

International co-operation on clinical data and research is vital to paediatric oncology services, says Dr Michael Capra

Sheila O'Kelly

Knowledge shared is patients' gain

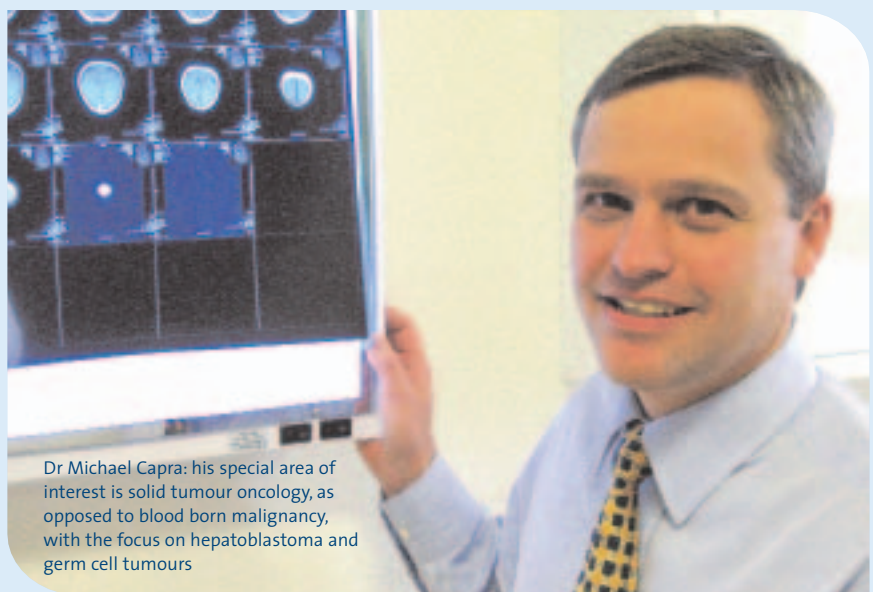
Dr Michael Capra, consultant paediatric oncologist, took up his post at Our Lady's Children's Hospital, Crumlin, at the beginning of December 2006. Dr Capra was formerly assistant professor, Department of Paediatrics, University of Toronto, which is affiliated with SickKids.

SickKids is the Hospital for Sick Children in Toronto, Canada, and is a healthcare, teaching and research centre dedicated to children.

Dr Capra was born and brought up in South Africa although he was schooled internationally. He left South Africa in 1992 to further his paediatric post-graduate training in the UK. That was where he met his Irish wife, Louise Kyne.

"Louise is a general paediatrician who did medicine in Galway; her training in Dublin; and she then went to the UK to do further paediatric training," said Dr Capra.

They chose to come to Dublin to be near Louise's family, and because a position as



Dr Michael Capra: his special area of interest is solid tumour oncology, as opposed to blood born malignancy, with the focus on hepatoblastoma and germ cell tumours

paediatric oncologist became available in Crumlin.

They have two daughters aged 3 and 5.

Dr Louise Capra is working in a locum position in Temple Street Children's Hospital.

"Our coming to Dublin was good timing.

There is great excitement for the future. It's an exciting time to be part of the metamorphosis of the paediatric service in Dublin."

Toronto structure similar

The structure of oncology services in Toronto and Crumlin are very similar, said Dr Capra.

"SickKids is a very big world renowned children's hospital. It is much the same as what we have here in Crumlin in that Crumlin is a stand-alone paediatric hospital. And within the paediatric hospital, the oncology department is exactly the same as in Toronto."

However, the resources available in Toronto are quite different.

"The patient numbers we were seeing in Toronto was approximately 350 new patients a year compared to 120-150 in Crumlin. In Toronto we had 26 consultants and here we have five."

So that means there is a ratio of:

- One consultant for every 13 new patients in Toronto
- One consultant to an average of every 27 new patients in Crumlin.

"This means that the emphasis in Crumlin on the clinical workload is significant. In the North American centres there is more protected time from the clinical side for academic endeavours and research. However, the people here are extremely resourceful and extremely good time managers and some still manage to do some excellent research. But the patients in Toronto and Crumlin are exactly the same. The pathology is exactly the same."

