HOT SPOT

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

10 years

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Volume 11, Issue 3, August 2009

Editorial

By Cyril Danjoux, MD, FRCP(C)

This issue of **Hot Spot** has two educational inserts: the first is written by Dr. Rena Buckstein about chronic lymphocytic leukemia (CLL) and the second by Drs. Mark Pasetka and Carlo DeAngelis on "Treatment of chemotherapy- and radiotherapy-induced nausea and vomiting (CINV/RINV)."

Dr. Monica Branigan provides us with useful insights in her article entitled "Limits of the duty of care: Lessons from the Golubchuk Case."

Ms. Gunita Mitera, Drs. Alysa Fairchild and Rebecca Wong share with us their research on "A multi-centre assessment of the adequacy of cancer pain treatment using the Pain Management Index."

Dr. Carlo DeAngelis continues to inform us on "Opioid dose equivalency: Part 3—Opioid switching with morphine-like opioids."

Dr. Ewa Szumacher has once again compiled the latest events in continuing medical education. Ms. Gunita Mitera provides us with a review of the Annual Hospice Palliative Care Conference, which took place in April 2009. We hope you continue to find this issue of **Hot Spot** informative, useful and enjoyable.

Limits of the duty of care: Lessons from the Golubchuk case

By Monica Branigan, MD, MHSc (Bioethics)

Samuel Golubchuk died at the age of 84 on June 24, 2008, after seven-and-a-half months on life support in a Winnipeg ICU. His case raises many questions about decision-making at the end of the life and the limits of physicians' and other health care providers' duty to care. When admitted to the ICU in December, Mr. Golubchuk was provided with life support, as it was hoped that his pneumonia was reversible. Eventually, his doctors wanted to remove the life support and feeding tube when they were convinced that the therapy did not have the ability to restore organ function. The family refused on the grounds that Mr. Golubchuk was an Orthodox Jew and would want aggressive measures to preserve life. The family sought and received an interim injunction from a judge on February 13 that prevented the team from removing life support until the matter could be settled in court. Three physicians from the ICU team felt that they could no longer ethically provide treatment to the patient and removed themselves from the case. In May, one of the physicians wrote that further treatment was "tantamount to torture." "This is grotesque. To inflict this kind

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In this issue of HOT SPOT:

A multicentre assessment of the adequacy of cancer pain treatment using the Pain Management Index

By Gunita Mitera, MRT(T), Alysa Fairchild, MD, and Rebecca Wong, MD

Pain secondary to bone metastases is often recurrent and debilitating for patients with advanced cancer. However, despite the existence of pain management guidelines such as those developed by the World Health Organization (WHO) in 1986 (revised in 1996), under-treatment of cancer pain remains prevalent. The Pain Management Index (PMI) developed by Cleeland et al. is a validated method of determining congruence between a patient's reported pain intensity and strength of analgesic prescribed (Cleeland, Gonin, Hatfield, Edmonson, Blum, Stewart, et al., 1994). This measure is endorsed by the Agency for Health Care Policy and Research (AHCPR) and WHO guidelines (Cleeland, Gonin, Hatfield, Edmonson, Blum, Stewart, et al.). A retrospective multicentre study was conducted where the primary objective was to determine pain management adequacy in patients with painful bone metastases, referred for out-patient palliative radiotherapy (RT) using the PMI. The secondary objective was to assess geographic differences in pain severity and PMI.

A retrospective review of data collected prospectively for patients referred to the Rapid Response Radiotherapy Program (RRRP), the Bone Metastasis Clinic, and the Pain Clinic at the Odette Cancer Centre (OCC) in Toronto, Ontario, was performed. Patient data from similar databases from the Palliative Radiation Oncology Program (PROP) at the Princess Margaret Hospital (PMH) in Toronto, and the Rapid Access Palliative Radiotherapy Program (RAPRP) at the Cross Cancer Institute (CCI) in Edmonton, Alberta, were also obtained after ethics approval was secured. Data from the OCC were collected from January 1999 to December 2008, while data from the PMH and RAPRP were available from 2007 to 2008. Data extracted included patient age, gender, Karnofsky Performance Status (KPS) and/or Palliative Performance Scale (PPS), primary cancer site, pain score on the Brief Pain Inventory (BPI) or the Edmonton Symptom Assessment System (ESAS), and analgesic use upon referral for RT consultation.

Cleeland's PMI was calculated by subtracting the patient-rated pain score at initial clinic visit from the analgesic score. Pain scores were assigned 0, 1, 2 and 3 when patients reported no pain (0), mild (1 to 4), moderate (5 to 6) or severe pain (7 to 10) respectively on the ESAS or BPI. Analgesic scores of 0, 1, 2 and 3 were assigned when patients were using no pain medication, non-opioids, weak opioids (e.g., codeine) and strong opioids (e.g., morphine) respectively. A negative PMI suggests inadequate pain management. Descriptive statistics were compiled and Chi-square test was used to evaluate the relationship between PMI and centre, and PMI and pain intensity.

Our study cohort consisted of 2,011 patients. The incidence of negative PMI and moderate–severe pain was 25.1% and 70.9% respectively. For each of the three participating centres, the incidence of negative PMI was 31.0%, 20.0%, and 16.8%, and this was significantly different ($p<0.0001$). The incidence of patient-rated severe pain was also significantly different and correlated with a negative PMI ($p<0.0001$) at 55.5%, 48.2%, and 43.4% respectively. Mild and moderate pain was not correlated with a negative PMI score.

