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Dr. Jon Pritchard
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On 7th June, 2007, Jon Pritchard's friends, colleagues and past patients joined his family at a memorial service in London to celebrate his life and achievements. Jon was Paediatric Editor of *EJC* from 1994 – 2005 and died in January at the age of 64. He had been diagnosed with a glioblastoma early in 2006.

Jon Pritchard was responsible for the re-engagement of the paediatric oncology community with *EJC* and he had high regard for the journal's philosophy of addressing all aspects of cancer research and treatment in one publication. He was, as an editor, as he was in all aspects of his life – imaginative, enthusiastic and sometimes controversial. He loved a challenge and he was masterful in seizing the value of a lateral thought or a chance observation in almost any situation – the more complicated the better. He disliked electronic communication and would always prefer a phone call or a personal note to sort out a problem and it was here that his enthusiasm and personal charisma worked to full effect to overcome most obstacles. He was enthusiastically European and more widely internationalist in his outlook. His passion for improving care for children with cancer across the world is evidenced by his outstanding contributions to many fields, but particularly to the international collaborations in neuroblastoma, hepatoblastoma and histiocytosis, which he instigated and drove forward.

Jon Pritchard was one of the first full-time paediatric oncologists in the United Kingdom and in Europe. He published and lectured widely, but the legacy of his knowledge, influence and enthusiasm is best seen in the ongoing work of those he inspired, encouraged and trained.

Professor Michael Stevens
University of Bristol, UK
EJC Editor Paediatric Oncology

I first met Jon Pritchard in 1980 after my then 5-year-old son Hamish was diagnosed with neuroblastoma. I was a demanding parent. I needed to know every scientific aspect of my child's condition and to be intimately involved with every clinical procedure, but Jon coped with all the challenges I produced. He answered my endless questions, he embraced my longing to be an integral part of the caring team and he sensitively sought to make me feel valued. His creed of closely involving parents enabled me to cope with what I knew I was facing: the cruel treatment and eventual death of my son.

Two years later, Jon was instrumental in the birth of the Neuroblastoma Society which has sought to fund research into neuroblastoma. He was a trustee for the first years of its existence. He would often phone excitedly to discuss his latest crusade, enlisting my help or encouraging me to write or speak about my experience at medical meetings. Jon firmly believed that the sick child's parents should be heard. He had firm convictions that medical members of the caring team had something to learn from us. Those who listened and received the message became more effective carers.

Antonya Cooper,
Co-founder and Chair of the
Neuroblastoma Society

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The American Society of Clinical Oncology held its 43rd Annual Meeting in Chicago, Illinois on 1–5 June, 2007. EJC's Scientific Editor, Robert Day-Webb, reports from Chicago (pp. 1886–1887)

Chemotherapy for liver metastases

Peri-operative FOLFOX4 may help patients with colorectal cancer who have resectable liver metastases. An international study found, for the first time, that the addition of chemotherapy significantly improved progression free survival (PFS) compared to surgery alone.

The EORTC Intergroup phase III study (*Proc Am Soc Clin Onc 2007 Late Breaking Abstract #5*) concluded that peri-operative FOLFOX4 reduced the risk of relapse in patients with liver metastases considered resectable on imaging. The impact was greater among patients whose metastases were actually resected. The treatment was deemed safe and appeared well tolerated, leading the authors to suggest that it should become the new standard.

Between 2000 and 2004, 364 patients were randomised to either surgery alone or 6 cycles of FOLFOX4 prior to surgery and 6 cycles of FOLFOX4 after surgery. At 3 years, peri-operative FOLFOX4 significantly improved PFS by 9.2% and reduced the risk of relapse by 27% among patients for whom resection was successful.

'This approach may become the standard of care for patients with liver metastases from colorectal cancer that can be surgically removed,' said Professor Bernard Nordlinger, lead author (Ambroise Pare Hospital, France).

Despite these promising results, concerns remain. Pre-operative chemotherapy could cause liver damage that would be avoided if all chemotherapy were given post-operatively. It was suggested at the meeting that the next phase III trial should look at comparing neoadjuvant to adjuvant therapy.

