PERSONAL DATA

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ACADEMIC DATA

2006-2012: Degree in Medicine and Surgery at Complutense University of Madrid. Turnover attached to General Hospital Universitario Gregorio Maranon

Official School of Languages: English 5 years. **Advanced Level B2.**

Postgraduate Diploma: Fundamentals Cancer Research Methodology at the University of Barcelona : July 2015 to March 2016.

Thromboembolic disease expert at University of Alcala de Henares: March 2016 December 2016

Member of the Working Group of Oncogeriatria SEOM.

Master Molecular Biology CNIO:September 2016.

4th year resident in Medical Oncology University Hospital of Fuenlabrada.

First of all, the way of working is awesome. Peter Mc Callum is the only Cancer Centre in Australia, so they receive patients from other hospitals, especially in the region of Victoria, but also the rest of the country.

I am going to detail certain aspects of the hospital organisation that we could introduce in Spain:

-Each medical oncologist carries a **specific pathology**, so the study, specialization and management of each tumor subtype is greater than we can get in Spain having to dedicate to several types of tumors.

-With difference to Spain, they have more **support** by **nursing** and coordinators of clinical trials, so can have more dialogue with the patient (almost 30 minutes) and e-mail/number phone to call the hospital if any doubts

-Support For Young adults and adolescents **(OnTrac).**

-Also **clinics are closely** from Surgery and Radiation Oncology to share doubts or see patients from other specialists.

-Weekly **sessions** are organized (MDM and war round too). The hospital have several registrars (managers of the war, that I have seen with more than 40-50 patients), also fellowships specialized in certain pathologies with monographic clinics.

-Many **clinical trials.** In Spain it would be ideal a center like this one to centralize; regarding sarcomas are rare tumours so many patients have to come from other places where they do not have clinical trials to get another opportunity.

- **Journal Club:** important to share ideas, reflections, criticisms to articles…

-As ideas to contribute in Spain is the fact of being **more critical** when evaluating studies. It also takes into account more than in Spain the **opinion of the patient,** direct questions, well informed.

In relation to Sarcoma unit (Susie Bae, Jayesh Desai, Anne Hamilton):

Peter Mc Callum Cancer Center is Victoria's reference center for being the only public cancer hospital, as well as the rest of Australia (population> 20 million inhabitants)
Weekly **multidisciplinary committee** (MDM) with presence of traumatologist, plastic surgeon, pathologist, radiologist, medical oncologist and radiation oncologist, with more than 30 weekly cases. Important in deciding also metastesectomies, according to location, especially the pulmonary ones depending on the clinical course of the disease.
The structure is that initially localized ones (newly operated or newly diagnosed), with a sheet in which is collected from each of one, the tests which are performed or pending, histologic diagnosis, who refers, when will be revised next time and the proposed committee plan.

Regarding the general principles, I detail to learn in Spain:

- ✓ Access to Pegfilgastrim, so an injection is scheduled the next day of administration of Doxorubicin.
- ✓ Protocols on eviq.com, are provided to the patient on the first visit to review doubts.
- ✓ An echocardiogram / ventriculography is performed systematically prior to the administration of anthracyclines, at 300 mg and at the end of the 6 cycles.
- ✓ If cardiopathy, caelyx not approved and epirubicine less eficacy, so doxorubicine 60 mg/m2 is the preferred choice.
- ✓ If it is a young patient, goserelin is added to preserve ovarian function and to achieve future gestation. In male patients, sperm conservation too.
- ✓ Baseline audiology previous to cisplatin
- ✓ Most cycles are administered in an ambulatory way, except for Osteosarcoma / Ewing for the 5 days of ifosfamide + etoposide, methotrexate.
- ✓ Reevaluation every 2-3 cycles (PET-CT if non metastatic disease, even FLT if non avid FDG)
- ✓ Referral for psychosocial support: all patients between the ages of 15-25 years old.

I emphasize the management by pathologies (many of them, not seen in Spain in my training):

• **Schwannoma:** usually localized, perform MRI as local staging and neurofibromatosis screening. If malignant(MPNST), after surgery: RT +/- QT adjuvant . In metastatic disease, Doxorubicin→Ifosfamide→Pazopanib

• **Metastasic chordoma:** frequent localization of metastases is in lungs. Imatinib in a metastasic setting as a treatment with more experience.