Other authors have used the PMI to describe the incidence of under-medication. Of 26 international studies, the incidence of negative PMI scores ranged from 8% to 82% [weighted mean of 43%] (Deandrea, Montanari & Moja, 2008). In our patients with bone metastases presenting for consideration

Limits of the duty of care: Lessons from the Golubchuk case

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of assault on him without a reasonable hope of benefit is an abomination. I can't do it." (National Review of Medicine, 5(7), 2008 July)

When conflicts such as these reach a Human Rights Commission, tribunal or court they must balance the rights of physicians to conscience with those of their patients to religion. The College of Physicians and Surgeons of Ontario has suggested the following general principles to consider: (CPSO Policy: Physicians and the Ontario Human Rights Code)

- "There is no hierarchy of rights in the Charter; freedom of religion and conscience, and equality rights are of equal importance;
- Freedom to exercise genuine religious belief does not include the right to interfere with the rights of others;
- Neither the freedom of religion nor the guarantee against discrimination are absolute. The proper place to draw the line is generally between belief and conduct. The freedom to hold beliefs is broader than the freedom to act on them.
- The right to freedom of religion is not unlimited; it is subject to such limitations as are necessary to protect public safety, order, health, morals, or the fundamental rights or freedoms of others;
- The balancing of rights must be done in context. In relation to freedom of religion specifically, courts will consider how directly the act in question interferes with a core religious belief. Courts will seek to determine whether the act interferes with the religious belief in a "manner that is more than trivial or insubstantial." The more indirect the impact on a religious belief, the more likely courts are to find that the freedom of religion should be limited.

Of course, the real question is, are the courts the appropriate forum to resolve these issues? Many institutions have policies that clearly outline the process for conflict medication and negotiation.

of radiotherapy, this was 25%. Differences were observed between centres. Potential reasons for this may include differences in referral pattern, access to pain specialists, and how the pain score was captured, i.e., worse versus average pain. Further investigation into the reasons for these differences in the adequacy between centres may provide insight into improving pain management.

Details of this study will be presented at the Canadian Association of Radiation Oncology 23rd Annual Meeting in Quebec City, Quebec, and the American Society for Radiation Oncology 51st Annual Meeting in Chicago, IL.

References

Cleeland, C.S., Gonin, R., Hatfield, A.K., Edmonson, J.H., Blum, R.H., Stewart, J.A., et al. (1994). Pain and its treatment in outpatients with metastatic cancer. **N Engl J Med, 330,** 592–596.

Deandrea, S., Montanari, M., Moja, L., & Apolone, G. (2008). Incidence of undertreatment in cancer pain. A review of published literature. **Ann Oncol, 19,** 5–7.

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Opioid dose equivalency: Part 3— Opioid switching with morphine-like opioids

By Carlo DeAngelis, PharmD

In Part 2 of this series, the parenteral to oral conversion for hydromorphone was referenced as 1:5. However, clinically, the more conservative ratio of 1:2 is used, as is seen in the example given.

Optimizing pain control requires a careful evaluation of the patient, and this is particularly true prior to and after opioid switching. The first consideration is the justification for changing the patient's current opioid regimen. In addition to the obvious desire to optimize pain control, there are many reasons for wanting or needing to change the current opioid analgesic regimen including: induced side effects, limitations in being able to deliver/take the required dose conveniently (e.g., too many tablets to take or volume of drug to administer orally or parenterally), loss of use of the current route of administration (e.g., loss of the oral route due to inability of the patient to swallow, or change in the patient's mental state or level of consciousness).

It is important that before deciding to change the current opioid treatment regimen one has tried to optimize it. One must be certain that the change is necessary before embarking on the opioid conversion process, since this process, for reasons mentioned in Part 1 of this series, is empirical at best, may lead early on in the process to worsening of pain or side effects and requires close follow-up of the patient.

Having decided that opioid switching is necessary and is the best strategy for the patient, the first consideration is to which opioid to switch. In choosing the opioid to switch to, there is a need to take into account the patient's clinical condition (e.g., renal function), the goal of the change, and the availability of strengths and dosage forms for the new opioid. A common switch is from the week opioid codeine (usually due to poor pain control or inability to deliver higher doses due to limitation in the availability of dosage forms and strengths) to morphine or another more potent opioid. Another frequently encountered scenario is the switch away from morphine (due to side effects often related to declining renal function) to either hydromorphone or oxycodone. Once the choice of new opioid has been made, it is important to ensure the use of dose conversion ratios developed from chronic dosing of opi-

These policies, such as Decision Making and Conflict Resolution Regarding Futility in the Use of Life Support at Sunnybrook contain a final proviso to withdraw life support if the family or substitute decision-maker cannot find another institution willing to accept transfer of care. The argument has been made that if physicians do not retain the right to remove life support once instituted, they may be more reluctant to offer it in cases where benefit is not clear.

But let us consider what is really happening here. I believe that Daniel Callahan said it best:

"Death has been moved out of nature into human responsibility."

While, in this case, religion was the stated reason for requesting that life support be continued, in many other cases the human reluctance of family members to make decisions they feel are not theirs to make is operating. While nature still dictates that we all must die, it no longer dictates exactly how or when this will happen in our affluent society. We, as patients, make many decisions that impact on how and when we will die: whether to screen for cancer, receive chemotherapy or other treatments, smoke or exercise to name a few. However, what varies tremendously from person to person and family to family is how we react to this choice. Do we see these choices on how to influence the manner and timing of our death as welcome expressions of our autonomy or unwelcome burden? And, at the heart of the matter, who decides what choices will be offered or withdrawn?

