

# OVERVIEW OF ADULT SOFT TISSUE SARCOMA

APRIL/MAY 2009

by Dr Andrew Parasyrn

Sarcomas are malignant tumours arising from mesenchymal tissue. They are rare and can arise from any site in the body. They represent less than 1% of all cancers diagnosed in Australia. Soft tissue sarcomas make up approximately 80% of sarcomas with the remainder arising from bone.

Sarcomas are not thought to arise from benign lesions and there is no clearly defined aetiology. Predisposing factors include genetic predisposition, exposure to radiation or chemotherapy, chemical carcinogens and lymphoedema.

Soft tissue tumours range from completely benign to aggressively malignant (i.e. sarcomas). An intermediate category includes tumours such as desmoid tumours that are locally aggressive but do not metastasise. The ratio of benign soft tissue tumours to sarcomas is at least 100:1.

## CLASSIFICATION

The World Health Organisation classifies sarcomas according to the tissue of origin or the normal tissue the tumour most closely resembles. In adults the most common extremity (limb) sarcoma is liposarcoma followed by malignant fibrous histiocytoma (MFH). In the retroperitoneum the majority are liposarcomas or leiomyosarcomas. Common head and neck sarcomas include angiosarcomas, MFH and liposarcoma. Soft tissue sarcomas occur at any anatomical site but appear more common in the thigh, buttock and groin followed by the torso, upper extremity, retroperitoneum and head and neck.

## GRADING AND STAGING

The most common system of grading soft tissue sarcomas is the FNCLCC (French Federation Nationale des Centres de Lutte Contre le Cancer) which looks at tumour differentiation, mitotic rate and amount of tumour necrosis. This grading system, however, is not applicable to all soft tissue sarcomas (e.g. malignant peripheral nerve sheath tumours which are all high grade). Staging systems for sarcomas like the American Joint Committee on

Cancer (AJCC) attempt to predict the likelihood of distant metastasis and survival. They do not accurately predict local recurrence which is more a function of adequacy of surgical resection and/or the use of radiotherapy. AJCC staging incorporates grade, tumour size, depth of tumour (superficial or deep), lymph node metastases and the presence or absence of distant metastatic disease.

## CLINICAL PRESENTATION

The usual clinical presentation is of a lump that is commonly painless. When pain is present it can occasionally be explained by pressure on local nerves or bone. The tumour tends to grow by direct extension and infiltration of adjacent structures. Growth along tissue planes is common with tumours rarely breaching major facial planes or bone. Sarcomas don't tend to spread to lymph nodes except for certain subtypes (rhabdomyosarcoma, epithelioid sarcoma and clear cell sarcoma). The lung is the most common site of metastatic disease.

## DIAGNOSIS

Once a possible diagnosis of soft tissue sarcoma is made, referral should be made to a sarcoma specialist for evaluation and management. Decisions regarding management should be made in the setting of a multidisciplinary team.

## INVESTIGATIONS

Investigations may include X-rays, Ultrasound, CT or MRI. MRI is a very useful modality for certain primary sites because of its superior soft tissue contrast. It delineates facial planes, bones, vessels and nerves better than CT. Chest CT is the investigation of choice for working up the presence of lung metastases and as a baseline for future comparison. It should be done with every suspected sarcoma. PET/CT scanning is being used more frequently with soft tissue sarcomas. The sensitivity for PET/CT is greater for higher grade sarcomas. PET/CT may help in the diagnosis of occult metastatic disease and be useful in planning which area of a large sarcoma to biopsy to give the greatest yield.

Biopsy is the crucial step in the management of these tumours although this may not always be possible. Biopsy, including core biopsy, incisional biopsy and excisional biopsy, needs to be carefully planned by the treating sarcoma surgeon so as to not compromise definitive treatment.

## TREATMENT

The only potentially curative treatment is surgery. Surgery with clear, adequate (or good quality such as fascial) margins is the aim although not always possible. Local control is improved by radiotherapy, especially with high grade tumours. The timing of radiotherapy is unclear. Pre-operative or neo-adjuvant treatment has the benefit of lower doses and smaller fields. The risk of wound complications is however higher. Newer techniques with neo-adjuvant chemo-radiotherapy where the chemotherapeutic agent (doxorubicin) sensitises the tumour to radiotherapy therefore decreasing the dose of radiotherapy necessary are being used. The role of adjuvant chemotherapy remains uncertain and should be individualised. The most commonly used agents are doxorubicin and ifosfamide.

## PROGNOSIS

Prognosis is dependent on a number of factors and Memorial Sloan Kettering Cancer Centre have developed a nomogram based upon their experience to predict 12 year sarcoma-specific death.