• **Chondrosarcoma:** several subtypes, for conventional or clear cell non-response to chemotherapy. If mesenchymal or dedifferentiated, same chemo to Ewing.

• **Giant cells:** Denosumab, just like Spain. Initially denosumab weekly x 3 weeks, then once a month. If good response, try surgery and no “adjuvant” denosumab.

- **Dermatofibrosarcoma protuberans**: when no resectable or metastatic, imatinib.

• **Undifferentiated Pleomorphic Sarcoma:** like Spain, lung surgery is attempted if good ECOG and indolent disease.

• **Synovial (mtx):** In general, Doxorubicin first line, ifosfamide second line or D+I in first line due to high sensitivity to ifosfamide if long DFS and well tolerated. If ECOG 0-1: dacarbazine monotherapy in 3rd line, pazopanib or gemcitabine + docetaxel. Not usual adjuvant chemotherapy even if many local recurrences.

- **Pigmented Villonodular synovitis (PVNS):** incidence of 1 / million inhabitants. Important surgical resection, but high local extension, is attempted IMATINIB or clinical trials. In all targeted therapy visit every 2 weeks in the beginning. Also in non metastatic disease, Ytrium. Clinical trial: Plexxikon (inhibits CSF1R,KIT and FLT3 kinases).

• **Desmoid / Fibromatosis:** first discard mutation in APC, for screening of Gardner's Syndrome and with it digestive study with colonoscopy. If an aggressive disease, tamoxifen, imatinib, sulindac, or the combination of both tamoxifen + sulindac is initiated. However if aggressive disease or progression to it, QT (methotrexate, adriamycin ...) is preferred as the response rates are up to 70% while rest <40%. I have seen a case which also progresses after chemo, then Pazopanib approved.
Short survival due to high local growth rather than metastasis. I saw a patient progressing and chemotherapy was elected due to high risk of intestinal perforation. RT is rarely used, if it is believed that after surgery it will be necessary, it has seen the same result alone as RT + surgery.
If asymptomatic and not well tolerated treatment, wait and see.

• **Ewing:** childhood tumor, just as rare with one case per million inhabitants. EuroEwing 2012 trial: Vincristine + Doxorubicin + Cisplatin + EI alternative x 14 cycles (if non metastatic 9 prior surgery and 5 after surgery without Doxorubicin). Arm B: VIDE x 6 cycles →surgery and then VA(actinomycin) I or VAC (locally advanced and metastasic disease) x 8 cycles. GCSF (alternative days)or Pegfilgastrim after each part.

If local recurrence, surgery.

For second line, current study RECCUR comparing Topotecan + Cyclophosphamide, High dose of Ifosfamide, Gemcitabine + Docetaxel or Irinotecan + Temozolamide. Usually use this last scheme, being days 1 to 5 every 3 weeks x 3-6 cycles.

If they are cured: first two years, surveillance every 3 months, 2 to 5 years every 6 months and at 5 years the revision is annual.

• **Osteosarcoma:** MAP (methotrexate week 4,5,9,10,15,16,20,21,24,25,28,29 + Adriamycin 1,6,12 and 17,22,26 + Cisplatin week 1,6,12 and 17) if <30 years, Doxorubicin + Cisplatin in >30 years GCSF after each AP. They need income since they need high doses of methotrexate, they need also leucovorin.
Same than in Spain, Surgery at 11 weeks. If lung metastasis, planning surgery at the same time than primary tumor or after chemo with a new PET-CT.
Second line usually Irinotecan + Etoposide.

• **Angiosarcoma:** first line usually Taxol weekly (3 weeks and rest 1) until tolerance / progression. They perform weekly tests but the doctor sees them every 3 weeks.
Since it is a highly taxol-sensitive tumor, depending on when it progresses, sometimes rechallenge taxol again if >3-6 months from previous or are elderly patients. In the progression: Doxorubicin / Caelyx or taxol if the first line was Doxorubicin, and pazopanib in 3rd line.
If it is radioinduced and the tumor has been a breast cancer, they try to avoid it. Regarding good results with propranolol 40 mg bidaily as maintenance treatment, also seen in one patient (Pasquer 2016).