In the end, physicians and health care workers cannot be compelled to provide care that falls outside of the standard of care. Families cannot be compelled to accept treatment plans that do not meet their goals of care. If we do not put energy and resources into resolving this stalemate, we leave no option but to turn to the courts. Samuel Golubchuk shows us that the court option is far from ideal.

oids, as these ratios take into account the build-up of potentially active metabolites and more closely reflect the cancer pain situation. Various conversion tables or calculators for chronically administered opioids are available (Fallon, Honks, & Cherny, 2006; Berdine & Nesbit, 2006; Ross, Riley, Quigley, & Welsh, 2006; Gammaitoni, Fine, Alvarez, et al., 2003). However, the detail often provided (e.g., to one or two decimal places) gives one the impression of the need for precision, which is unnecessary. Returning to the concept that the opioid conversion ratio is just a starting point rather than a precise equianalgesic dose, it seems practical to simplify the arithmetic. With this in mind, a useful dose equivalency to remember for the most commonly used opioid analgesics is: codeine 100 mg = morphine 10 mg = oxycodone 5 mg = hydromorphone 2 mg. Once the starting dose of the new opioid has been calculated, it would then be adjusted upwards or downwards depending on the patient's clinical situation and the strengths available. The following case provides an example of such an approach:

An elderly patient with metastatic breast cancer in good pain control is experiencing excess sedation from her current regimen of oral morphine. The patient's renal function was assessed and was found to have deteriorated significantly from the time when she was first started on morphine and there appears to be no other obvious cause to the increase in sedation. A decision has been made to switch the patient to hydromorphone since there is reduced potential for build-up of active opioid metabolites compared to morphine, which may be the cause of the excess sedation.

Current total daily morphine dose:
Dose of around-the-clock sustained release formulation of morphine:
120 mg three times daily = 360 mg/24 hours

Dose of breakthrough regular release morphine used:
Prescribed 25 mg every two hours as needed; on average uses two doses in 24 hours
25 mg × 2 doses = 50 mg/24 hours

Total daily oral morphine dose: 360 mg + 50 mg = 410 mg

Using the above mentioned 10 mg of morphine = 2 mg of hydromorphone (i.e., hydromorphone is five times more potent than morphine or a 5:1 ratio) the equivalent oral hydromorphone dose would be:
410 mg morphine ÷ 5 = 82 mg hydromorphone

Erring on the conservative side, when switching from one opioid to another, it is customary to reduce the dose of the new opioid by 25% to 30% to take into account incomplete cross-tolerance and reduce the chance for side effects.

The total daily dose of hydromorphone would therefore be:
82 mg hydromorphone × 0.75 = 61.5 mg (0.75 is 75% of the calculated dose or from the other perspective a 25% dose reduction; a conservative approach given the patient's current clinical condition where the reason for switching is because of side effects rather than poor pain control)

Hydromorphone sustained release formulation is available in 3 mg, 6 mg, 12 mg, 18 mg, 24 mg and 30 mg capsule strengths. To simplify the conversion process it was decided to maintain the three times daily dosing schedule for the around-the-clock sustained release formulation. The dose for sustained release oral hydromorphone to be taken three times daily would be calculated as follows:
61.5 mg hydromorphone ÷ 3 = 20.5 mg

Once again erring on the conservative side, it was decided that the patient's new regimen would be 18 mg of hydromorphone sustained release formulation given three times daily. Keeping in mind the potential need for future dose titration, it was decided to use a combination of 12 mg and 6 mg capsules.

The patient's new opioid regimen would therefore be:
Hydromorphone sustained release formulation 1 × 12 mg capsule and 1 × 6 mg capsule taken together three times daily (i.e., every eight hours).

The breakthrough hydromorphone dose would be calculated as follows:

A commonly agreed upon rule of thumb for calculating the breakthrough dose is that it should be 10-20% of the total daily dose administered in divided doses (Gammaitoni, Fine, Alvarez, et al., 2003; Hanks, de Canno, Cherny, et al., 2001). For our patient this would be:
54 mg/24 hours × 0.1 = 5.4 mg in divided doses

If the desired dose frequency for breakthrough medication is every two hours, the dose to be administered every two hours would be:
5.4 mg/24 hours ÷ 12 doses / 24 hours = 0.45 mg/dose

The hydromorphone regular release formulation is available in 1 mg, 2 mg, 4 mg and 8 mg tablet strengths. Thus, the patient could be given hydromorphone 1 mg and told to take one tablet every two hours as needed for breakthrough pain.

References

Berdine, H.J., & Nesbit, S.A. (2006). Equianalgesic dosing of opioids. **Journal of Pain and Palliative Care Pharmacotherapy, 20**, 79–84.

Fallon, M., Honks, G., & Cherny, N. (2006). Principles of control of cancer pain. **British Medical Journal, 332**, 1022–1024.

Gammaitoni, A.R., Fine, P., Alvarez, N., et al. (2003). Clinical application of opioid equianalgesic data. **Clinical Journal of Pain, 19**, 286–297.

Hanks, G.W., de Canno, F., Cherny, N., et al. (2001). Morphine and alternative opioids in cancer pain the EPAC recommendations. **British Journal of Cancer, 84**, 587–593.

Ross, J.R., Riley, J., Quigley, C., & Welsh, K.I. (2006). Clinical pharmacology and pharmacotherapy of opioid switching in cancer patients. **Oncologist, 11**, 765–773.

2009 Annual Hospice Palliative Care Conference

By Gunita Mitera, BSc, MRT(T)

The first collaborative conference hosted by the Hospice Association of Ontario (HAO) and the Ontario Palliative Care Association (OPAC) took place April 19–21, 2009, in Toronto. With more than 500 attendees, the research conducted within the Rapid Response Radiotherapy Program at the Odette Cancer Centre was selected to be showcased at this conference through 15 poster and oral presentations. Each research project was presented by the research students and radiation therapist.

