

HOT SPOT

The Newsletter of the Rapid Response Radiotherapy Program
of the Odette Cancer Centre



Volume 10, Issue 2, May 2008

Editorial

By Cyril Danjoux, MD, FRCP(C)

The days are getting longer and the temperature is climbing. Spring has arrived.

Congratulations to Dr. Mary Vachon, our long-time, loyal contributor to **Hot Spot**, who was awarded the Lifetime Achievement Award for 2008 by the **International Journal of Palliative Nursing** in London, England, March 7, 2008. Since she left Sunnybrook, Dr. Vachon has been awarded the National Hospice and Palliative Care Researcher of Distinction for 2001, and her Professorship at the University of Toronto. Her article in this issue is entitled Resilience in Professional Caregivers, which complements the one in the last issue on Resilience in patients and family members.

Who benefits from referral to palliative medicine services? The article by Dr. Leah Steinberg, Dr. Anita Chakraborty and Dr. Niren Shetty describes the project to answer that question by the Mount Sinai team.

Advanced Directives is a brave attempt to ensure that we get what we want during end-of-life care. Some of the medico-legal and ethical issues are addressed by Blair Henry in his article, Advanced Directives or Advanced Troubles?

In children, advanced care planning is even more complex. Maria Rugg addresses the limited use of advance directives and challenges within pediatrics in her article Advanced care planning in pediatric palliative care.

The educational insert by Dr. Anne Horgan and Dr. Jennifer Knox is about Sorafenib in the treatment of advanced hepatocellular cancer.

Our colleagues saw their work recognized by many awards. Three years in a row, RRRP students have won the prestigious Marion J. Todd Memorial Award (Cli Epi) from the University of Waterloo. Amanda Hird is the winner of Marion J. Todd Memorial Award. In 2006, Kristin Harris and Meagan Doyle from RRRP shared the award and Nicole Bradley was the winner in 2005. Amanda Hird, Kristin Harris and Nicole Bradley also won the Student of the Year in their faculty three years in a row.

Kate Gardiner, the student of Dr. Jeff Myers, received the 2007 Science Co-op Student of the Year award. Amanda and Kate were chosen to represent the

University of Waterloo in the national and provincial co-op competition. Dr. Jeff Myers was awarded the National Employer of the Year by the Canadian Association for Co-operative Education for 2008. At the 18th Annual Ontario Provincial Conference on Palliative and End-of-Life Care, Amanda Hird and Shaelyn Culleton both won the Best Oral Presentation award. Dr. Lawrence Librach received the Dorothy Ley Award of Excellence. We are very proud of our colleagues and students for their accomplishments.

Relax and enjoy the spring issue of **Hot Spot**.

Resilience in professional caregivers

By Mary Vachon, RN, PhD

The last issue of Hot Spot addressed resilience in patients and family members, reflecting on my nephew Andrew and his new bride, Katherine. On February 8, Andrew's 28 birthday, Katherine died. Her funeral was held on their three-month wedding

anniversary. Katherine was a planner. When they were unable to go on their honeymoon, she planned to go to England to say goodbye to her grandmother. She was in England the week before she died, accompanied by

continued on page 2...

In this issue of HOT SPOT:

Resilience in professional caregivers

Are some GIM patients missing a palliative medicine consult when they might benefit from it?

Advanced directives or advanced troubles?

Advance care planning in pediatric palliative care: Do we really know what they are asking?

Dr. Mary L.S. Vachon

Improving cancer pain control: Helping patients to gain the most benefit from their medication

Dr. S. Lawrence Librach

Continuing Medical Education

Insert:

Sorafenib in the treatment of advanced hepatocellular cancer

Are some GIM patients missing a palliative medicine consult when they might benefit from it?

By Leah Steinberg, MA, MD, CCFP, Anita Chakraborty, MSc, MD, CCFP, and Niren Shetty, MD, CCFP

The Palliative Medicine Consult Service (PMCS) at Mount Sinai Hospital performs consultations for approximately 400 patients per year. These patients are referred primarily from the surgical and general internal medicine (GIM) services. The majority of referrals from these services are for patients with a diagnosis of metastatic cancer. In the 2006/2007 fiscal year, Mount Sinai's GIM admitted more than 2,000 patients. Of those admissions, approximately 275 patients were

referred to the palliative medicine service. With the support of the Centre of Excellence in Medicine at Mount Sinai Hospital, we are undertaking a chart audit of patients admitted to GIM to determine if there are additional patients who might benefit from referral to the PMCS.