*Memorial Sloan-Kettering Cancer Centre sarcoma nomogram available at <http://www.mskcc.org/mskcc/html/6181.cfm> (accessed 25 Jan 2009).*

## SUMMARY

Soft tissue sarcomas are rare tumours that require careful evaluation and management by a sarcoma specialist and multidisciplinary team. Adequate surgical resection along with adjuvant or neo-adjuvant radiotherapy gives the best chance of cure.



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# TARGETED CANCER THERAPY – TOWARDS PERSONALISED MEDICINE

by Dr Patricia Kho

Traditionally chemotherapeutic drugs have been discovered empirically by screening chemical libraries or natural products without a priori knowledge of the target. In contrast, recently, in the era of molecular biology, "targeted therapies" have emerged in cancer therapeutics and can be defined as drugs developed against a specific target based on its important biological function in cancer. Hopefully, detailed knowledge of the target in specific malignancies could: 1. Increase efficacy of the drugs by understanding mechanisms of drug resistance and 2. Produce predictive biomarkers that will enable more precise prescribing. The following are some examples of different classes of targeted therapies available in breast and colorectal cancers.

## BREAST CANCER

Trastuzumab (Herceptin) is a humanised monoclonal antibody directed against human epidermal growth factor, HER-2 (also known as c-erbB-2), a tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family. Her-2 is overexpressed in 25-30% of breast cancers and is associated with poorer prognosis as activation results in increased cell proliferation, angiogenesis, invasive growth and resistance to apoptosis. Four large randomised studies investigating the role of trastuzumab in the adjuvant treatment of Her-2 positive disease consistently showed a 33% reduction in risk of death (p=.015) and a 4% absolute survival benefit at 4 years in the trastuzumab containing arm. In Her-2 metastatic breast cancer (MBC), trastuzumab plus docetaxel was significantly superior to docetaxel alone in response rates, overall survival (OS) (median 31.2 v 22.7 months) and progression-free survival (PFS) (median 11.7 v 6.1 months). Cardiac toxicity is a concern with a 2.9-4.1% incidence of

congestive heart failure. Patients are screened at baseline and every three months while on treatment.

Lapatinib (Tykerb) is an oral dual tyrosine kinase targeting both ErbB-1 and ErbB-2 receptors intracellularly. A phase III trial of patients with heavily pre-treated HER-2 positive MBC were randomised to capecitabine and tykerb orally for 2 weeks every 3 weeks. The median PFS was significantly longer in the tykerb arm (36.9 weeks vs 19.7 weeks) with a trend towards improved OS and fewer central nervous system metastases. Her-2 positive patients are at higher risk of brain metastases and Lapatinib is a small molecule which is capable of penetrating the blood-brain barrier. It is well-tolerated and toxicities are nausea, fatigue, rash, diarrhoea, acne or dry skin. Clinical trials are underway examining the potential benefits of lapatinib in combination with trastuzumab in the adjuvant.

## COLORECTAL CANCER (CRC)

Bevacizumab (Avastin), a humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF) has potent anti-angiogenesis and anti-tumour activity. Mechanisms of action of anti-VEGF therapy in cancer are far from fully understood. 3 effects are reported – 1. Pruning of tumour vessels; 2. Normalisation of tumour vasculature, thus promoting delivery of chemotherapy; and 3. Reduction of blood-circulating tumour endothelial cells and progenitor cells. In a Phase III study evaluating the addition of bevacizumab to irinotecan and 5FU in previously untreated metastatic CRC, there were major improvements in RR (34.8 to 44.8%), PFS (6.2 to 10.6 months) and OS (15.6 to 20.3 months). The toxicities of anti-VEGF agents include hypertension, proteinuria, arterial thromboembolic events and bowel perforations or haemorrhage. Efforts

to identify biomarkers to guide patient selection for anti-VEGF treatments are ongoing.

## CETUXIMAB (ERBITUX) AND PANITUMUMAB (VECTIBIX)

Cetuximab is a chimeric anti-EGFR monoclonal antibody shown to be effective as single agent or with irinotecan in irinotecan-resistant metastatic CRC and more recently in the first line setting. The combination of cetuximab and irinotecan in the landmark study of irinotecan-resistant metastatic CRC showed a significant increase in RR (22.9 vs 10.8%) and median PFS (4.1 vs 1.5 months). Panitumumab, a humanised anti-EGFR monoclonal antibody has also been shown to prolong progression free survival in heavily pre-treated metastatic CRC as monotherapy. Recently, KRAS wild-type CRC was established as a predictive factor for anti-EGFR therapy. Approximately 66% of CRC are KRAS wild-type. RR in KRAS wild-type patients treated with cetuximab and irinotecan are significantly higher compared to mutant KRAS patients (42% vs 0%) with improved PFS. The same findings were noted in the panitumumab treated KRAS wild-type patients. All patients now undergo KRAS testing prior to treatment with either cetuximab or panitumumab.