- **Leiomysarcoma:** uterine and no uterine, usually Doxorubicin in 1st line, then ifosfamide and 3º line with gemcitabine + docetaxel /dacarbazine/ Pazopanib or trabectidine in 3rd line (difficult access in Australia)
  In uterine leiomyosarcoma, more likely gemcitabine + docetaxel as 2nd line.
- **Liposarcoma myxoid:** Doxorubicin→Ifosfamide→Gemcitabine+ Docetaxel→Dacarbazine→Eribulina→ Inmunotherapy trial (BGB A317)

• **CIC-DUX-Sarcoma:** a special type of sarcoma recently described and with poor prognosis, so treatment equals Ewing.
• **Endothelioid hemangioendothelioma:** Same treatments to Spain, little experience for the few cases described: Bevacizumab. Taxol, Pazopanib, Celecoxib, Caelyx
• **Alveolar sarcoma (ASPS):** poor response to chemotherapy, metastatic surgery and treatment with pazopanib are attempted.

- **Rhabdomyosarcoma:** (chemo from Pediatric Guidelines, COG D9803): VAC (vincristine, Dactinomycin, Cyclophosphamide) +- RT if non metastatic disease.
- **Solitary Fibrous Tumor/Hemangiopericytoma:** usually resistent to chemo, pazopanib 800 mg daily.

- **GIST**:same indications than in Spain. Imatinib for first line, sunitinib 2nd line. No adjuvant in wild type and exon 11 800 mg imatinib instead of 400 mg.

<u>According TKI,</u> I have learned a lot since they have high management in several types of tumors such as villonodular synovitis, dermatofibrosarcoma protuberans, chordoma or hemangioperitocytoma and so, in case of slow progression if the dose had previously been reduced, usually try to give a new opportunity and increase doses before going to chemotherapy, since these tumors do not respond to conventional treatment and TKIS are well-tolerated oral drugs.
Also dose reductions (usually as a palliative treatment, try to slow down quickly to avoid suspension, pazopanib to 600 o 400 mg, imatinib to 300 or 200 mg).
If tiredness, usually reduce to 200 mg imatinib and if well tolerated, up to 300.
If neutropenia, usually reduce to 300 mg

According to bening tumors, I have also learned about radiologic images and pathology too in MDM. Surveillance by Surgery.

Regarding issues which are still in controversy, I emphasize:

- No usual adjuvant chemotherapy, unless the location is problematic in case of relapse as is the cervical region, or at risk of local complications or sensitive tumors such as liposarcoma or synovial sarcoma which are more sensitive to chemo.
- If metachronic disease (lung); no “adjuvant” chemo after lung metastesectomy
- Neoadjuvant RT after chemo or alone (after Doxorubicin + Ifosfamide in synovial sarcoma). If chemo x 6 cycles (reevaluation after 2-3). In case of Ewing, first week is combined with Doxorubicin, then they restart it after 4-6weeks of finishing RT.
- No usual combination of two drugs such as anthracycline + ifosfamide in metastatic disease, except for young patient with high tumor burden.
- If slow progression and no symptons, “watch and see” closely (leiomyiosarcoma if indolent behaviour, after good local control)
- On progression, trabectidine for lipo and leiomyosarcoma, pazopanib for non-adipocytes or eribulin for adipocytes (I have seen it used in 3rd line, days 1 and 8, the doctor only see patients on day 1 with analytical)
- RT in case of near margins, deep margins,> 5 cm.
- Neoadjuvant in cases of >5 cm or unresectable, with concomitant RT. Avoiding doxorubicin + RT at the same time in relapse or metastatic disease.
- 3 cycles of antracycline + ifosfamide and no 5 cycles in case of adjuvant setting.
- Palliative surgery not if not complete surgery can be guaranteed because of the risk of disemination. In uterine sarcomas, try it if spotting or pain.
- If asymptomatic tumor, even in rabdomiosarcoma, if 1st line chemo with stable/ partial response, wait and see is an option to discuss with the patient.
- PET-CT available for staging, not necessary in the surveillance. Usually CT chest.
- If PET-CT FDG non avid, try with FLT(fluorothymidine) PET-CT (available):relation to KI67 and response to treatment, some studies with breast, lung and brain cancer. I have seen a case of synovial sarcoma, non avid FDG and avid for FLT, confirmed in surgery.
- Lung metastasis: if asymptomatic, first RT for local control and then QT (only QTRT if high sensivity to QT). If control disease after >12 months, 1-2 lung nodules, try metastasectomy.
- Older patients, maintenance: cyclofosfamide. Avoiding Ifosfamide, usually second line with dacarbazine.