The way registrars work in Crumlin and Canada is different however.

"The middle-grade registrar base is an integral part of clinical management in Ireland. It is the same internationally, but there is more of a consultant-led service in Toronto compared to here. But in paediatric oncology, consultants generally lead the service internationally because it is such a hands-on discipline.

"The mid-ranking registrar in Toronto is called a fellow. They have completed their paediatric training and are already sub-specialising within paediatrics.

"In Crumlin most of our registrars are going through their paediatric training and do a six months clinical attachment in oncology.

"Whereas Toronto, being an international training centre, attracts paediatricians who have nearly or already completed training, but now want to sub-specialise directly in oncology.

"There were 35 fellows at SickKids and about five registrars in Crumlin. That shows

how resourceful the people here are."

Dr Capra said that when there is funding and resources, clinical services can be separated from education and research. This boosts resources for training junior staff.

Special interest

Dr Capra's special area of interest is solid tumour oncology as opposed to blood born malignancy. He has special interests in hepatoblastoma and germ cell tumours and has links with international collaborative research.

"I would highly recommend that registrars who want to further specialise or further train, think about going abroad – the majority of Irish graduates do. Irish doctors are extremely well qualified. It brings imported medical expertise here – not in people but in training."

The emphasis in oncology research now centres around:

- National and international collaboration
- Increased diagnostic ability
- Further refinements of treatment options.

This means that when a patient is treated they benefit from national and international research. In turn, the clinical information from that patient is pooled and contributes to the international oncology database.

"This is essential because in any one centre the numbers of paediatric oncology cases are very small. For statistical power, and to glean any type of inference from data, you need many more patients. The way to do that is to pool all patients together.

"The collaborative group that we belong to here in Dublin is the Children's Cancer Leukaemia Group (CCLG) formerly the UK CCSG. It comprises 21 centres in the UK and Ireland. CCLG forms part of SIOP (International Society of Paediatric Oncology).

"It takes a few years for data to mature and then it is published in one of the many peer-reviewed medical journals."

Cross-pollination

"That is one thing that has changed in the last 10 years on the two sides of the Atlantic. There is now the beginning of cross pollination of ideas. Now there is even the same trial looking at osteogenic sarcoma within SIOP and CCLG."

When people collaborate internationally they contribute to the international paediatric oncology centres.

"The mere fact that we are involved means there is continuous sharing of data and ideas. Therefore we are continuously updating our understanding," said Dr Capra.

"The world is becoming a small place

now so regardless of where you live or practise your medicine, electronic communication means that everyone can be up to speed very quickly."

Clinical trials

An important area in paediatric oncology is to get as many patients on to a clinical trial as possible, said Dr Capra.

Parents are enthusiastic about trials but they need to be explained and informed consent has to be obtained. It is generally not experimental therapy. It's not straight out of the laboratory.

Another development in paediatric oncology over the last 10 years is that there is increased diagnostic ability at a molecular biological level.

"Our understanding of the biology of tumours is forever increasing. That is extrapolating into more sensitive exploratory procedures that we can use to interrogate tumours," said Dr Capra

Techniques

"There have also been improvements in surgical techniques especially for brain tumours. Radiotherapy is refined. The greatest challenge in paediatric oncology is that you have a developing and growing child and our cytotoxic (cell-killing) therapy exerts its action on normal cells too.

"Radiotherapy is a blunderbuss so any cell within the field gets irradiated, thereby possibly limiting future growth, amongst other effects, in this area. So if you can refine it so that the tumour gets destroyed but normal tissue is undamaged – you have a better result," said Dr Capra.

Future developments

Dr Capra would like to see Ireland continue to take part in collaboration at the national and international level.

From a local point of view, he would like to see Crumlin with more suitable bricks and mortar, "It is long overdue and would be a breath of fresh air. At the moment the building in Crumlin – for patients and parents alike – is not an uplifting environment. I am anticipating facilities at the proposed new National Children's hospital to be a considerable improvement."