The titles of each presentation were as follows:

1. Bisphosphonates in combination with radiotherapy for bone metastases: A literature review
2. Change in urinary markers of osteoclast activity following palliative radiotherapy for bone metastases
3. Skeletal related events (SREs) in patients with metastatic bone disease
4. Shortening the European Organization for Research and Treatment of Cancer Bone Metastases Module (EORTC QLQ-BM22)
5. Quality of life measures used in radiation therapy trials for metastatic spinal cord compression patients: A literature review
6. Are baseline ESAS symptoms related to pain response in patients treated with palliative radiotherapy for bone metastases
7. Assessment of cancer pain management in an outpatient palliative radiotherapy clinic using the pain management index
8. Minimally invasive treatment of tumour-related vertebral compression fractures and other metastatic bone lesions
9. Validation of meaningful change in pain scores in the treatment of bone metastases
10. Palliative radiotherapy for painful bone metastases in the elderly: Not a trade off
11. Symptom clusters in metastatic cancer: A critical appraisal
12. Gender differences in the ESAS score in patients with advanced cancer
13. Determining the accuracy of health care professionals in predicting the survival of patients with advanced metastatic cancer
14. Palliative performance scale: Examining its inter-rater reliability in an outpatient palliative radiation oncology clinic
15. The palliative performance scale: Examining correlation to Karnofsky Performance Scale in an outpatient palliative clinic.

This was a very well-attended multidisciplinary palliative care conference that served as a platform where colleagues from near and far could exchange ideas and experiences within the hospice and palliative care setting. This conference truly did represent the essence of "One vision, One voice," which was the theme of the conference. We look forward to attending again next year.

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Continuing Medical Education 2009–2010

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 lists the national and international CME activities in palliative medicine that are of interest to our readers. Please forward details of the CME activities to: **Ewa.Szumacher@sunnybrook.ca**

- September 18–19, 2009—2nd Annual Hospice and Palliative Care Conference, UCSF Fresno Center for Medical Education and Research, Fresno, California 93701. (415) 476-4251 / (415) 476-5808; E-mail: **info@ocme.ucsf.edu**
- September 24–27, 2009—Preconference Seminar Dates: September 22–23, 2009, NHPCO's 10th Clinical Team Conference, Facility-Based Hospice Forum, Scientific Symposium, and Pediatric Intensive, Soaring to New Heights in Interdisciplinary Care. Hyatt Regency Denver, Denver, Colorado **www.nhpco.org/i4a/pages/Index.cfm?pageID=5356**
- September 24–27, 2009—International Conference on Cultural Connections for Quality Care at the End of Life, Perth, Western Australia **www.conlog.com.au/palliativecare2009/**
- September 30, 2009—Scottish Partnership for Palliative Care Annual Conference, Royal College of Physicians of Edinburgh; **claire@palliativecarescotland.org.uk www.palliativecarescotland.org.uk/index.php?id=210**
- September 30–October 3, 2009—23rd CARO Annual Scientific Meeting, Quebec City, Quebec, **www.caro-acro.ca/Meetings___Education.htm**
- October 1–2, 2009—French conference: putting palliative care into practice, Education Administrator, St. Christopher's Hospice; Tel: +44 (0)20 8768 4656; **education@stchristophers.org.uk www.stchristophers.org.uk/education**
- October 15–16, 2009—4th International Trondheim Conference on Palliative Care. Treatment, research and organizational issues, Trondheim, Norway; Tel: +47 73 86 97 49; Elin Steen, **elin.steen@ntnu.no www.palliative.no**
- October 15–17, 2009—Cancer Education Conference. The Art and Science of Cancer Education & Evaluation, Crowne Plaza – Houston Reliant Park, Houston, TX; **www.regonline.com/Checkin.asp?EventId=719607**
- October 16, 2009—'Innovation, Innovation, Innovation!' Defining, developing and demonstrating supportive care at the end of life, Education Administrator, St. Christopher's Hospice, London, UK; Tel: +44 (0)20 8768 4656, Fax: +44 (0)20 8776 5838, E-mail: **education@stchristophers.org.uk www.stchristophers.org.uk/education**
- October 23 & December 4, 2009—Advance care planning, Education Administrator, St. Christopher's Hospice, London, UK; Tel: +44 (0)20 8768 4656, Fax: +44 (0)20 8776 5838, E-mail: **education@stchristophers.org.uk www.stchristophers.org.uk/education**
- November 9–13, 2009—Multiprofessional week in palliative care, Education Administrator, St Christopher's Hospice, London, UK; Tel: +44 (0)20 8768 4656, Fax: +44 (0)20 8776 5838, E-mail: **education@stchristophers.org.uk www.stchristophers.org.uk/education**
- November 24–26, 2009—Help the Hospices Conference 2009, Third multidisciplinary conference, Harrogate International Conference Centre, London, UK; **www.helpthehospices.org.uk/our-services/running-your-hospice/education-training/2009conference/**
- October 8–11, 2009—American Academy of Pain Management – 20th Annual Clinical Meeting, Sheraton Phoenix Downtown Hotel, Phoenix, AZ; **www.aapainmanage.org/conference/Conference.php**
- October 18–21, 2009—2009 Canadian Hospice Palliative Care Conference, Winnipeg, MB; **www.chpca.net/events/calendar_of_events.htm#oct09**
- October 26–27, 2009—20th Annual Palliative Care Conference, Fantasyland Hotel, West Edmonton Mall, Edmonton, AB; Ph: (780) 735-7727 **Kathy.Robberstad@albertahealthservices.ca**; **www.palliative.org/PC/Edu/CallforAbstract2009.pdf**
- November 1–5, 2009—51st Annual ASTRO Meeting, McCormick Place; Chicago, IL; **www.astro.org/Meetings/AnnualMeetings/index.asp**
- February 11–14, 2010—IXVII International Conference of Palliative Care of IAPC, Trichirappalli, Tamilnadu; India; Contact: Dr. T. Mohanasundaram; E-mail: **drmohs.trichy@hotmail.com**
- March 7–11, 2010—16th International Conference on Cancer Nursing (ICCN), Atlanta, GA; **www.isncc.org**
- June 10–12, 2010—6th Research Forum of the EAPC, Glasgow, UK; Mike Bennett **m.i.bennett@lancaster.ac.uk**
- August 29–September 2, 2010—13th World Congress on Pain, Montréal, QC; **www.iasp-pain.org/Montreal**

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Chronic lymphocytic leukemia (CLL)

Dr. Rena Buckstein, MD, FRCPC, Head Hematology Site Group, Co-Director of MDS Research Program

HOT SPOT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world. The overall incidence is 4.6/100,000 with a median age at diagnosis of 72.