Investigation/ Clinical Trials Australia:
OLARUTUMUMAB +- Doxorubucin
INMUNOTHERAPY: BGB A 317 (similar but higher activity tan PD1 antibodies)
→ more sensitive for myxoid lyposarcoma

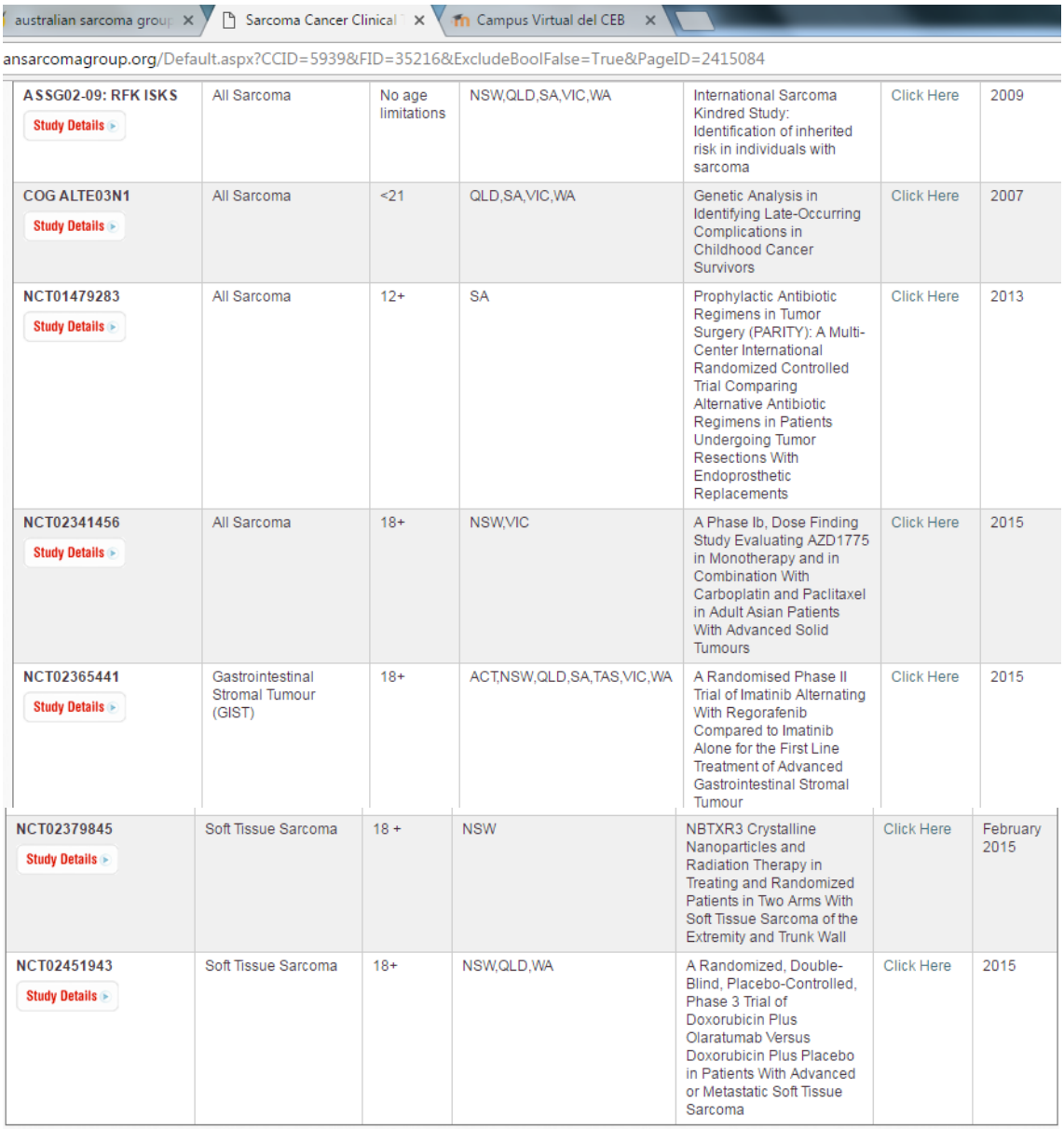
NOTCH Inhibitors: desmoid after progression to hormonotherapy / NSAIDS.

PLEXXIKON(inhibits CSF1R,KIT and FLT3 kinases): Pigmented Villonodular Synovitis.