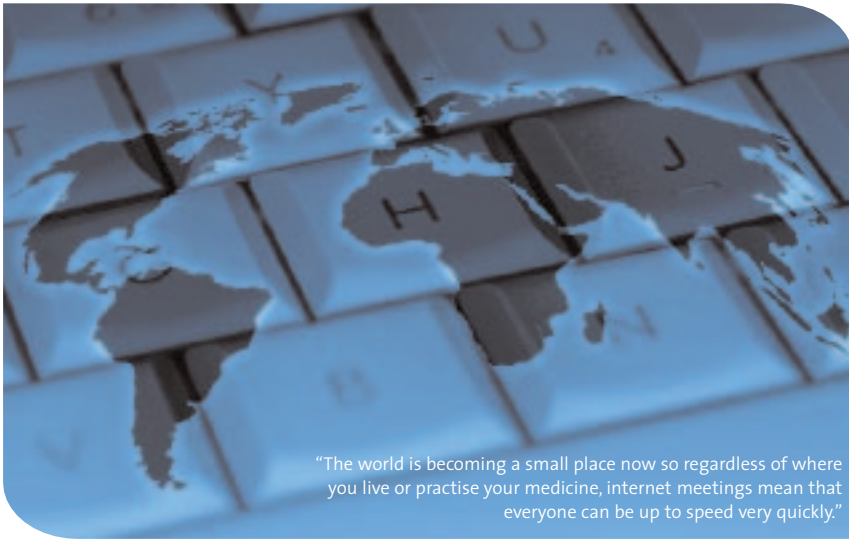
Parents

Parents now are much more informed due to internet and increased media publicity on health issues, said Dr Capra.

"They are more educated generally and more demanding, and rightly so, of expert, up-to-date efficient care. Evidence-based medicine and accountability tends to follow that, which benefits everyone," said Dr Capra

GP guidelines

"For a GP to have a patient in their practice who has a paediatric oncological diagnosis is



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relatively rare. We are developing guidelines for GPs in Ireland for referral patterns. And that is the beauty of being the national paediatric centre – GPs have one point of call – and communication is good. That is tremendous. They don't have to jump through many hoops to get a consultant.

Paediatric cancer

Compared to adults, very few children develop cancer. It is so rare that it may not occur to a GP that that is the problem.

"That is often the issue when we see parents for the first time. There is a lot of anger for the time it takes for a diagnosis to be made, specifically with brain tumours, because they are so difficult to diagnose. The symptoms they present with often masquerade as benign conditions.

"It is a great challenge internationally to diagnose. It's not the diagnosis at the top of the list, therefore it is not thought of often. And often diagnosis can be delayed.

"GPs have a very difficult job. They have to be jack-of-all-trades, they need high levels of suspicion, while at the same time not causing too much anxiety and they need to be efficient with their diagnostic ability.

"We see patients right at the end of the pyramid when it's easy to diagnose," said Dr Capra.

"If you look at overall survival, there has been a fantastic improvement in survival in paediatric cancer over the last 30 years. This is due to better treatment and benefit from clinical trials."

Life in Ireland

When asked to compare living and working in Ireland to Toronto, Dr Capra said there was a wonderful personable approach in Ireland.

"People are very resourceful and will go that extra mile. Being a relatively small country and being the national haematol-

ogy oncology unit, we are in the enviable position that we have maximum co-ordination of services at a single centre.

"That has been proven. The difficulty is the geographic distance our patients have to travel. Public transport and the road system are not enviable.

"Therefore our reliance on shared care centres, and our co-operation with our paediatric colleagues across the country is vital.

"That is what I believe is the strength of the unit here. It is not just this unit, it is the support we get from our other paediatric colleagues who are doing as much as they can locally to support the patient through the illness."

A child who has cancer will get most of their treatment in Crumlin, but some of the relatively simple chemotherapy administration can be given locally.

"This regional co-operation relies on excellent communication; and sharing of ideas about education and training.

"Some standards of care for oncology patients cannot be delivered in the local centres. But education and training is ongoing to facilitate the referring centre to be an integral component of the future management of the patient."

This would mean that more care could be done locally and people could avoid unnecessary travelling.