The disease incidence increases dramatically with age (33/100,000 > age 75) with 75% diagnosed above the age of 65.

CLL is classified as an indolent B cell lymphoma and is identical to small lymphocytic lymphoma (SLL) immunophenotypically, cytogenetically and histologically. Their treatments are interchangeable.

CLL is diagnosed by one or more of peripheral blood, bone marrow and lymph node testing. CLL cells have a characteristic immunophenotype (CD19+, CD20+, CD23+, CD38+, sIgw) and are one of only two B cell lymphomas that express the T cell marker CD5.

CLL is considered an incurable disease like most indolent lymphomas (without an allogeneic stem cell transplant). Therefore, the goals of therapy in most patients are disease control and extension of life. The classical clinical prognostic markers are:

- The Rai or Binet staging systems summarized in Tables One and Two. Fifty-five per cent of patients present with Binet stage A disease.
- The lymphocyte doubling time and BM histologic pattern.

Newer biological prognostic factors that refine the clinical stages further include:

- The mutational status of the immunoglobulin genes (IgVH).
- The karyotype.
- Over-expression of CD38.
- Increased β2 microglobulin.
- Increased expression of ZAP70.

Some of these factors are also prognostic for response to specific therapies. For example, patients with 17p deletions or p53 mutations respond less well to purine analogues and better to alemtuzumab.

Indications for treatment

In 2008, NCI guidelines were established to define criteria for initiating treatment:

- Evidence for progressive bone marrow failure.
- Massive, progressive or symptomatic splenomegaly.
- Massive nodes or progressive or symptomatic lymphadenopathy.
- Progressive lymphocytosis with an increase > 50% over two months or a lymphocyte doubling time of < 6 months.
- Autoimmune anemia and or thrombocytopenia poorly responsive to corticosteroids/standard therapy.

Any one of the following symptoms should also be present: unintentional weight loss within six months, significant fatigue, inability to work or perform usual activities, night sweats for > 1 month or unexplained fevers for ≥ 2 weeks without evidence for infection.

What guides therapy choice

Therapy is guided by symptoms, age, performance status, co-morbidities and the ability to travel for intravenous agents. In many instances, a watch and wait approach is adopted initially in asymptomatic low-disease-burden patients and this has been supported by randomized controlled trials.

When treatment is indicated, options include single agent alkylator (e.g., chlorambucil), single agent purine analogue (e.g., fludarabine), hybrid alkylator/purine analogue (bendamustine), fludarabine with cyclophosphamide, alemtuzumab (anti-CD52 antibody), and the addition of Rituximab to any one of the above.

Chlorambucil: while chlorambucil is often prescribed for frailer, more elderly patients, its use is associated with low CR rates (< 10%) and short remission durations (1 to 1.5 years). In a Cochrane meta-analysis of four randomized trials, purine analogues were associated with improved RR and PFS compared with chorambucil (HR 0.7, p<0.00001), but not OS (HR 0.89, p=.07).

FC has been shown to be superior to F alone in several large European cooperative group studies achieving remissions in up to 95% of previously untreated patients, higher complete remission rates (25% to 40%) and longer progression-free survival (32 to 48 months). Until recently, FC was considered in many countries to be the standard recommended first line therapy for untreated symptomatic CLL.

Adding Rituximab

Rituximab as monotherapy at traditional dosing is largely ineffective in CLL due to low CD20 expression and soluble CD20 consuming antibody. It may, however, sensitize CLL cells to chemotherapy and augment the chemotherapy response rates, depth and durations as seen with follicular lymphoma.

More recently, two large phase III trials in both first line and second line CLL have studied the effects of adding rituximab to a fludarabine-cyclophosphamide backbone and were presented at the American Society of Hematology Annual Meeting in 2008.

In the first trial **(CLL8)**, patients with untreated active CLL were randomized between either FC (n=396) or FCR (n=404) for six cycles. The schedule of chemotherapy is in Figure One. The primary endpoint was progression-free survival and the secondary endpoints were OS, response and safety.

With a median follow-up of 25.5 months, FCR was associated with improved median PFS (42.8 months versus 32 months p=.000007), higher CR rates (44.5% versus 23%, p< .01) and less primary progressive disease (3%

Table One. Rai Classification System

Stage	Description	Median survival (months)	Risk status (Modified Rai)
0	Lymphocytosis, lymphocytes in blood > 15 × 10^9/L and > 40% lymphocytes in the bone marrow	140	Low
1	Stage 0 with enlarged nodes	100	Intermediate
2	Stage 0–1 with splenomegaly, hepatomegaly or both	70	Intermediate
3	Stage 0–2 with hemoglobin < 11 g/dL or Hct < 33%	20	High
4	Stage 0–3 with plts < 100 × 10^9/L	20	High

Table Two. Binet Classification System

Stage	Description	Median Survival (months)
A	Hemoglobin > 10 g/dL and platelets > 100 × 10^9/L and < 3 involved nodal areas	Comparable to age-matched controls
B	Hemoglobin > 10 g/dl and platelets > 100 × 10^9/L and > 3 involved nodal areas	84
C	Hemoglobin < 10 g/dL and/or platelets < 100 × 10^9/L and any number of involved nodal areas	24

versus 8%, p <.01). Overall survival was not statistically different. FCR was associated with greater grade 3/4 neutropenia (34% versus 21%, p < .0001), but no increased incidence of infections or treatment-related death.

Minimal residual disease (MRD) as assessed by flow cytometry was significantly associated with progression-free survival regardless of treatment received with best PFS achieved with < 10^{-4} cells (49.6% of patients, PFS not reached) compared with ≥10^{-4} and < 10^{-2} (36.8% of patients, 34 months) ≥10^{-2} (13.6% of patients, 15 months).