Some patients see clinicaltrials.gov, also a national web to find clinical trials: http://www.australiansarcomagroup.org/

ansarcomagroup.org/Default.aspx?CCID=...

Study ID	Sarcoma Type	Age	Australian Location	Study Title	Eligibility Criteria	Open
ACTRN12608000214336 Study Details	Sarcoma	13+	ACT,NSW,SA,VIC,WA	A Pivotal Trial to Determine the Efficacy and Safety of AP23573 when Administered as Maintenance Therapy to Patients with Metastatic Soft Tissue or Bone Sarcomas.	Click Here	2007
ACTRN12610000444088 Study Details	Sarcoma	18-60	WA	Improving lower limb function in patients with major muscular loss or denervation following resection of a sarcoma.	Click Here	2010
ACTRN12610000796088 Study Details	Leiomyosarcomas, Adenosarcomas, Carcinosarcomas and Undifferentiated Uterine Sarcomas	18+		Phase II study of aromatase inhibitors in women with potentially hormone responsive recurrent/metastatic gynaecological neoplasms	Click Here	2011
ACTRN12613000423718 Study Details	Rhabdomyosarcoma, Soft tissue sarcomas, Osteogenic sarcoma, Ewing sarcoma	0-21	NSW,WA	A phase I study of vinorelbine, cyclophosphamide and Rapamycin for recurrent malignancies in children	Click Here	2011
ACTRN12613000987763 Study Details	Sarcoma	18-60	VIC	A pilot surveillance study investigating whole body magnetic resonance imaging and other diagnostic procedures in people at high risk of cancer	Click Here	2013
ACTRN12615000527561 Study Details	All Sarcoma	15-25	SA,TAS	A pilot randomised controlled trial of a structured exercise intervention after the completion of cancer treatment in adolescents	Click Here	2015



ASSG02-09: RFK ISKS Study Details	All Sarcoma	No age limitations	NSW,QLD,SA,VIC,WA	International Sarcoma Kindred Study: Identification of inherited risk in individuals with sarcoma	Click Here	2009
COG ALTE03N1 Study Details	All Sarcoma	<21	QLD,SA,VIC,WA	Genetic Analysis in Identifying Late-Occurring Complications in Childhood Cancer Survivors	Click Here	2007
NCT01479283 Study Details	All Sarcoma	12+	SA	Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY): A Multi-Center International Randomized Controlled Trial Comparing Alternative Antibiotic Regimens in Patients Undergoing Tumor Resections With Endoprosthetic Replacements	Click Here	2013
NCT02341456 Study Details	All Sarcoma	18+	NSW,VIC	A Phase Ib, Dose Finding Study Evaluating AZD1775 in Monotherapy and in Combination With Carboplatin and Paclitaxel in Adult Asian Patients With Advanced Solid Tumours	Click Here	2015
NCT02365441 Study Details	Gastrointestinal Stromal Tumour (GIST)	18+	ACT,NSW,QLD,SA,TAS,VIC,WA	A Randomised Phase II Trial of Imatinib Alternating With Regorafenib Compared to Imatinib Alone for the First Line Treatment of Advanced Gastrointestinal Stromal Tumour	Click Here	2015
NCT02379845 Study Details	Soft Tissue Sarcoma	18 +	NSW	NBTXR3 Crystalline Nanoparticles and Radiation Therapy in Treating and Randomized Patients in Two Arms With Soft Tissue Sarcoma of the Extremity and Trunk Wall	Click Here	February 2015
NCT02451943 Study Details	Soft Tissue Sarcoma	18+	NSW,QLD,WA	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin Plus Olaratumab Versus Doxorubicin Plus Placebo in Patients With Advanced or Metastatic Soft Tissue Sarcoma	Click Here	2015

As we see even in these centers, slow recruitment, some recruiting for more than 5 years.

I have also had time to study more about sarcomas, Dr Susie Bae has explained me a lot of interesting things during these weeks, and also have seen last recents news in ASCO 2016 and recent studies in PUBMED as RECCUR, GEDDID, or read the pilot ones who have given the drug indication as Demetri for trabectine, studies of GEIS and Italian Group of 3-5 cycles adjuvant chemo, …
A nice experience with many patients seen, meetings, toxicity and organisation to try to introduce into Spain. As rare tumours, I will be less afraid if I have to see these types of tumours as an oncologist now, knowing also sensitivity to chemo, in terms of stop treatment or thinking about Clinical Trials too.