There are very few audits of this nature published in the medical literature. Unfortunately, there is also no validated tool for determining which patients would benefit from a referral to

a consult service in palliative medicine. A Hamilton-based group, Slaven et al. (2007) recently developed and described a tool for collecting these data. Using this tool, we are undertaking a chart audit of a random sample of 250 charts of patients admitted to the GIM service at MSH over the fiscal year 2006/2007. With these data, we can begin to examine the palliative medicine needs of the GIM patients at MSH, as well as the future personnel requirements for our PMCS at MSH.

Resilience in professional caregivers

... continued from page 1

Andrew and one of her bridesmaids who served as her "lady's maid". Her spirit will live on in those whose lives she touched.

Ablett and Jones (2007) studied resilience and well-being in palliative care nurses. Drawing on the work of Rutter (1985), they note that the promotion of resilience does not lie in an avoidance of stress, but rather in encountering stress at a time and in a way that allows self-confidence and social competence to increase through mastery and appropriate responsibility. They used a qualitative methodology to describe hospice nurses' experience of their work to understand the factors that help to promote resilience and mitigate the impact of workplace stress and to explore the processes nurses use to continue to work in palliative care and maintain a sense of well-being. Themes from the analysis related to underlying interpersonal factors that influenced nurses' decisions to begin and continue working in palliative care, and their attitudes towards life and work and to

each nurse's "job-person fit". Emergent themes included concepts such as the following: an active choice to work in palliative care, past personal experiences influencing caregiving, personal attitude towards caregiving, personal attitudes toward life (and death), awareness of one's own spirituality, and personal attitudes towards work. Central to these themes was the extent to which nurses chose to work in the area of palliative care and were committed to it, believing they "could make a difference" to the people for whom they were providing care. Awareness of both their own mortality and spirituality were additional prominent themes. The authors compared the nurses' sense of purpose about their work and involvement with two theoretical concepts from the literature that explain resilience, the personality constructs of hardiness and a sense of coherence. Hardiness involves a sense of commitment, control and challenge. Commitment refers to a sense of meaning and purpose in life; control refers to a sense of autonomy over one's life; and challenge is akin to a zest for

life that leads an individual to perceive change as an opportunity for growth. Change, rather than stability, is seen as normal. Coherence sees one's life as being comprehensible, manageable and meaningful.

The nurses exhibited high levels of commitment and imputed a sense of meaning and purpose to their work. Comparing the data obtained from the nurses with the construct of hardiness, all of the nurses in the study had a high degree of commitment to their role and perceived themselves to have a high degree of control and autonomy over their workload. Some viewed the challenge associated with work as an important factor in gaining a sense of satisfaction and achievement, but others disliked change and preferred a degree of stability in their work.

When the themes were compared with sense of coherence, the nurses ascribed meaning to their work, and a sense of purpose. They perceived their work as manageable, and were driven by a wish to meet the needs of their patients and enhance their quality of life. An awareness of their own

Advanced directives or advanced troubles?

By Blair Henry, Clinical Ethicist, Sunnybrook Health Sciences Centre

The judge stood beside her bed, speaking softly, catching but unable to hold her gaze: “I can tell you that it will be more difficult for me to render my decision after having met you, but I wish you good luck. And if you change your mind, the court will be very happy, but I understand. I want to say goodbye and I will think a lot about you...”

(The words of Justice Dufour of the Quebec Superior Court, in rendering his decision in the Case of Nancy B., 1992.)

These words were taken from the seminal Canadian case involving a young woman from Quebec in her early twenties, stricken by a paralyzing disorder, ventilator dependent, and unable to breathe on her own: Nancy B. concluded that she could not go on. However, the medical team who’d looked after her for more than two

mortality and spirituality led them to perceive aspects of their work as comprehensible. Those nurses that disliked change indicated their need for stability in an uncertain world. The authors suggested there was a divergence in the data about response to change; this was consistent with the main variance between a sense of coherence and a sense of hardiness. There is a need for stability inherent in a sense of coherence and change is seen as exciting opportunity for growth in hardiness. The authors suggest that a sense of coherence might explain resilience for some caregivers, while hardiness explains resilience for others. The key factor seems to be the individual’s attitude towards change. The implications for staff training and support suggest that factors promoting resilience, particularly hardiness and a strong sense of coherence, could be developed through staff training packages. Reflective practice may enable staff to acknowledge the impact of working in end-of-life care and to address their own issues.

years was uncomfortable in granting her wish; necessitating the legal system to step in to make the final decision. Her wish was granted and Nancy B. died peacefully (by all accounts) under mild sedation.