Job satisfaction

Dr Capra thinks of his profession as a wonderful and very privileged one.

"To be able to care for children and their families through extremely difficult times is a privilege.

"Generally we have good results but inevitably we cannot save all the children. What patients and parents want, apart from a cure, is for us to shepherd them through this journey."

**ALIMTA® (PEMETREXED DISODIUM)
REPUBLIC OF IRELAND
ABBREVIATED PRESCRIBING INFORMATION**

Presentation: Glass vials containing pemetrexed (dioxane) equivalent to 500mg of pemetrexed, in a sterile, white to off-white, yellow or green-yellow lyophilized powder. **Uses:** Alimta is indicated in combination with cisplatin for the treatment of chemotherapy-naïve patients with unresectable pleural mesothelioma. Alimta is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after prior chemotherapy. **Dosage and Administration:** The drug is to be administered intravenously, under the supervision of a physician qualified in the use of cytotoxic anti-cancer therapy. Malignant pleural mesothelioma: Pemetrexed in combination with cisplatin has been investigated using a three-week (21-day) cycle. Pemetrexed is used at 500mg/m² of body surface area (BSA), given by ten-minute infusion, on day 1 of each 21-day cycle. Cisplatin is used at 75mg/m² BSA, given by two-hour infusion, approximately 26 minutes after completion of the pemetrexed infusion on day 1 of each cycle. Adequate anti-emetic treatment and hydration for cisplatin treatment must be given. Non-small cell lung cancer: The recommended dose of pemetrexed is 500mg/m² BSA, given by ten-minute infusion, on day 1 of each 21-day cycle. Pre-irradiation: Supplement with 1000 mcg/m² methotrexate on days 11 and 12 and oral folic acid (500 mg/1000 mcg tablets) to reduce toxicity for full details see Summary of Product Characteristics (SPC). To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of and the day after pemetrexed administration – this should be equivalent to 4mg of dexamethasone administered only twice a day. Monitoring: Monitor prior to each dose for complete blood cell count, including a differential white cell count and platelet count. Absolute neutrophil count should be ≥ 1500 cells/mm³ and platelets $\geq 100,000$ cells/mm³. Prior to each dose, collect blood chemistry tests to evaluate renal and hepatic function. Dose adjustments to pemetrexed and/or cisplatin at the start of a subsequent cycle should be based on laboratory haematological counts or laboratory cardiovascular toxicity. If necessary, delay or withhold treatment in the presence of haematological toxicity, neurotoxicity, and/or impaired renal function. (For full information on dose reduction see SPC) Children and adolescents: Not recommended for use in patients under 18 years of age. Renal impairment: Patients with creatinine clearance ≥ 30 mL/min require no dose adjustment other than those recommended for all patients. Use in patients with creatinine below 30 mL/min is not recommended. See also Warnings and Special Precautions. **Plasma treatment:** Patients with hepatic impairment, such as bilirubin ≥ 1.5 -times the upper limit of normal and/or transaminase ≥ 5 -times the upper limit of normal (aspartate aminotransferase ≥ 5 -times the upper limit of normal) (hepatic metastases present), have not been specifically studied. **Contra-indications:** Hypersensitivity to pemetrexed or to any of the excipients. Concurrent yellow fever vaccine. Breast-feeding. **Warnings and Special Precautions:** Myelosuppression is usually the dose-limiting toxicity. Patients must be instructed to avoid folic acid and vitamin B₉ as a prophylactic measure. Pre-treatment with dexamethasone for equivalent can reduce the incidence and severity of skin reactions. Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in combination with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors including dehydration or pre-existing hypertension or diabetes. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to administration. Serious cardiovascular events, including myocardial infarction and cerebrovascular events, have been uncommonly reported when pemetrexed is given in combination with other cytotoxic agents; most of these patients had pre-existing cardiovascular risk. Concurrent use of live attenuated vaccines is not recommended. **Interactions:** Concurrent administration of nephrotoxic drugs and substances that are also tubularly secreted could potentially result in delayed clearance of pemetrexed. If necessary, creatinine clearance should be closely monitored. Patients must avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) with long elimination half-lives for at least 3 days prior to, on the day, and at least 2 days following pemetrexed administration. In patients with normal renal function, creatinine clearance ≥ 30 mL/min, high doses of NSAIDs such as ibuprofen ≥ 1600 mg/day and aspirin at higher doses (at 3g daily) may decrease pemetrexed elimination and increase the occurrence of adverse events. Patients with mild to moderate renal insufficiency (creatinine clearance from 30 to 50 mL/min) should avoid taking NSAIDs (eg, ibuprofen, or aspirin at higher doses) for 2 days before, on the day of, and 2 days following pemetrexed administration. There is a possible interaction between oral anticoagulants and pemetrexed; therefore, increase the frequency of International Normalized Ratio monitoring (INR) if treated with oral anticoagulants. **Pregnancy and Lactation:** Avoid in pregnancy and do not use in breast-feeding women. Pemetrexed can be genotoxic; sexually mature males are advised not to father a child during treatment and up to 6 months thereafter. Due to the possibility of irreversible infertility men are advised to seek counselling on sperm storage before starting treatment. Women of childbearing potential must use effective contraception during treatment. **Drinking, etc.:** It has been reported that pemetrexed can cause xerostomia. Patients should be cautioned against drinking or operating machinery. **Undesirable Effects:** Haematological: Very common: Anaemia, leucopenia, thrombocytopenia, neutropenia, leucocytosis. Frequent: Neutropenia and infection without neutropenia. Uncommon: Pancytopenia. Gastro-intestinal: Very common: Nausea, vomiting, stomatitis/dyspepsia, diarrhoea, flatulence, constipation. Common: Dyspepsia, abdominal pain. Rare: Colitis. General: Very common: Fatigue. Common: Fever, myalgia/malaise. Metabolic and nutrition: Common: Dehydration. Nervous system: Very common: Neuropathy - sensory. Common: Myalgia - motor, dysgeusia. Renal and urinary: Very common: Creatinine elevation, creatinine clearance decreased. Common: renal failure. Haematology: Common: SPOFF (ALT) elevation and SPOFF (AST) elevation, increased DDT. Rare: Cases of hepatitis, potentially serious, have been reported during trials. Skin and subcutaneous tissue: Very common: Rash/desquamation, alopecia. Common: Ulcerative, allergic reaction/hypersensitivity, erythema multiforme, pruritus. Cardiovascular and cerebrovascular: Uncommon: Myocardial infarction, angina pectoris, cerebrovascular accident, arrhythmias, transient ischaemic attack. Usually when given in combination with other cytotoxic agents and with pre-existing cardiovascular risk. Common: Chest pain. For full details of these and other side-effects, please see SPC, which is available at the following addresses in Local Categories: **Local Marketing Authorisation Holder and Holder:** Eli Lilly (Ireland) Ltd, Eli Lilly Nederland BV, Grünstrag 1-5, NL-3991 RA Houten, The Netherlands. **Date of Preparation or Last Review:** 26 January 2007. **Full Prescribing Information is Available From:** Eli Lilly and Company Limited, Lilly House, Priestley Road, Westminster, Harrogate, HG2 9JG, England; Boehringer Ingelheim (UK) Ltd, 990 Chiswick Avenue, Uxbridge, Middlesex, Ux8 3NX, UK; or Eli Lilly and Company (Ireland) Limited, Hyde House, 45 Adelaide Road, Dublin 2, Republic of Ireland. Telephone: Dublin (31) 661 4377.

References: 1. ALIMTA Summary of Product Characteristics, Eli Lilly January 2007. 2. Hanna N et al. Randomised Phase III Trial of Pemetrexed versus Docetaxel in Patients with Non-Small Cell Lung Cancer Previously Treated with Chemotherapy. *J Clin Oncol* 2004; 22(18):1589-97. 3. Vogelzang N et al. Phase III Study of Pemetrexed in Combination with Cisplatin versus Cisplatin alone in Patients with Malignant Pleural Mesothelioma. *J Clin Oncol*, 2003; 21(24):2636-2644.

*ALIMTA (pemetrexed dioxane) is a trademark of Eli Lilly and Company.

