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Targeted therapy in cancer in the 21st century

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Therapies targeting signalling pathways have become the hallmark of advances in cancer therapy in the 21st century. Most therapies target circulating ligands, extracellular receptor domains of transmembrane receptor tyrosine kinases (RTKs), intracellular ATP-binding domains of RTKs or second-messenger pathways.

Ligand inhibitors

Monoclonal antibodies (MoAbs) directed against circulating ligands responsible for cell growth and metastasis inhibit cancer progression. Bevacizumab, a humanised antivascular endothelial growth factor (antiVEGF) MoAb, is active when combined with chemotherapy in treating colorectal, breast and lung cancer. The addition of bevacizumab to chemotherapy increases the survival of patients with metastatic colorectal cancer by 6 - 12 months.[1]

Denosumab, a MoAb against receptor activating NFκ-B (RANK) ligand, inhibits osteoclastic activity in metastatic bone disease. Randomised studies comparing denosumab with bisphosphonates in patients with bone metastases due to various malignancies are ongoing.

Monoclonal antibodies against extracellular ligand-binding domain of RTKs

Most epithelial cancers overexpress epithelial growth factor receptor-1 (EGFR-1). Cetuximab, a chimeric MoAb against EGFR-1, is active in metastatic colorectal cancer failing irinotecan chemotherapy, when added to irinotecan.[2] Matuzumab, a humanised antiEGFR-1 MoAb, and panitumumab, a fully human anti-EGFR-1 MoAb, are under investigation in metastatic colorectal cancer.[3]

About 20% of breast cancer patients overexpress EGFR-2/*her-2* which implies a poor prognosis. The advent of trastuzumab, an anti-*her-2* MoAb, has revolutionised the treatment of these women. Recent studies in early breast cancer have shown an approximately 50% reduction in relapse with trastuzumab following standard adjuvant chemotherapy.[4]

All B-cell lymphomas express CD20, making it a useful therapeutic target. Rituximab, a chimeric antiCD20 MoAb, has become standard of care in most B-cell lymphomas including chronic lymphocytic leukaemia, follicular, mantle cell and diffuse large B-cell lymphomas.[5-7]

Epratuzumab, a humanised anti-CD22 MoAb, is also under investigation in B-cell lymphomas,[8] while alemtuzumab, a humanised antiCD52 MoAb, is approved for CLL patients failing standard fludarabine chemotherapy.

MoAbs can be made more effective by attaching a radioisotope. Ibritumomab tiuxetan, an Y^{90}-labelled murine antiCD20 MoAb, and tostitumomab, an I^{131} - labelled MoAb, have greater activity than rituximab in CD20+ lymphomas.[9]

Gemtuzumab, a humanised antiCD33 MoAb, is approved by the FDA in patients over 60 years in whom standard chemotherapy for acute myeloblastic leukaemia (AML) has failed.[10]

Small molecules blocking intracellular ATP-binding domain of RTKs

Once ligands bind to their extracellular receptor, signals are transmitted to the intracellular domain. Tyrosine aminoacids are phosphorylated by converting ATP to ADP. Molecules designed to block ATP from attaching to its binding domain will inhibit tyrosine phosphorylation and block signal transduction.

Gefitinib and erlotinib, tyrosine kinase inhibitors (TKIs) blocking the ATP-binding domain of EGFR-1, have been extensively investigated in non-small-cell lung cancer (NSCLC) with limited success.[11-13]

CML was the first human cancer linked due to molecular abnormality. The p210 *bcr-abl* fusion protein, due to translocation between chromosomes 9 and 22, known as the Philadelphia chromosome, results in chronic myeloid leukaemia (CML).[14] Imatinib, a TKI - blocking ATP-binding domain of *bcr-abl*, has revolutionised treatment of CML. The IRIS study showed a 92% major cytogenetic response, and 87% complete cytogenetic response to imatinib in newly diagnosed CML patients at 5 years.[15]

Up to 4% of patients on imatinib progress, usually due to mutations of imatinib binding site. This usually occurs 1 - 2 years after starting therapy. Nilotinib, an imatinib analog, which requires less stringent binding, and dasatinib, a combined *src-abl* TKI are active in imatinib resistance.

Imatinib also blocks the ATP-binding site of *c-kit* RTK. The majority of patients with GIST have *c-kit* mutations and respond to imatinib therapy.

A number of other small molecules also show promise in solid tumour malignancies including:

Sunitinib, which inhibits *c-kit*, PDGF-R and VEGFR-2 kinases, has recently been approved by the FDA for newly diagnosed patients with renal cell carcinoma (RCC) and patients with gastrointestinal stromal tumour (GIST) failing imatinib.[16]

Sorafenib, which inhibits Raf1 and VEGFR-2 kinase, shows activity in hepatoma, as well as in RCC patients in whom first-line immunotherapy has failed.[17]

Lapatinib, a combined EGFR-1/*her-1* and EGFR-2/*her-2* inhibitor, is active in breast cancer patients failing trastuzumab, and is now the subject of studies in advanced as well as early breast cancer patients.[18]

Vandetanib, which inhibits EGFR-1 and VEGFR-2, is being studied in lung cancer, while vatalanib, a VEGFR-1 and VEGFR-2 inhibitor is being studied in colorectal cancer.