Canadians (on both sides of the bed) naturally disdain the idea of having the legal system used as a means to reaching what, at first glance, seems to be a clearly medical decision. However, I fear that unless we can navigate managing differences more effectively this, too, may change in the future! Many are awaiting the recent Winnipeg ruling with some fear and trepidation.

From a bioethical perspective, people like Nancy B. were seen as heroes. She, along with several others over the past 40 years, have established common-law precedents in Canada, which have effectively forged a means to solicit, hear, and appreciate the patient’s wishes into the medical decision-making process—even when those wishes appeared contrary to best medical advice. To this end, legislation has been enacted that recognizes people want more control over decisions involving their own care. Defining best interest has been taken out of the realm of “objective science”, and placed squarely into the hands of the person living with its consequences.

Judge Dufour intimates how difficult it was for the court to make its ruling (and this after only knowing Nancy B. for a short period of time). One can only imagine how heart-breaking this must have been for the medical staff that, having cared for Nancy B. during the previous two years of her illness, was now charged with the task of withdrawing her life support. Makes one reconsider the definition of heroism—or at the very least expand its construct!

Public fears over protracted suffering, being trapped or locked into an existence you never wanted became commonplace both in real life (most recently in the Terri Schiavo case) and, more generally, in the public’s imagination thanks to a plethora of popular television dramas dealing with vexing life-and-death dilemmas. This culture coupled with a human propensity to disavow living in the moment—we’re not content with just thinking about how bad things are now—we want to project

misery and suffering into the future as well, and this has fuelled the advent of advanced directives.

However, despite its dramatic initiation into the medico-legal world, the popularity of advanced directives hasn’t yet translated itself into common public practice. In fact, I would venture to say if its ideals are being kept alive today, it’s coming more from the medical than from the public sector! Soliciting advanced directives and treatment preferences is more often initiated by medical staff when patients enter the system. I believe that understanding the subtle forces driving this change in praxis might be illuminating!

Science has not outpaced the imagination of the common man—patients and families are more experienced with the medical system and in some cases they are now demanding more than what the medical team feels comfortable in delivering (Nancy B. in reverse!). The ethical and legal terrain of treatment withdrawal has been well explored and there is greater confidence in managing these on behalf of the medical team.

Concerns over the appropriate allocation of limited resources aside, questions over a lack of common understanding or societal consensus have come to the fore. Life still seems inherently valued—but to what cost? And by whom? What has happened to the debate between quality versus quantity of life? What has this meant to the once sacred place of death in our society? Is it so feared and so disvalued that life at all cost needs to be prescribed? Where once we feared getting sick, living with dependence and disability—has there been a subtle shift to where now we fear losing life itself at any cost?

In life there has always been a discord between wanting, needing, and getting. Medicine is no stranger to this discord. Advanced directives can help clarify the wanting, but without a fulsome discussion to balance out the needing and the getting we may be in store for more advanced troubles ahead.

I wonder what Judge Dufour would have to say now? But more importantly—to whom?

Advance care planning in pediatric palliative care: Do we really know what they are asking?

By Maria Rugg, RN, MN, CHPCN(C), Advanced Practice Nurse, Palliative and Bereavement Care Service, The Hospital for Sick Children

Limited use of advance directives or advance care planning within pediatrics relates to difficulties in using documents generally meant for an older population, structured often as discussions for physicians to have with patients. This is not a practical approach to the family-centred care philosophy taken in pediatrics. The few studies that have examined advance care planning in pediatrics thus far have been limited to the study of parental and adolescent attitudes to directives or end-of-life care planning. While it has been acknowledged that pediatric end-of-life care is very stressful on health care professionals (HCPs) for many reasons including: lack of knowledge, attitudes about death and dying, and lack of experience in death and dying. The difficulties in pediatric health care in understanding and predicting children's future needs and HCPs reluctance to confront emotionally challenging outcomes directly with parents often add to the limitations of the advance care planning process.