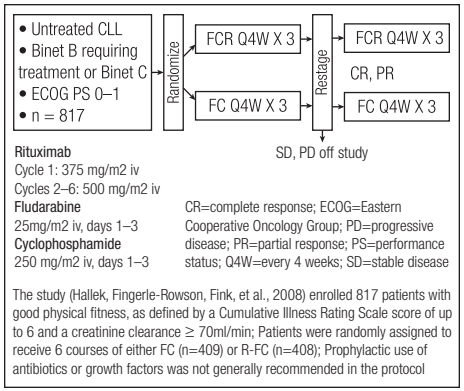

Figure One: Study design of CLL8 randomized controlled trial

A higher percentage of FCR-treated patients achieved maximal MRD in the peripheral blood (66% versus 34%, p=.005) (Figure Two).

Rituximab use in relapsed disease

The German CLL Study Group examined FCR versus FC (in the same dose and schedule as CLL8) in previously treated patients with CLL **(REACH study).** REACH was an open-label, multicentre, randomized phase III trial to evaluate the efficacy and safety of FCR versus FC in relapsed or refractory patients with CD20 positive CLL. The primary endpoint was PFS.

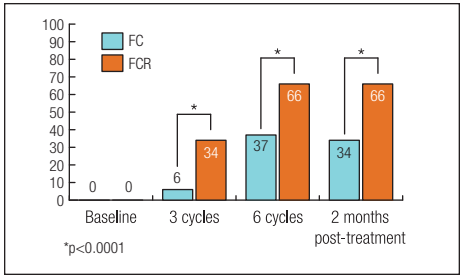

Figure Two. Per cent of patients achieving MRD in CLL8

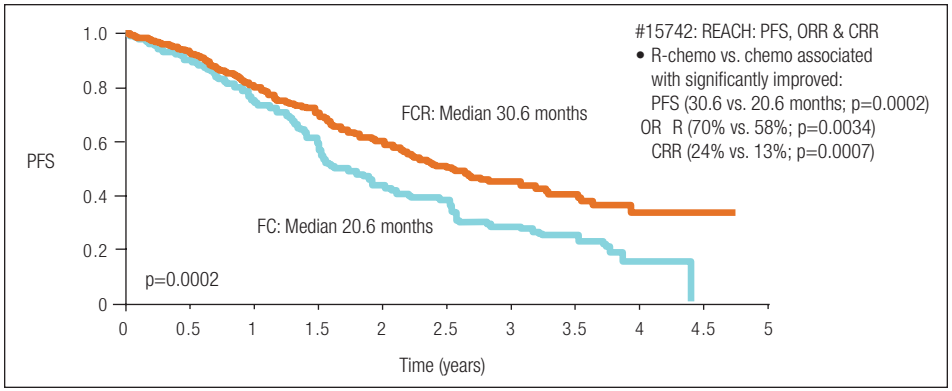

Figure Three. PFS in the German CLL REACH trial

Five hundred and fifty-two patients were randomized 1:1. The majority of patients had received one prior therapy with alkylator (66%) or COP/CHOP (18%) and 16% had previously been treated with Fludarabine as monotherapy.

With a median follow up of 25 months, PFS was prolonged by 10 months in the FCR arm (30.6 months) versus 20.6 months (p=0.0002, HR 0.65 95% CI: 0.51–0.82) (Figure Three).

The overall and response rates were also higher with FCR compared with FC (ORR 70 versus 58%; CR 24.3 versus 13%).

FCR was well tolerated with higher rates of grade 3/4 hematologic toxicity (chiefly neutropenia) compared with FC alone (55.7% versus 39.4 %). Notably, there were no differences in infections between the two arms.

Future randomized trials in CLL to look out for

- Rituximab-fludarabine (RF) versus Rituximab-chlorambucil in first line.
- Rituximab-bendamustine versus FCR in first line.
- RF versus observation in asymptomatic patients with higher risk CLL (unmutated VDJ rearrangements) first line.
- RF versus RF + lenalidomide consolidation versus FCR in relapsed disease.

Conclusions

The addition to Rituximab to the FC backbone in either untreated or relapsed/refractory CLL:

- Improves PFS by 13 and 10 months respectively.
- With relatively short follow-up, does not improve OS.
- Increases neutropenia, but not infections or treatment-related mortality.
- Achieves higher rates of complete remission and minimal residual disease (MRD).
- Higher degrees of MRD achievement correlate with improved PFS regardless of treatment received.

Key references

Hallek, M., Fingerle-Rowson, G., Fink, A., et al. (2008, December). Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL) [Abstract 325]. **Program and abstracts of the 50th American Society of Hematology Annual Meeting,** San Francisco, CA.

Boettcher, S., Fischer, K., Stilgenbauer S, et al. (2008, December). Quantitative MRD assessments predict progression-free survival in CLL patients treated with fludarabine and cyclophosphamide with or without rituximab: A prospective analysis in 471 patients from the randomized GCLLSG CLL-8 trial [Abstract 326]. **Program and abstracts of the 50th American Society of Hematology Annual Meeting,** San Francisco, CA.

Robak, T., Moiseev, S., Dmoszynska, M., et al. (2008, December). Rituximab, fludarabine, and cyclophosphamide prolong progression-free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone: Final results from the international randomized phase III REACH trial [Abstract 15742]. **Program and abstracts of the 50th American Society of Hematology Annual Meeting,** San Francisco, CA.

