non-Hodgkin's lymphoma and some types of leukaemia.

Molecular Biology & Tumour Markers

- Role in specific therapeutic interventions. For example her-2/neu oncogene overexpression in breast cancer. Herceptin is a monoclonal antibody targeted to the gene product.
- BRCA 1 & 2 in family screening for breast cancer.

Tumour Markers Basics

- **Normal levels do not exclude underlying neoplasm.**
- **High levels are not necessarily diagnostic**
- **Different methods not always comparable. Follow-up by different lab can mislead.**
- **"Shotgun" requesting approach: You will end up trying to explain lots of raised results!**

Sandwell and West Birmingham Hospitals NHS

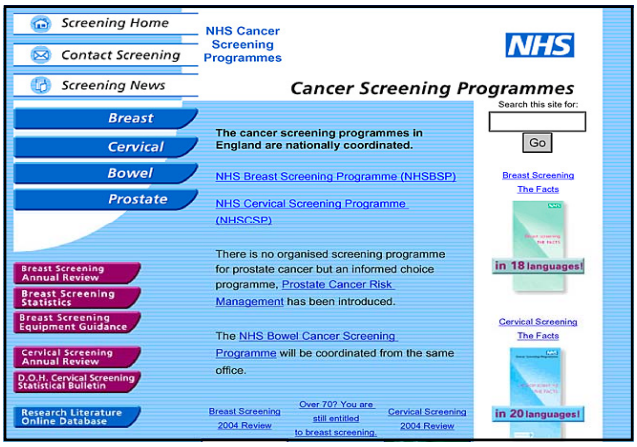
Audit of Tumour Marker Use in a Large Hospital

Hull Royal Infirmary: McGinley PJ, Kilpatrick ES.
Annals Clin Biochem 2003; 40: 643-7

1997/8 - 2001/02 saw 125% increase in tumour marker requesting.

Looked at 12 months requesting = 27,000 tests
- CA125 (ovarian)– 612/3616 on male subjects.
- CA 15/3 (breast follow-up) 98/374 on men
PSA (Ca prostate) 12/11,585 were on women.

Conclusion: Inappropriate screening, use before a diagnosis and poor understanding of use of tumour markers.



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NHS Cancer Screening

- **www.cancerscreening.nhs.uk**

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WHO 10 Principles of Screening

- Condition is an important health problem
- Natural history well understood
- Recognisable at an early stage
- Treatment is better at an early stage
- Suitable test exists
- Acceptable test exists
- Adequate facilities exist to cope with abnormalities detected
- Screening is done at repeated intervals when the onset is insidious
- The chance of harm is less than the chance of benefit
- The cost is balanced against benefit

Cancer Screening Guidance

Current Guidance to Screen
Breast cancer
Cervical cancer
Bladder Cancer
Colorectal and Bowel
Ovarian cancer

Explicit Policy Not to Screen
Prostate cancer **EL (97) 12**
Neuroblastoma

Colorectal Cancer Screening

New National Screening Programme

- **Phased in from April 2006.**
- **Patient's ages between; 60 – 69 years.**
- **Faecal occult blood sample posted to reference laboratory. Result in 48 hours.**
- **Follow-up colonoscopy.**

Prostate Cancer/PSA

- Adenocarcinoma of prostate is commonest cancer in men. 50% of 80 year olds.
- Prostate Specific Antigen is a serine protease found in seminal fluid. Produced by normal and abnormal prostate cells.
- **Not Diagnostic**: PSA levels increase in benign prostatic hypertrophy as well as carcinoma.
- **Increased in:** prostate ischaemia, urinary retention, acute renal failure, rectal examination.
- < 4 ug/L in health, but 30% or patients with organ confined cancer also have such levels. Main use is in monitoring treatment/ recurrence.
- **Test Improvements:** Age related reference ranges, doubling time, and free/bound PSA.

Prostate Cancer Screening

EL (97) 12 June 1997
Population Screening for Prostate cancer

•Population screening including the use of PSA should not be provided by the NHS or offered to the public until there is new evidence of an effective screening technology.
•The NSC has considered the evidence for introducing screening for prostate cancer. There is no evidence of benefit resulting from population screening.
• …. Do not introduce or plan the purchase of population screening until NSC recommends ..

NHS Advice ….

- To date, prostate cancer screening fulfils only the first condition. …. The UK National Screening Committee has recommended that a prostate cancer screening programme should not be introduced in England at this time.

http://www.cancerscreening.nhs.uk/prostate/index.html

Use of Tumour Markers

Screening: Limited role due to lack of sensitivity and specificity of current markers.

Diagnosis: Most primary tumours diagnosed by clinical, radiological and tissue examination.

Prognosis: Some markers can help to predict outcome.

Detecting Relapse, Response to Therapy: Here of most use.

Use of Tumour Markers

- Normal levels do not exclude malignancy
- High levels do not rule out many other diseases
- 'Shotgun' requesting not appropriate
- Only use in conjunction with imaging and histological techniques
- TMs best used to **MONITOR** a patient's progress rather than diagnose it.

Measurement of TMs

Assays routinely used
- Immunoassay - (most routine TMs)
- HPLC (metanephrines, 5HIAA)
- Colourimetric (FOB)

Specimen types
- Serum
- 24hr urine
- Faeces