New hope for liver cancer patients

The kidney cancer drug sorafenib has been shown to significantly prolong the overall survival of patients with advanced hepatocellular carcinoma (HCC), according to a new study. This is a significant advance in the management of advanced liver cancer as no effective systemic treatment currently exists.

Results from the international phase III placebo-controlled Sorafenib HCC Assessment Randomized Protocol (SHARP) Trial demonstrated the effectiveness of sorafenib (Nexavar) as a treatment for advanced liver cancer. The drug extended patients' overall survival by 44% *(Proc Am Soc Clin Onc 2007 Late Breaking Abstract #1)*.

In the study, 602 patients with HCC, the most common type of liver cancer, were randomised. Half received sorafenib and the other half, placebo. Patients who took sorafenib survived an average of 10.7 months, compared to 7.9 months for those on placebo. The drug was also found to be well-tolerated by patients with manageable side effects.

'Because there are no therapies that significantly improve survival for the thousands of patients with liver cancer, these findings demonstrate the compelling study results of Nexavar as the new reference standard of care for the first-line treatment of HCC,' said Dr. Josep M. Llovet (Mount Sinai School of Medicine, New York), lead author.

'Although much progress has been made in cancer research, the number of lives lost to liver cancer is increasing,' said Dr. Jordi Bruix (Hospital Clinic of Barcelona, Spain), co-investigator. 'These results represent a significant achievement – sorafenib could become the first widely approved new therapy for this difficult-to-treat cancer.'

The findings are now being prepared for health authority review by the drug developers Onyx Pharmaceuticals and Bayer HealthCare Pharmaceuticals. If approval is given, sorafenib will indeed become the first widely approved effective systemic treatment for liver cancer patients.

Sorafenib is currently approved for the treatment of renal cell carcinoma in the US and Europe and is also being studied as a potential treatment for lung and breast cancer and melanoma.

'Inadequate follow-up of childhood survivors'

Most adult survivors of childhood cancer are not receiving appropriate follow-up despite a significant risk of developing later therapy-related health problems, a major study found.

The Childhood Cancer Survivor Study (*Proc Am Soc Clin Onc 2007 #6502*) included 8522 long term survivors and found that only one-third had received care related to their prior cancer. Some survivors (12%) – particularly men, those without insurance and those on low incomes – had received no care at all within the previous 2 years.

Nearly two-thirds of childhood survivors develop at least one chronic health problem in adulthood as a result of their prior cancer and in 28%, the condition is severe or life-threatening.

'We were disappointed by these findings,' said Dr Paul Nathan, (Hospital for Sick Children, Toronto, Canada) the study's lead author. 'Breast cancer and cardiac problems are conditions that, while not entirely preventable, are treatable if they are picked up early. But we found that the majority of patients are not getting the tests they need to be diagnosed in a timely manner.'

The authors said that survivors need to be aware of their increased health risks and doctors should follow the latest guidelines on long term follow-up.

Improved relapse-free survival in melanoma

Long-term treatment with a modified interferon improves relapse-free survival in melanoma, according to the largest adjuvant trial ever conducted in patients with stage III disease.

A phase III EORTC study included 1256 patients with stage III melanoma. They were randomly assigned either to observation or to receive 5 years' treatment with pegylated interferon-alpha2b (PEG-IFN).

Median relapse-free survival was 34.8 months in the PEG-IFN arm compared with 25.5 months in the observation arm, a significant and sustained effect. However, there was no significant difference between the two study arms in either distant metastasis-free survival or overall survival. Patients with only microscopic nodal involvement (sentinel node positive) appeared to have greater benefit in terms of both relapse-free survival and distant metastasis-free survival (*Proc Am Soc Clin Onc 2007 #8504*).

Lead investigator, Dr. Alexander Eggermont, (Erasmus University Medical Center, the Netherlands) said, 'Advanced stage melanoma remains difficult to treat and a need still exists to find treatment options. These findings demonstrate the benefit of an increased relapse-free survival despite no difference in overall survival.'

Study participants will continue to be followed for survival assessment for a total of 10 years.