As a result, HCPs often feel unable to engage in and provide meaningful discussions with parents/guardians. In turn, parents/guardians do not consider it sufficient just to have their child's needs understood, but believe that their own

needs must also be well understood in order for them to feel engaged in "shared decision making". Recent studies have continued to highlight how ill equipped HCPs feel in having these types of discussions, and ongoing differences amongst how HCPs and families perceive these communications.

Discussions about end-of-life care often occur with families during the advance care planning process. However, lack of engagement by HCPs with families in these much-needed discussions has not been thoroughly explored. Family-centred care theory has become an essential construct of care delivery across the continuum of children's health care. Its broad concepts of parental participation, partnership and collaboration in decision making, and care of the entire family are reflective of similar constructs of the shared decision-making framework: partnership, shared decision making and completeness.

In general, most of the literature has focused on adults', surrogates' or health care professionals' understanding of, or use of advance care directives. Within pediatric health care, the literature has focused on adolescents with an oncology diagnosis and their parents, and their attitudes towards the use of advance directives. Children facing

life-threatening illness go beyond just oncology diagnoses and are often facing advancing chronic disease and frailty that have treatment goals that are continually changing and challenging families and health care professionals. The little pediatric literature that does exist states that parents want to engage in the process, but need to feel engaged and listened to. As is suggested by available research, living with a child who has progressive life-threatening illness has a profound impact on families, often resulting in a multitude of disruptions that affect their quality of life. As HCPs, we often intervene to promote the health and welfare of families, but we often do not have a clear understanding of what kind of support is appropriate or how to provide that support. Often what impedes that type of support is lack of knowledge about legislation or what to say, experience in end-of-life care and our own attitudes around end-of-life care planning. In the spirit of the advance care planning process, the shared decision-making model as a conceptual framework provides an excellent framework to begin to explore how to frame advance care planning as a relatively unknown and unexplored frontier in communication with children and families in the world of pediatric palliative care.

Dr. Mary L.S. Vachon



Dr. Mary L.S. Vachon is a nurse, psychotherapist, author and cancer survivor who has given more than 1,600 lectures around the world on issues related to occupational stress, cancer, bereavement, survivorship, and spirituality. She has written more than 160 publications including the chapter on The Emotional Care of the Dying Person for the **Oxford Textbook of Palliative Medicine** (editions 1-4), and has written the chapters on occupational stress in oncology and

palliative care specialists in several leading international textbooks for physicians, nurses and other health professionals.

Dr. Vachon has worked at Massachusetts General Hospital, the Clarke Institute of Psychiatry and Sunnybrook Health Sciences Centre. She is currently a Psychotherapist and Consultant in Private Practice, Professor in the Departments of Psychiatry and Public Health Sciences at the University of Toronto and Clinical Consultant at Wellspring, of which she is a co-founder.

She is the recipient of many awards including: the Mara Morgenson Flaherty Lectureship of the Oncology Nursing Society for Excellence in Psychosocial

Oncology in 1985, the Carmelita Lawlor Lectureship in Community Palliative Care, Department of Family and Community Medicine, University of Toronto, 1995, the Dorothy Ley Award for Excellence in Palliative Care received from the Ontario Palliative Care Association in 1997, an Alumnae Achievement Award from Massachusetts General Hospital Nurses' Alumnae Association, 1998, the National Hospice and Palliative Care, Distinguished Researcher Award, 2001 for her continued contribution to the field of palliative care from the beginning of the specialty until the present time, and the Lifetime Achievement Award of 2008 of The International Journal of Palliative Nursing.

Improving cancer pain control: Helping patients to gain the most benefit from their medication

By Carlo DeAngelis, PharmD

Despite our heightened awareness of the occurrence of cancer-related pain, its effective management remains a challenging clinical problem. There are many factors that have been identified as contributing to poor cancer pain control. From the health care professional perspective, knowledge, attitudes and misconceptions about the use of opioids remain significant barriers to adequate pain control in our patients. Similar barriers exist for patients and their caregivers. This knowledge gap and associated misconceptions in our patients and their caregivers may manifest as poor adherence to a prescribed regimen, thus contributing to poor pain control.