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Treatment of chemotherapy- and radiotherapy-induced nausea and vomiting (CINV/RINV)

HOT SPOT

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Pathophysiology

Chemotherapy-induced nausea and vomiting (CINV)

- Neuronal connections from the abdominal portion of the vagal nerve that lead to the brain stem appear to play the largest role in CINV. Numerous receptors (5-hydroxytryptamine [5-HT_3], neurokinin-1 [NK-1], and cholecystokinin-1 [CK-1]) for neurotransmitters are located on the ends of these vagal nerve connections, which also lie in close proximity to endocrine cells of the proximal small intestine (Hesketh, 2008). Through either direct intestinal or blood-borne mechanisms, chemotherapeutic agents stimulate these endocrine cells to release their mediators (5-HT, Substance P, and cholecystokinin), which, when binding to their appropriate receptors, creates a vagal stimulus that arrives in the brain stem, ultimately activating the emetic reflex (Hesketh).

5-Hydroxytryptophan (5-HT—Serotonin)

- Serotonin receptors are grouped into seven main families; of these, the 5-HT_3 group of receptors have been found to occur in the highest frequency in the gut (Herrstedt, 2008). Agents designed to block these receptors have been shown to produce antiemetic effects and now form the backbone of nearly all antiemetic regimens—5-HT_3 Receptor Antagonists (RAs).

Substance P

- Receptors for Substance P (neurokinin-1) are found throughout the central nervous system, as well as in the gastrointestinal tract (Hesketh, 2008). Evidence suggests that unlike 5-HT_3 RAs, the main site of action for NK-1 RAs is likely in the CNS (Hesketh).

Radiotherapy-induced nausea and vomiting (RINV)

- The onset and duration of RINV are felt to be shorter than in patients receiving chemotherapy (Horiot, 2004). Description of an "acute radiation syndrome" includes a sudden episode of nausea and vomiting typically occurring within 90 minutes of treatment and lasting roughly five hours (Horiot).

Risk factors

Chemotherapy

- Age: Younger patients are at greater risk of experiencing CINV than are older patients (<50 years versus >50 years of age) (Hesketh, 2008; Schwartzberg et al., 2009; National Comprehensive Cancer Network [NCCN], 2009).
- Gender: Female patients are at greater risk of experiencing CINV than are male patients (Hesketh, 2008; NCCN, 2009).
- Alcohol use: Previous history of high amounts of alcohol use reduces the chances of experiencing CINV (Hesketh, 2008).
- Previous experience: Patients who have previously experienced CINV are at greater risk than those who have not. Also, patients who have a high expectation that they will experience CINV are more likely to have this occur (Hesketh, 2008).
- Chemotherapy: The dose, schedule, and route of administration of the chemotherapeutic agent(s), as well as the inherent emetogenic potential of each antineoplastic contributes to the risk of developing CINV (NCCN, 2009).

Radiotherapy

- The factors that have been attributed to increasing the risk for RINV secondary to radiation are the portion of the body that is receiving the radiation (e.g., upper abdomen), single and total dose, fractionation, and field size of the radiation itself (NCCN, 2009; Feyer, 2004). Patient-related risk factors include age (< 55 years), gender, concurrent or recent chemotherapy, and psychological state (Feyer).

Phases of CINV

- *Anticipatory:* This represents the time period before chemotherapy is administered, often occurring just prior to receiving the treatment. It is a learned response that has arisen due to previous CINV experience (severity and duration contribute to this) (NCCN, 2009).
- *Acute:* This phase is considered to be the initial 24 hours immediately after chemotherapy has been administered.
- *Delayed:* This is the time period that begins after the initial 24 hours following chemotherapy (i.e., hour 25 onwards).
- *Breakthrough:* Not a phase per se, but represents the instances where vomiting is not controlled despite prophylaxis with anti-emetic medications and/or requires rescue medications (NCCN, 2009).
- *Refractory:* Emesis occurring in treatment cycles where prophylaxis and/or breakthrough medications have failed in previous cycles (NCCN, 2009; MASCC, 2008).

Emetogenic potential

Chemotherapy

- *Highly Emetogenic Chemotherapy (HEC):* A risk of emesis in >90% of patients (e.g., Cisplatin, carmustine, cyclophosphamide (≥1500 mg/m^2), procarbazine) (MASCC, 2008).
- *Moderately Emetogenic Chemotherapy (MEC):* A risk of emesis in 30% to 90% of patients (e.g., Doxorubicin, oxaliplatin, Epirubicin, Irinotecan, cyclophosphamide [<1500 mg/m^2], temozolamide) (MASCC, 2008).
- *Low-Risk Emetogenic Chemotherapy (LEC):* A risk of emesis in 10% to 30% of patients (e.g., Paclitaxel, docetaxel, gemcitabine, trastuzumab, 5-Fluorouracil, capecitabine) (MASCC, 2008).
- *Minimally Emetogenic Chemotherapy:* Denotes a risk of emesis in <10% of patients (e.g., Bleomycin, vinblastine, vincristine, vinorelbine, fludarabine, Methotrexate [oral], chlorambucil, hydroxyurea) (MASCC, 2008).

Radiotherapy

- *High Risk:* Total Body Irradiation (TBI) (MASCC, 2008).
- *Moderate Risk:* Upper abdomen. (MASCC, 2008)
- *Low Risk:* Lower thorax region, pelvis, cranium (radiosurgery), craniospinal. (MASCC, 2008)
- *Minimal:* Head and neck, extremities, cranium, breast. (MASCC, 2008)

Recommendations

(MASCC 2008) (*Revisions expected for 2009)*

Chemotherapy

- Patients receiving HEC are recommended to receive the following medications to prevent CINV:

Treatment of chemotherapy- and radiotherapy-induced nausea and vomiting (CINV/RINV)

HOT SPOT

Acute: a 5-HT_3 RA, dexamethasone, and aprepitant (or fosaprepitant)
Delayed: aprepitant and dexamethasone (for those patients receiving cisplatin and the above acute antinauseant regimen).