Smoking 'reduces irinotecan efficacy'

Patients who continue to smoke during irinotecan treatment may be putting themselves at risk of treatment failure, say researchers from the Netherlands (*Proc Am Soc Clin Onc 2007 #2506*). At the same time, they may suffer fewer side effects.

A study led by Floris A. de Jong, PhD, (Erasmus University Medical Center, the Netherlands) found that smoking during treatment significantly affected both the pharmacokinetic and toxicity profile of irinotecan.

The retrospective analysis included 190 patients (49 smokers and 141 non-smokers) who received irinotecan. Complete toxicity data was available for a subset of 134 patients. Smoking lowered the exposure of patients to both irinotecan and its active metabolite SN-38. Consequently, smoking also reduced the incidence of SN-38 exposure-related neutropenia. The incidence of delayed-onset diarrhoea in smokers also appeared lower.

The results indicated that smoking significantly affects the efficacy of irinotecan by effectively decreasing the dose of the drug in the body. The exact mechanism by which this happens is not yet clear, but it is thought to involve key irinotecan metabolising enzymes such as CYP3A and UGT1A.

The study raises several questions. Should clinicians encourage smokers to quit, give smokers a higher dose of the drug to compensate for their lower exposure, or simply reconsider the use of irinotecan therapy for smokers?

Hyperthermia in sarcoma patients

Regional hyperthermia therapy combined with chemotherapy nearly doubled both disease-free and progression-free survival among patients with high grade sarcomas in a phase III European study. The hyperthermia/chemotherapy combination was compared with chemotherapy alone.

The study was run by EORTC and European Society for Hyperthermic Oncology (ESHO) and included 340 patients with locally advanced, high grade soft tissue sarcomas. They were randomly assigned to receive either chemotherapy alone or chemotherapy combined with regional hyperthermia. Treatments were given before and after surgery and radiation therapy.

Patients who received the combination therapy had a median disease-free survival of 31.7 months, compared to 16.2 months for those receiving the chemotherapy alone. The median local progression-free survival was 45.3 months in the combined therapy group, compared to 23.7 months for patients who received chemotherapy alone. Improved tumour responses were seen in patients receiving the combined therapy (*Proc Am Soc Clin Onc 2007 #10009*).

'This is the first randomized phase III clinical trial ever conducted in the use of regional hyperthermia in combination with standard chemotherapy,' said lead author Dr. Rolf D. Issels (Munich University Medical Center, Germany). 'The take-home message is that precise targeting of regional hyperthermia can now be routinely applied to patients with locally advanced, high grade soft tissue sarcoma.'

Ginseng 'may reduce fatigue'

The herb ginseng could help reduce cancer-related fatigue, a pilot study has found (*Proc Am Soc Clin Onc 2007 #9001*).

Until now, the only proven way of reducing fatigue is for patients to exercise regularly and other treatment options are needed. Ginseng, long used in traditional Chinese medicine, is promoted as an adaptogen (a product that increases the body's resistance to stress) and is already used by many cancer patients. However, to date, no rigorous scientific study on its true benefit has been conducted.

In this study, 282 patients were randomly assigned to receive either placebo or one of three daily doses of American ginseng. After 8 weeks, a quarter of the patients taking the higher daily doses perceived feeling at least moderately better, compared to only 10% for those taking the lowest dose or placebo. One third of the patients on the two higher doses also reported being satisfied with the treatment, compared to 24% of those patients on the lowest dose and just 13% on the placebo. Additionally, ginseng was well tolerated.

'Further studies are needed to determine the definite benefit, and we cannot recommend routine use of ginseng for fatigue in cancer patients at this time,' said Dr. Debra Barton, the study's lead author (Mayo Clinic, Minnesota).

Dose scheduling optimisation 'may overcome pleural effusions'

Dose schedule optimisation of dasatinib (Sprycel) could provide the key to reducing pleural effusions in chronic myeloid leukaemia (CML), suggests a study presented at 12th Congress of the European Hematology Association, (June 7–10, 2007, Vienna, Austria). Pleural effusions necessitate dose reductions and/or interruptions and can restrict the overall efficacy of treatment.