The appropriate prescribing of analgesic medication is only the first step to good pain control. Patient non-adherence to their analgesic regimen may be related to factors such as a poor understanding of how to use their medication, lack of a well-defined goal/outcome, misconceptions about the use and effects of opioid medications, experience of side effects and the

influence of family members, caregivers and friends. In addition, it is not surprising that patients and caregivers find it difficult to maintain adherence to a prescribed medication regimen as, often, these patients are on an average of five or six medications.

Part of the solution to ensuring patient adherence to recommended pain management therapy is recognizing the potential for the occurrence of non-adherent behaviour. Only then can we begin to ask the questions to identify patient concerns that contribute to poor medication-taking behaviour and implement strategies that facilitate good medication-taking behaviour. The solutions need to be built on a foundation of a good medication history, which not only identifies what medications patients are taking and how, but what they know about the medication, what their expectations are with respect to pain control from the prescribed regimen and whether they are experiencing side effects or have any difficulties or concerns in taking their medications.

From this foundation, we can begin to modify our prescribing to facilitate the taking of analgesic medication, manage side effects and educate our patients. Our education of the patient and/or their caregiver must focus on the importance of taking medication as prescribed and the purpose of the various medications being prescribed with a clear explanation of how they should be taken, as well as the prevention and management of side effects. Our evaluation of barriers to good medication-taking behaviour and patient/caregiver education must be ongoing. As the patients' disease progresses, new symptoms will arise along with new concerns and questions from the patient/caregiver about the prescribed medication regimen. It is our responsibility, as members of the patients' care team, to provide the patients and their caregivers with the knowledge and tools that will facilitate the taking of the medication regimen as prescribed. Only then can patients expect to gain the most benefit from their medication.

Dr. S. Lawrence Librach

Dr. Librach's involvement in palliative care began in 1978. Dr. Librach now serves as the Director of The Temmy Latner Centre for Palliative Care at Mount Sinai Hospital. This centre includes a Home Palliative Care Program, an Inpatient Palliative Care Consult Team, a Psychosocial-Spiritual Program, a Children's Program and academic programs in education and research.

Dr Librach is the W. Gifford-Jones Professor in Pain Control and Palliative Care at the University of Toronto, where he also holds the position of full professor in the Department of Family and Community Medicine. He is the Director of the Division of Palliative Care in the Department of Family and Community Medicine at the University of Toronto. Dr. Librach is also an associate in the

Joint Centre for Bioethics and the Centre for Studies in Pain at the University of Toronto and the Buehler Centre for Aging at Northwestern University in Chicago. He was the physician leader of the national Educating Future Physicians for Palliative and End of Life Care Project (EFPPEC), which introduced curriculum in palliative and end-of-life care to Canada's 17 medical schools. He is an education consultant to the Education in Palliative & End of Life Care (EPEC) project in the U.S. He is a member of the board and president of the Canadian Hospice Palliative Care Association.

Dr. Librach is the recipient of a number of awards from a number of organizations including the Canadian Hospice Palliative Care Association, the Ontario Palliative Care Association, the

College of Physicians and Surgeons of Ontario, and the University of Toronto.

Dr. Librach's academic interests are wide-ranging, but the development and implementation of education programs is an area of special interest. He has delivered more than 500 lectures and workshops.

Dr. Librach has published extensively and is the author of the **Pain Manual** (more than 150,000 copies distributed) and co-edited a textbook, **Palliative Care: Core Skills and Clinical Competencies**.



Continuing Medical Education 2008

By Ewa Szumacher, MD, MEd, FRCP(C)

Continuing Medical Education (CME) can update health care professionals on the latest advances for modifications to their clinical practice. At the request of the CME organizers, Hot Spot will list the national and international CME activities in palliative medicine that are of interest to our readers. Please kindly forward details of the CME activities to:

Ewa.Szumacher@sunnybrook.ca

• April 29-May 1, 2008 – **The 7th Palliative Care Congress, The Palliative Care Research Society, The RCN Palliative Care Nursing Group and The Association for Palliative Medicine of Great Britain and Ireland**, Glasgow, United Kingdom,
www.pccongress.org.uk

• May 2-4, 2008 – **Catholic Health Association of Canada's 2008 Annual Convention 400 Years: Full of Spirit – Full of Life**, Quebec City, Quebec, Tel: (613) 731-7148 ext: 257, **www.chac.ca**, **sdeliencourt@chac.ca**