Small molecules blocking second-messenger signalling pathways

These include farnesyl transferase inhibitors, tipifarnib and lonafarnib, blocking *ras* pathways, which are under investigation in pancreatic, breast and haematological malignancies and mTOR kinase inhibitors, temsirolimus and everolimus, which block

the Akt/PI-3 kinase pathway. Temsirolimus has promising activity in high-risk RCC.

Conclusions

Novel therapies targeting signalling pathways are important advances in cancer therapy in the 21st century. These therapies, which target circulating ligands, extracellular or intracellular domains of RTKs, or second-messenger pathways, are becoming widely used in the treatment of solid tumour and haematological malignancies, both as single agents or combined with standard chemotherapy regimens.

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Complementary and alternative medicines in oncology

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The use of complementary and alternative medicines (CAM) is widespread. In South Africa it has been found that 30-80% of patients attending oncology clinics use CAM. This cannot be ignored, and the topic should be discussed with patients in an appropriate manner. Whereas the use of many CAM may be seen as medically harmless, this view does not hold for all CAM, and harm can be caused to patients. In recent years the use of CAM has become an accepted fact internationally, to the extent that the National Institute of Health of the United States has a National Center for Complementary and Alternative Medicine (NCCAM), and many medical schools have CAM departments. The mission of the NCCAM is to 'support rigorous research on CAM, to train researchers in CAM, and to disseminate information to the public and professionals on which CAM modalities work, which do not, and why'.

Definitions

The term CAM is generally regarded as encompassing a group of healing philosophies, diagnostic approaches, and interventions that do not belong to the politically dominant (conventional) health system of a particular society. Some authors separate CAM into 'alternative' therapies used instead of conventional therapy, and 'complementary' therapies that are combined with conventional therapy. It has been said that 'alternative medicine' has become the politically correct term for questionable practices formerly labelled quack and fraudulent. To avoid confusion, CAM should be classified as genuine, experimental, or questionable. *Genuine* alternatives have met science-based criteria for safety and effectiveness. *Experimental* alternatives are unproven but have a plausible rationale and are undergoing responsible investigation. *Questionable* alternatives are groundless and lack a scientifically plausible rationale. Ideally the term CAM should not exist. There should only be scientifically proven, evidence-based medicine or unproven medicine, for which scientific evidence is lacking.

The use of complementary and alternative medicines (CAM) is widespread.

A more recent trend is for some medical practitioners to offer 'integrative' medicine, a combination of conventional and alternative medicine. It is claimed that integrative medicine provides the best of both approaches. This of course is nonsense, and such an approach would be laughed at if applied to other scientific disciplines. Biologists would 'integrate' creationism with Darwinian evolution; chemists would 'integrate' alchemy into modern scientific chemistry; geologists would 'integrate' the belief that the world is only 6 000 years old (and flat) with modern dating of rocks; physicists would 'integrate' perpetual motion machines with the conservation of energy and the laws of thermodynamics; and astronomers would 'integrate' astrology and astronomy. Of course, this is ridiculous. It's not a good idea to integrate unproven theory or beliefs with valid scientific knowledge.

Dangers of unproven medicine

Unproven therapies can be harmful in a number of ways:

- **Economic cost:** millions of rands are spent annually in South Africa on therapies of no proven value, often by people who cannot afford to do so, but are driven by a desperate need.
- **Direct harm:** a number of so-called 'natural' remedies are in fact toxic, and may result in physical harm; a number of studies have associated the use of CAM

with worse quality of life and shorter survival; CAM may result in multiple drug interactions, leading to decreased efficacy or increased toxicity.

- **Indirect harm:** the use of CAM may cause failure or delay in obtaining effective therapy, turning the curable into the incurable and resulting in premature death.
- **Psychological harm:** By offering false hope, quackery steals the most precious thing terminal patients have – time. The belief that patients have nothing to lose by using CAM is very wrong. Most people faced with a terminal disease can make a reasonable psychological adjustment to the fact, and use their remaining time wisely. Quacks discourage people from making this difficult adjustment by reinforcing their denial. Such people usually die unprepared because preparation for death is an admission of failure.

The South African context

When diagnosed with cancer, patients are faced with an onslaught of unproven CAM products forced upon them by well-meaning people and unscrupulous quacks. Products ranging from vitamins to fight the cancer (no proven benefit, and cancer cells may also benefit from vitamins), antioxidants (shown to be ineffective or detrimental), various immune boosters (no proven value), and a variety of off-the-wall therapies such as insulin potentiation therapy, ozone therapy, oxygen infusion therapy and electromagnetic treatment, are on offer. Practitioners should be familiar with the current CAM fashions and should be able to discuss these in some detail with patients and family. The use of unproven therapies should be discouraged and the use of complementary drug therapies together with proven therapy avoided, due to potential drug interactions. Patients should be provided with access to objective information about CAM (see Further Reading).