These recent advances in targeted therapy have enabled medical oncologists to predict treatment response, aid in prognostication and eliminate unnecessary toxicities. As multiple molecular pathways exist for each cancers, there is still much to be done but we are a step closer to personalisation of cancer treatment.



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SYDNEY ADVENTIST HOSPITAL

# DEALING WITH THE AFTERMATH OF ADVERSE OUTCOMES IN HEALTH CARE

by Dr Gary Klopfer

Adverse outcomes are commonplace and inevitable in the healthcare setting. They may be an exacerbation of the original disease process, an unavoidable result of treatment, a result of human error or a system failure.

The aftermath of an adverse incident or outcome requires careful management for the benefit of the patient, his/her relatives, and all those involved in the care of the patient. It is possible, with poor management, to make an adverse result much worse for all concerned.

## EMOTIONS

In the wake of a bad outcome, emotions will run high not only in those affected but also the carers. This will be particularly so if the incident was sudden or unexpected, if a great deal of effort failed to avert a bad result, if human error or suboptimal management played a part, or if there were differences of opinion as to management. Box 1 lists some of the emotions that health care workers may experience in these circumstances.

### BOX 1: EMOTIONS

- Disappointment
- Pity (for patient, colleague, oneself)
- Self-doubt, question own competence
- Self-blame
- Guilt
- "If only" feelings
- Shame
- Fear (of repercussions)
- Anger, blame (self, others)
- Surprise (at colleague's performance)
- Denial (of error, management of crisis, outcome)
- Shock

## AGENDAS

There will also be people with agendas (Box 2) – whether they were actually involved in the incident or not.

### BOX 2: AGENDAS

- Confess (person making error)
- Blame other(s)
- Report (other person)
- Absolve oneself of guilt (perceived or real)
- Preserve reputation, practice
- Protect, comfort other(s)
- Hide emotions
- Cover up (self, colleague, hospital or practice)
- Influence others' perception or recollection of events
- May like other person but disagree/disapprove of their actions
- Chance to target an old enemy
- Vindication ("saw it coming")
- Hierarchical issues within workplace
- Reluctance to get involved
- Reluctance to give unconditional support/assistance
- Perspective of incident biased by hindsight or poor outcome
- "Wouldn't have happened to me"

The following plan applies to the management of all adverse medical incidents, in or out of hospital.

### DE-BRIEFING

Firstly, there should be one or more de-briefings as soon as possible after every adverse event or outcome, whether major or minor. The purpose of the de-briefing is many-fold:

- Education – what went wrong & what was done to rectify it
- Everyone can unburden after the incident
- Enables those with differing views of the cause, course & management of the incident to air their views & possibly reach agreement:
  - for their own peace of mind
  - for resolution of ongoing conflict, anger, guilt
  - to minimise the medicolegal impact for individual/s, hospital or practice

- Decide who is going to speak to the patient & family and what is to be said
- Plan & discuss ongoing management
- Prepare staff for possible police enquiry in Coroner's cases

All involved (even remote witnesses) should be included and, in serious cases, the de-briefing should be convened and run by a senior person not present at the incident. In sudden, serious or disturbing cases, involved personnel should be removed from the workplace immediately and for as long as necessary. More minor incidents may allow for a less structured de-briefing, but some form of de-briefing is advisable after all incidents, however minor. All discussions in the de-briefing should be blame-free, and everyone's views and concerns should be heard and dealt with, regardless of whether they are shared or appreciated by others.

In reality, for a variety of reasons, de-briefings after adverse incidents rarely take place, and when they do, they rarely achieve the aims listed above.

Without adequate de-briefing, those involved are often left with differing interpretations of the incident, leading to unresolved emotions and issues. This is more likely to affect the junior participants, e.g. nurses or young doctors. They may require emotional support and empathy, and they may emerge with the feeling that their concerns (eg about management) are not heeded or validated, or that they are being forced into accepting a position they are uncomfortable with.

### DISCLOSURE TO PATIENTS

Patients or their relatives want to know the circumstances of an adverse event – in some cases even that an adverse event has taken place! They usually accept that mistakes happen, things can go wrong. They also want to know if it's likely to happen again and what is being done about that. Very few patients want to blame somebody or seek financial compensation. They are far more likely to institute complaints or litigation if they feel that they can't get answers or that something is being kept from them. It is therefore important that doctors and institutions inform their patients

of all adverse outcomes in a frank, open manner. "Open Disclosure" (Box 3) is now well established and encouraged in Australia and overseas.