• May 8-9, 2008 – **Providence Health Care Conference Spirituality: The Invisible Ingredient in Health & Healing**, Vancouver, British Columbia, Tel: (604) 806-8528, **psihota@providencehealth.bc.ca**

• May 28-31, 2008 – **5th Research Forum of the European Association for Palliative Care (EAPC)**, Trondheim, Norway, **www.eapcnet.org/congresses/Research2008.html**

• June 4-8, 2008 – **5th World Conference on Breast Cancer**, Winnipeg, Manitoba, **www.wcbcf.ca**, **admin@wcbcf.ca**

• August 17-22, 2008 – **12th World Congress on Pain, The International Association for the Study of Pain**, Glasgow, United Kingdom,
www.iasp-pain.org/2008Congress.html

• October 26-29, 2008 – **2008 Canadian Hospice Palliative Care Conference**, Charlottetown, Prince Edward Island,
www.chpca.net

Continuing Medical Education Activities

• University of Western Ontario Certificate in Palliative Care and Death Studies (on-line)

• Service Provision in Hospice/Palliative Care, **www.advancedprofessional education.com**

• Hospice Palliative Care Multidiscipline Certificate – Humber College,
pamela.mckintuck@humber.ca

• Temmy Latner Centre for Palliative Care – Mount Sinai Hospital,
www.tlpc.org

• RTS Perinatal Bereavement Support Training, **www.pbso.ca**

• Comprehensive Bereavement Skills Training – COPING Centre – Cambridge,
www.griefsupport.cc

• Humber College Annual Conference on Palliative Care – Toronto,
www.palliativecare.humber.on.ca

• Ian Anderson Continuing Education in End of Life Care – Toronto,
www.cme.utoronto.ca/endoflife/

• Bereavement Ontario Network Conference (each September),
www.bereavementnetwork.ca

• National Conference of Hospice Palliative Care – Canada,
www.chpca.net

• Palliative Care Certificate Program, Distance Program – Grant MacEwan College, Edmonton,
www.macewan.ca/palliative

• Compassionate Care for the Terminally Ill (4 non-credit distance program) – Grant MacEwan College, Edmonton,
www.macewan.ca/palliative

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Sorafenib in the treatment of advanced hepatocellular cancer

HOT SPOT

By Anne Horgan, MB, BCh, MRCPI, and Jennifer Knox, MD, MSc, FRCPC

Background

- Hepatocellular cancer (HCC) is the sixth most common cancer in the world
- Third most common cause of cancer-related mortality globally
- One of the few cancers that has incidence and mortality rates that are increasing in western countries
- 1,350 Canadians diagnosed with HCC in 2007
- Important risk factors include: Hepatitis B, Hepatitis C, all causes of cirrhosis, including alcohol abuse and metabolic diseases, as well as environmental toxins (e.g., aflatoxin)

Treatment options for advanced hepatocellular cancer

- Treatment is challenging as there are two disease entities: the malignant tumour with the propensity to invade underlying vascular structures and the cirrhotic liver
- Hepatic reserve, as indicated by the Child-Pugh classification, as well as disease stage, dictates therapeutic options
- 50% to 60% of patients present with advanced, inoperable disease, with a median survival of six months
- Systemic treatments using chemotherapy (doxorubicin or combinations) have not shown a survival benefit in patients with advanced HCC

Sorafenib

- Sorafenib is a multitargeted, orally active, small molecule tyrosine kinase inhibitor. It blocks tumour cell proliferation by targeting the Raf kinase signalling pathway and has an antiangiogenic effect by targeting the intracellular portion of the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)

Evidence for Sorafenib for the treatment of HCC

Phase II Single Agent Therapy:

- International, phase II study in advanced HCC
- 137 patients—Child-Pugh A (72%); Child-Pugh B (28%)
- 41.6% achieved partial response, minor response or stable disease
- Most common grade three toxicities reported were fatigue (9.5%), diarrhea (8%) and hand-foot skin reaction (5.1%). No grade four toxicities
- Comparison between Child-Pugh A and B patients revealed similar adverse events and dose intensity delivered between the two groups

Phase II Combination Therapy:

- Randomized phase II study, with 96 patients (see Table One)
- Doxorubicin plus sorafenib compared to doxorubicin plus placebo