In the phase III study (*Proc Eur Hem Assoc 2007 #0359*), 662 patients with chronic phase CML which was resistant or intolerant to imatinib were randomised to receive one of four doses of dastatinib:.100 mg QD, 50 mg BID, 140 mg QD or 70 mg BID. At a median duration of treatment of 8 months, similar haematologic and cytogenetic response rates and progression free survival results were observed in all groups. Side effects, however, were significantly different. Pleural effusions and thrombocytopenia were both markedly reduced in the 100 mg QD group compared with the current standard, 70 mg BID arm (P=0.024 and P=0.004 respectively). In addition, there were fewer dose interruptions and the lowest number of patients discontinued treatments for drug-related toxicity in the 100 mg QD group.

Presenting the data, Professor Andreas Hochhaus, (Universität Heidelberg, Annhein, Germany) said: 'The study shows that we can optimise side effects without impairing the efficacy of dasatinib. My personal recommendation is that patients should now be given 100 mg QD, but this requires further registration.'

A second study (*Proc Eur Hem Assoc 2007 #0360*) showed dasatinib to be effective and have an acceptable safety profile as a first line treatment in patients with previously untreated CML. In the phase II study, 35 patients with previously untreated chronic phase CML were randomised to either 100mg of dasatinib once daily or 50 mg twice daily.

Results showed that 77 % of patients at 3 months, 92 % at 6 months and 95 % at one year had a complete cytogenetic response. This compares favourably with historical data on patients treated at MD Anderson who took imatinib (Glivec) as first-line therapy.

Dr. Ehab Atallah (University of Texas M.D. Anderson Cancer Centre, USA), said: 'Our hypothesis is that treating with dasatinib first will produce an earlier response, which may translate to a better overall survival. We haven't proved it here, but these early results are encouraging.'

Dasatinib received its EU licence in November 2006 and is currently approved for use in patients whose disease is unresponsive or becomes resistant to imatinib.

Janet Fricker

Nilotinib in imatinib-resistant patients

Nilotinib (Tasigna) demonstrates a low rate of cross-intolerance with imatinib, reports a study by G Rosti (Institute of Hematology and Oncology, Bologna, Italy).

In the study (*Proc Eur Hem Assoc 2007 # 0860*), 316 imatinib-resistant or intolerant patients with CML in chronic phase were treated with nilotinib. Researchers found that 70 % of patients were imatinib resistant and 30 % were imatinib intolerant. Major cytogenetic response was observed in 52% of patients, of which 34% were complete. Approximately one third of patients had Grade 3 and 4 thrombocytopenia and leukopenia, but no serious episodes of fluid retention; pleural or pericardial effusions were observed.

Clinical trials are due to start for nilotinib in newly diagnosed chronic CML patients and chronic phase patients with a suboptimal cytogenetic response. Nilotinib is currently under review in Europe and the US for use in imatinib resistant and intolerant patients.

Janet Fricker was sponsored by BMS to attend the EHA meeting

Positive opinion for nelarabine

The European Medicines Agency (EMEA) has given nelarabine solution (Atriance) a positive opinion for the treatment of rare, difficult to treat leukaemias and lymphomas. The opinion covers patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to, or has relapsed following, treatment with at least 2 chemotherapy regimens.

There are only a few hundred cases of relapsed T-ALL each year in Europe. Patients with T-ALL and T-LBL tend to have a worse prognosis than patients with B-cell disease.

Nelarabine, made by GlaxoSmithKline (GSK), is administered intravenously and is converted first to ara-G and then to its active form, ara-GTP. Accumulation of ara-GTP in cells inhibits DNA synthesis and results in programmed cell death.

The EMEA's opinion was based on 2 multi-centre phase II trials, one in adults and the other in children (<21 years old). Adverse effects included haematologic toxicity, fatigue and nausea; severe neurological events have been reported.

Dr Paolo Paoletti, GSK's global head of oncology research, said, 'Nelarabine may offer some patients the chance to go on to have potentially curative treatment, such as a stem cell transplant.'