### BOX 3: OPEN DISCLOSURE

- Expression of regret ("sorry this has happened – not sure why, but we are investigating, and we'll keep you informed")
- Factual explanation of what happened
- No opinions, no blame or criticism (self or other), no admission of liability
- Consequences of the event and prognosis
- Steps being taken to manage the event and prevent a recurrence
- Any questions
- Offer second opinion
- Offer support (emotional, financial)
- "I'm going to reduce my fee because you will have extra costs"

It is very important that the doctor who is most closely involved with the adverse outcome be involved in subsequent discussions with the patient and/or the family. If others (e.g. ICU doctors, nurses, administrators) take over this role, the information they give may be inaccurate or biased, and the original doctor may become excluded, seen to be avoiding, or open to misunderstanding or blame.

Unfortunately doctors, even "good" ones, are not good at disclosing mistakes. The doctor may wish to spare the patient or family extra distress or may wish to avoid confrontation. The doctor may blame him/herself, and may want to minimise feelings of shame, guilt and fear of social or professional isolation. The climate of blame and litigation discourages disclosure. Doctors, MDO's, the HCCC, lawyers and medical administrators see only a fine line, if any, between open disclosure and admission of "guilt" and liability (although the law in NSW no longer regards an apology as an admission of guilt or proof of negligence - Civil Liability Act 2002 Pt 10).

### RECORD KEEPING

"If it's not recorded, it didn't happen"

As soon as practicable, detailed records of the incident should be made in the patient's medical record by all involved. Separate personal notes may also be written, to be kept for future use by individual personnel (marked as personal record, for what reason, with date and time). Records of the de-briefing(s) and all communications with the patient or the family should also be kept. Under no circumstances should existing records be altered. Corrections and additions, appropriately annotated and accurately dated, can be added to the records at a later time. An adverse outcome should be reported to the doctor's MDO.

Thus doctors frequently resort to alternatives to full disclosure:

- Withholding information from the patient or family
- Telling half-truths
- Using euphemisms for the mishap, or re-defining it as a "non-mistake" ('complication' or 'reaction')

- Downplaying the harm caused
- Blaming the patient (e.g. too fat, smoker)
- Blaming external factors: equipment, other staff
- Saying: "but I warned you this might happen"
- Saying: "you were lucky I acted so promptly after things went wrong"
- Rationalisation ("patient was going to die in any event")

- Avoidance and silence (e.g. not replying to letters of complaint, or allowing someone else to talk to the patient or relatives)

Patients and relatives may end up getting conflicting information from different health care professionals. They may sense that something is being kept from them. Like some of the junior doctors or nurses or practice staff mentioned above, patients and relatives may also have unresolved, unheeded concerns needing resolution and validation. They are more likely to institute complaints after other health care workers have raised or confirmed their suspicions that the doctor has not been open and honest with them. Ironically, suing the doctor or lodging a complaint with the HCCC will not directly address the patient/family's main quest for a sympathetic, frank explanation of how it happened and what is being done to ensure it doesn't happen again, so in the end neither party is satisfied (except the lawyers!).



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## SAN NEWS

The San's new 9 bed **Emergency Medical Unit (EMU)**, an addition to the existing 22 bed Emergency Care Department, is now operational. Opened in May by State Health Minister John Della Bosca, the EMU helps patients access to triage, medical consultations, diagnosis, treatment, discharge or admission. Patients will be allocated to certain areas based on their condition and needs.

The new dedicated purpose built **San Day Infusion Centre** is now open on level 4 of the San Clinic. Providing outpatient infusion treatments for patients with cancer, MS, Crohn's, neurological, blood, and other disorders and diseases, the new facility has 11 chairs including a private room for patients who require it.

Queries 9487 9591.

The new **San Pathology Collection Centre** are open soon at 1/2Hillcrest Road Pennant Hills.

Call 9980 6834 for collections or for other queries 9487 9500. The centre will open Monday to Friday 7.30am-5pm Saturday 8am-12noon.

# MAY 2009

1	Friday	
2	Saturday	
3	Sunday	Heart Week
4	Monday	
5	Tuesday	
6	Wednesday	
7	Thursday	
8	Friday	
9	Saturday	
10	Sunday	
11	Monday	SAH Emergency Medical Unit Official Opening
12	Tuesday	International Nurses Day
13	Wednesday	
14	Thursday	
15	Friday	
16	Saturday	
17	Sunday	
18	Monday	International Schizophrenia Awareness Week
19	Tuesday	
20	Wednesday	
21	Thursday	
22	Friday	
23	Saturday	
24	Sunday	Macular Degeneration Awareness Week
25	Monday	
26	Tuesday	SAH Womens Public Health Forum Free
27	Wednesday	
28	Thursday	
29	Friday	
30	Saturday	
31	Sunday	

**26TH MAY- FREE SAH WOMENS PUBLIC HEALTH FORUM**  
LEVEL 2 CONFERENCE ROOM  
BOOKINGS 9487 9871

**11TH MAY SAH EMERGENCY MEDICAL UNIT OFFICIAL OPENING**