Further Reading

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National Council Against Health Fraud: http://www.ncahf.org

Quackwatch: http://www.quackwatch.com

Advances in radiotherapy treatment

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It has always been possible to kill all cancers with radiotherapy – the critical point is to avoid killing the patient at the same time.

There are two ways of reducing the difference between cancer damage and normal tissue damage – the first is anatomical, with better target definition and radiation delivery, and the second is using the biological differences with fractionating therapy. I will start with the latter.

Radiobiological advantages to fractionation

Radiation damage manifests in two ways:

- acute damage to fast-dividing tissues such as mucosa – this is unpleasant but not usually life threatening
- late damage – this is due to constriction of small blood vessels that results in organ failure 1 - 10 years after radiation and may cause death, e.g. heart failure.

Dividing the radiation dose into smaller fragments specifically reduces the late effects – the reason for the standard fractionation of 60+Gy in 30+ fractions over 6 weeks. Several approaches have been used to try to exploit these advantages, from twice-daily small fractions to accelerated courses of treatment, but very few of these have shown major clinical benefits and most are impractical in busy radiotherapy departments.

Changing radiation sensitivity

- Increasing the sensitivity of the tumour to radiation is obviously attractive and there are several chemotherapy agents that have such an effect at relatively low doses, e.g. cisplatin and 5FU. Concurrent chemoradiation is also becoming important as there seems to be a synergistic effect between the chemo and the radiotherapy but care must be taken in these settings as the toxicity of the treatment also increases.
- Reducing normal tissue sensitivity to radiation – the only agent currently licensed for this use is amifostine and the results, unfortunately, have been disappointing.

Better anatomical definition of the target and organs at risk (OAR)

Over the last few years there have been enormous advances in imaging techniques and clarity. This enables not only better definition of the target but also identification of OARs. Combining different imaging modalities may also offer advantages – showing extension of tumour in one modality that may not easily be seen in another. This is particularly useful with biological based imaging, e.g. positron emission tomography (PET) or magnetic resonance spectroscopy that may be very sensitive but not have a clear anatomical specificity. If these images can be fused (using computer software) to an image modality that has high anatomical specificity but relatively poor biological specificity we are able to adapt our treatment portals to cover the area of disease far more accurately without unduly increasing complications by using classic 'extended fields' that encompassed all 'areas at risk'.

All current radiotherapy planning systems are based on 3-dimensional tomographic imaging (usually thin-slice CT scans) and most are able to also incorporate and fuse other image series (e.g. MRI, or even preoperative images if these are relevant).

Better systems of radiation delivery

- The initial advances in 'non-coplanar' or 'highly conformal' radiotherapy involved the ability to closely conform the radiation field to the shape of the tumour shielding normal tissue. Initially this was performed with individually made lead blocks but later multileaf collimators were developed. By altering the position of the gantry (radiation source) and the couch it also became possible to treat the

tumour from a variety of different angles, again improving the ability to reduce the dose to normal tissue. After these advances there were numerous studies, initially in prostate cancer, that showed that the dose to the prostate could be escalated significantly, improving local control without increasing toxicity. These clinical results have been confirmed in several other tumours, particularly non-small-cell lung cancer and head and neck cancer.

- Quality control and electronic portal imaging (EPID) – improvements in flat-screen technology have allowed the introduction of electronic check films of the patient on the treatment bed, in the treatment position, and allows these to be repeated as often as needed.
- Radiosurgery – very tightly focused radiation given, often in a single fraction, to well-defined intracranial targets, e.g. acoustic neuromas, arteriovenous malformations (AVMs) with accuracy of 0.1 mm using stereotactic techniques.
- Intensity modulated radiation therapy (IMRT). This technique has become extremely popular over the last few years and involves changing not only the shape of the beam but also the intensity of the dose given across the beam. It is highly dependent on complicated computer planning (inverse treatment planning) – where the planner can determine minimum or maximum clinically acceptable doses to specified organs or points. The clinical advantage (or disadvantage) of this approach is yet to be proven and the risks of induction of second malignancy may be higher.
- Image-guided radiotherapy (IGRT) and adaptive radiotherapy (ART) are methods to actually visualise the position of the target within the patient and to adapt the treatment plan using this information, possibly even on a daily basis. This may be achieved by implanted fiducials and orthogonal X-rays, ultrasound localisation or tomography.
- Tomotherapy involves a rotating radiation source as in a CT scan – this will allow real-time measurement of the dose actually delivered. Research units are treating patients.
- Charged particle therapy. The physics of charged particles is such that there is always a lower entrance dose and, after a bragg peak at a depth specific to the particle, there is no exit dose. Thus the dose distribution with these modalities will always be better than photons. There are currently several small hospital-based proton facilities and several units using heavy ions (such as C) but these are very expensive to set up and run.