Nelarabine received EMEA orphan drug status in June 2005, and, following the positive opinion, will now be considered by the European Commission for final marketing approval. In the US, where it is marketed as Arranon, it received orphan drug status in December 2003 and FDA approval in October 2005. Registration dossiers have been filed in Canada, Japan, Switzerland and Israel.

EJC News is edited by
Helen Saul
Tel.: +44 1865 843340,
E-mail address: h.saul@elsevier.com

PODIUM

Methodology in the Middle East

Dr. Mohamed Meshref (Cairo University and Kasr El Einy Cancer Centre, Cairo, Egypt) trained in Egypt and France and his main research interest lies in the treatment of bone and soft tissue sarcoma. He is a member of ASCO's international committee. In 2004, he attended the Flims workshop on methods in clinical cancer research and he is now attempting to disseminate ideas on methodology throughout Egypt.

How important was the Flims workshop to you?

It was one of 2 opportunities which changed my life: Flims, and receiving an international development and educational award from ASCO. In the Middle East, we think of Flims as more for European fellows, so it was a nice surprise when I was accepted.

What protocol had you suggested?

The project looked at customising treatment between high and low risk patients with Ewing's sarcoma, according to risk factors. The idea changed in discussions with my mentors, Jaap Verweij and Fatima Cardoso. You go to Flims with an amateurish idea and come back with professional way of thinking about clinical research. I set up the study on my return and it is still ongoing. Accrual is nearly finished and I'm expecting to follow up until the end of 2008.

Is there a research culture in Egypt?

Oncology was established as a specialism in Egypt in the 1950s and we have a lot of research but it is all on a small scale. Each centre is on its own; we don't have a multi-centre set-up, or cooperative groups. Our research groups are seldom approved to join European groups like EORTC; only a couple of people in the country have groups which are part of EORTC. It is difficult to set up working groups because the structure isn't there; there is no co-ordination between centres.

You came back from Flims with more than a study protocol?

I came back full of ideas. I began by giving small lectures to the younger generation of oncologists, trying to transmit the knowledge I'd gained on how to do clinical research. Then in the faculty where I'm lecturer, I began supervising research work and could implement what I had learnt.

The next step, 6 months ago, was to get together a group of people from different centres throughout Egypt and agree on a broad outline for cooperative work. We are setting up a multi-centre study on capecitabine (Xeloda) in metastatic breast cancer. It will involve 4 centres in Egypt: 2 in Cairo, and 2 outside. We wanted to see if we could agree on the protocol and how to co-ordinate the trial. If this trial is successful, the group will expand and more people will join.

What has been the Egyptian establishment's response to your ideas?

I have targeted my own generation of younger physicians and consultants who are craving for a better way of doing things. They are excited about making changes. Established heads of centres or departments are either not interested or they don't have the time: they may be heavily committed to other projects, and would find it difficult to become part of a cooperative group. We do not ask for their time; but we have to get approval for projects through committees. In general, though, if protocols have been accepted by ASCO or EORTC committees, they will approve them.

We are starting on a small scale with our multicentre study, and we want to use it to create a system of communication between ourselves. I don't know yet what will happen but I hope we will be able to overcome problems.

Are you looking to work with centres outside Egypt?

My aim is to create a cooperative group for Egypt and the surrounding area which focuses on research which is appropriate here. The emphasis in Europe or the US is on targeted therapy.

Here, questions on chemotherapy need to be explored, and research on epidemic diseases – liver and bladder cancer – needs to be conducted. Our problem is not a lack of ideas, but the system and organisation needed to carry out the trials.

We have to start with successful projects within countries and build good relationships. Once a strong core organisation exists, then we can take the next step.

What is your goal for the next 5 years?

To continue disseminating ideas about methods in clinical cancer research in the area. I'd like to get together the support and sponsorship for an annual workshop in Cairo. It would be difficult to replicate the practical part of Flims, but we could run a workshop for the whole area. We could have 3 to 4 days of lectures.

A lot of people here have no concept of clinical trials. Next year, there is a one-day advanced ASCO course in Egypt, so if this gets a good response, I would like to expand it into a mini-Flims.