- In those patients who are to receive MEC, the recommended antinauseants are:
  Acute: a 5-HT_3 antagonist, dexamethasone, and aprepitant or fosaprepitant (patients receiving an anthracycline plus cyclophosphamide)//a 5-HT_3 antagonist and dexamethasone (in patients NOT receiving an anthracycline plus cyclophosphamide).
  ** The recommended dose of dexamethasone in the acute setting with MEC is 8 mg IV × 1 dose.*
  Delayed: Dexamethasone or aprepitant (patients receiving an anthracycline plus cyclophosphamide and who were prophylaxed with the above antinauseant three-drug regimen in the acute period)// Dexamethasone alone (in patients who did not receive aprepitant in the acute period).
- The treatment recommended for patients being treated with LEC is:
  Acute: Dexamethasone (low dose)
- In patients being treated with minimally emetogenic chemotherapy regimens, no antiemetic should be routinely given before chemotherapy in patients without a history of nausea and emesis.

Special cases

- Multiple-day cisplatin: a 5-HT_3 antagonist plus dexamethasone for the *acute* phase and dexamethasone for the *delayed* phase.
- Anticipatory nausea and emesis—psychological techniques should be employed to deal with this case.

Radiotherapy

- Those patients who are at high risk for RINV should receive a 5-HT_3 antagonist plus dexamethasone.
- Patients receiving moderately emetogenic radiotherapy should receive a 5-HT_3 antagonist.
- Any patients receiving radiation therapy with low emetogenic potential should receive a 5-HT_3 antagonist for rescue.
- Those patients who are being treated with radiotherapy of minimal risk should receive either a dopamine antagonist or a 5-HT_3 antagonist for rescue purposes.

Medications

(MASCC, 2008)

Corticosteroids

Dexamethasone (Decadron®—Merck Frosst)

- HEC **Acute:** 20 mg × 1 dose, **Delayed:** 8 mg twice daily; MEC **Acute:** 8 mg × 1 dose, **Delayed:** 8 mg once daily or 4 mg twice daily; LEC **Acute:** 4–8 mg × 1 dose

5-HT_3 Receptor Antagonists

Ondansetron (Zofran®—GlaxoSmithKline)

- IV: 8 mg or 0.15 mg/kg; Oral: 16 mg/day

Granisetron (Kytril®—Roche)

- IV: 1 mg or 0.01 mg/kg; Oral: 1–2 mg/day

Dolasetron (Anzemet®—Sanofi-Aventis)

- IV: 100 mg or 1.8 mg/kg; Oral: 100 mg/day

NK-1 Receptor Antagonists

Aprepitant (Emend®—Merck Frosst)

- **Acute:** 125 mg orally once; **Delayed:** 80 mg orally once daily

Fosaprepitant (Emend® IV—Merck Frosst)

- **Acute:** 115 mg IV once

Anti-nauseants—Breakthrough/Refractory CINV
(Hesketh, 2008)

- *Prochlorperazine; Metoclopramide; Domperidone; Dronabinol; Olanzapine; Nabilone*

Helpful hints/facts

- It is the goal to prevent nausea and vomiting in all patients receiving cancer chemo- and/or radiotherapy (NCCN, 2009).
- It is always easier to PREVENT than to treat CINV.
- Choice of the antiemetic agent(s) used should be based on the emetic risk of the therapy, the patient's prior experience with antiemetics, and patient specific factors (NCCN, 2009).
- The lowest effective dose of medication should be used to treat CINV/RINV.
- Combination chemotherapy and radiotherapy increases the risk for nausea and vomiting (Feyer et al., 2005).
- The dexamethasone dose should be reduced by 40% if used concurrently with aprepitant or fosaprepitant (20 mg dose of dexamethasone should be reduced to 12 mg) (MASCC, 2008).
- All 5-HT_3 antagonists are equal in efficacy and adverse effect profile.
- Intravenous and oral formulations of antiemetzcs are equally efficacious and safe (5-HT_3 antagonists) (NCCN, 2009).
- 5-HT_3 RAs are most effective for the ACUTE phase of CINV. Corticosteroids and aprepitant (fosaprepitant) are effective in both the ACUTE and DELAYED phases (Baker et al., 2005).

** Revisions expected for 2009*

References

Baker, P.D., Morzorati, S.L., & Ellet, M.L. (2005). The pathophysiology of chemotherapy-induced nausea and vomiting. **Gastroenterology Nursing, 28**(6), 469–480.

Feyer, P. (2004). The importance of simple, easy-to-follow antiemetic guidelines. **Acta Oncologica Suppl. 15,** 5–8.

Feyer, P., Maranzano, E., Molassiotis, A., Clark-Snow, R.A., Roila, F., Warr, D., et al. (2005). Radiotherapy-induced nausea and vomiting (RINV): Antiemetic Guidelines. **Support Care Cancer, 13,** 122–128.

Herrstedt, J. (2008). Antiemetics: An update and the MASCC guidelines applied in clinical practice. **Nature Clinical Practice Oncology, 5**(1), 32–43.

Hesketh, P.J. (2008). Chemotherapy-induced nausea and vomiting. **N Eng J Med., 358**(23), 2482–94.

Horiot, J.C. (2004). Introduction. **Acta Oncologica Suppl. 15,** 3–4.

Multinational Association of Supportive Care in Cancer (MASCC). (2008) **Antiemetic Guidelines** (Based on: The consensus conference on antiemetic therapy 2004). Retrieved August 5, 2009, from http://data.memberclicks.com/site/mascc/MASCC_Guidelines_Update.pdf

National Comprehensive Cancer Network. (2009). **Clinical practice guidelines in oncology: Antiemesis.** V.3.2009. Retrieved August 7, 2009, from http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf

Schwartzberg, L.S., Hesketh, P.J., & Kris, M.G. (2009). **Chemotherapy-induced nausea and vomiting: Evidence-based management of a persistent problem.** Medscape CME. Retrieved August 6, 2009, from http://cme.medscape.com/viewarticle/701900.

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