- Most common grade three-four toxicities reported in the combination compared to the placebo arms were neutropenia (53% versus 46%) and fatigue (15% versus 15%), most certainly due to the doxorubicin
- Although this trial is strongly positive in favour of the doxorubicin plus sorafenib combination, it requires further study to determine if the benefit was owing to a positive interaction in the combination arm or to sorafenib alone

Phase III trials: SHARP

- The landmark SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial was the first phase III study to demonstrate an improved survival benefit for any drug in HCC (HR 0.69), positioning sorafenib as the new reference standard of care in advanced disease (see Table Two)

Table One.			
	Doxorubicin+ Sorafenib (n = 47)	Doxorubicin+ Placebo (n = 49)	<i>P</i> -value
TTP (months)	8.6	4.8	0.076
DCR (%)	81	57	
CR	0	2	
PR	4	0	
SD	77	55	
OS (months)	13.7	6.5	0.0049 (HR 0.45)
(TTP: time to progression; DCR: disease control rate; DCR=CR+PR+SD; CR: complete response; PR: partial response; SD: stable disease; OS: overall survival; HR: hazard ratio)			

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- This was an international, double-blind, Phase III, multicentre, randomized trial comparing sorafenib to placebo in patients with advanced HCC. Eligible patients were not suitable for other local or curative therapies, had preserved liver function (Child-Pugh A) and good performance status. Many had progressed after prior local therapies and chemo-embolization
- Overall, sorafenib was well tolerated (Table Three). Both arms had similar rates of serious adverse events (SAEs). The most frequently reported grade three or four SAEs in the sorafenib compared to the placebo arms were diarrhea (8% versus 2%) and hand-foot skin reaction (8% versus <1%)
- Time to symptomatic progression (TTSP) as measured in this study was not

different from placebo. The quality of life (QoL) endpoint warrants further study in this disease

- The survival advantage of 2.8 months is modest, but is in keeping with accepted progress seen in other refractory end-stage cancers with systemic agents. The median survival of 10.7 months is superior to any other median survival reported for advanced HCC in modern trials

Phase III Trials: Asia-Pacific Liver Cancer Trial

- The Asia-Pacific Liver Cancer Trial is a double-blind, randomized, placebo-controlled Phase III trial that has recently been completed
- 226 patients from China, Korea and Taiwan were enrolled and received either 400mg Sorafenib bid or placebo

- The results of this trial have not yet been published or presented. However, in August 2007 this trial was stopped early on the recommendation of the independent data monitoring committee after a planned review. This review demonstrated significantly improved overall survival, progression-free survival and time to progression in the sorafenib arm as compared to the placebo arm. Assuming this trial meets peer review standards, it is likely to lend further support for sorafenib in a more diverse HCC population

Conclusion

- Sorafenib, 400mg bid is the new standard for first-line treatment of advanced hepatocellular cancer

- While the benefits demonstrated to date are modest, it is the first agent to confer a survival benefit to patients with advanced HCC and validates the study of targeted agents in this challenging disease. The results to date support the use of sorafenib in similar patients to the SHARP trial

Future directions

- Assessment of sorafenib—in the adjuvant setting, after potentially curative treatments
 - after chemo-embolization
 - in patients with Child-Pugh B liver dysfunction
- Assessment of targeted agent combinations, to build on the benefit of sorafenib alone

	Sorafenib (n=299)	Placebo (n=303)	HR (95% CI)	P-value
Overall Response, n(%)				
CR	0	0		
PR	7(2.3)	2(0.7)		
SD	211(71)	204(67)		
PD	54(18)	73(24)		
TTP (months)	5.5	2.8	0.58 (0.44-0.74)	0.000007
TTSP (months)	NS	NS		0.77
OS (months)	10.7	7.9	0.69 (0.55-0.88)	0.00058

(CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; TTP: time to progression; TTSP: time to symptom progression; OS: overall survival; NS: non-significant)

Drug-related AEs (%)	Sorafenib		Placebo	
	All	Grade 3 / 4	All	Grade 3 / 4
Diarrhea	39	8	11	2
Hand-foot skin reaction	21	8	3	<1
Weight Loss	9	2	<1	0
Pain	8	2	3	<1
Vomiting	5	1	3	<1
Alopecia	14	0	2	0
Anorexia	14	<1	3	<1
Nausea	11	<1	8	1
Liver dysfunction	<1	<1	0	0
Bleeding	7	<1	4	<1