Welcome to the May issue. Starting with this issue, we have a couple of changes. We thank Drs. Rebecca Wong and Charles Hayter for their contributions in the Research Column and Historical Vignette. They will be replaced by Dr. Toni Barnes reporting on Palliative Radiation Oncology Group (PROG) Rounds and updates from the Temmy Latner Centre for Palliative Care co-ordinated by Ms Deborah Adams.

Our feature article is by Dr. Lou Andersson and Ms Nicole Bradley on do-not-resuscitate (DNR) orders. Dr. Mary Vachon highlights ‘Caught in the Middle: Midlife Adults with Cancer’. Dr. Karen Faith discusses ‘Lessons from My Dad’. Dr. Tanya Berrang provides PROG Rounds on ‘Palliative Radiotherapy: Knowledge among community physicians and nurses’. Dr. Stephen Jenkinson of the Temmy Latner Centre enlightens us on ‘Palliative Care and Children’.

We have two inserts this issue: ‘Latest Advances in Antiemetics’ by Dr. David Warr and ‘Management of Multiple Myeloma’ by Dr. Keith Stewart. We hope you continue to find Hot Spot useful.

The do-not-resuscitate (DNR) order – incidence of documentation in patient charts of patients referred for palliative radiotherapy

By Lou Andersson, RN, PhD, and Nicole Bradley BSc(C), Research Assistant

Patients with metastatic cancer who are seen in the Rapid Response Radiotherapy Program (RRRP) and the Bone Metastases Clinic (BMC) at the Toronto Sunnybrook Regional Cancer Centre have limited life expectancy. Clear documentation of DNR code status is imperative to avoid panic and unnecessary aggressive measures in situations where cardiopulmonary resuscitation (CPR) has no benefit and in order to maintain respect of the patient’s wishes at the end of life.

This study was conducted to examine the current practices of CPR and DNR documentation with metastatic cancer patients referred for the RRRP and BMC. Referral notes and any accompanying medical documentation notes were reviewed for all 209 patients seen in the RRRP and BMC from May to August 2004. Patients had a median age of 70 years, and median Karnofsky Performance Status (KPS) of 70. An equal proportion of males and females were seen and 23.4% were inpatients from hospital or hospice. The most common primary cancer sites were lung, breast, and prostate respectively and 57.9% had multiple sites of metastases.

Of the 209 patients, only 13 (6.2%) had any documented reference to CPR code status. Of these, eight patients were DNR coded and five were full code. There was a significant difference between the age, performance status and inpatient or outpatient status of patients with documented CPR code status. Patients with documented CPR code status were older (median age of 77, p=0.0347), had poorer performance status (median KPS of 40, p=0.0001), and were inpatients (69%, p=0.0004).

This study is limited by the small sample size. However, it clearly demonstrates that only a very small proportion of symptomatic advanced cancer patients referred for palliative radiotherapy had any documentation of CPR code status. Proper documentation is essential in the event of a catastrophic event and especially critical in an outpatient palliative cancer clinic, where the patient is often unknown to the health care providers. Future changes may include the identification of the CPR code status on our referral form.

In this issue: The DNR order - incidence of documentation in patient charts of patients referred for palliative radiotherapy; Does culture influence patients and families’ DNR decision making? Caught in the middle – mid-life adults with cancer; Lessons from my dad; Temmy Latner Centre Update on Palliative Care; Palliative Radiation Oncology Group Rounds.

Inserts - Management of multiple myeloma/Latest advances in antiemetics
Caught in the middle – mid-life adults with cancer

By Mary L.S. Vachon, RN, PhD

There is a popular concept of women “caught in the middle”, describing the role challenges faced by women simultaneously caring for young or teenaged children, and aging parents. This situation becomes more complicated when the middle-aged adult of either gender is also dealing with a serious cancer.

Each family has its own history: The adult child may have felt loved and cared for as a child, adolescent, and young adult, or there may have been a dysfunctional family system in which problems with addictions, abuse, unrealistic expectations, mental illness or other issues played a part. When there are unresolved previous problems, there will often be great difficulty dealing with a serious illness.

The experience of confronting one’s own serious illness, preparing for the possibility of one’s own death, dealing with issues involving one’s children and simultaneously worrying about family dynamics and issues involving one’s aging, ill or infirm parents presents many challenges for the mid-life adult, as well as the older parent.

Mid-life adults in this situation can feel torn, trying to balance their own health needs, the needs of their children and their parents. Trying to get their kids off to school, themselves to chemotherapy or for tests, and their parents to their doctor’s appointments can lead to many role conflicts. Trying to decide what they should do and what other family members might be asked to do can also be a challenge.

At times, older family members are more than happy to try to help the mid-life adult. At other times, the older parent, even those who are healthy, may resent being asked for help and may become irritated at the healthy spouse who may assume that the parent would be willing to help. Sometimes the cancer patient may have an understanding of the limitations of his/her parent and may simply be willing to accept what is offered, while the spouse may have higher expectations. This can lead to issues between the couple.

Older parents have great difficulty watching their children deal with serious illness and preparing their younger children for the possibility of their death. A middle-aged man was concerned about how his wife would handle family finances after he died. He tried to teach his young adolescent daughter about stock market investments, hoping that the daughter would be able to develop some skills in this area before he died, so that he could feel that the family finances would be appropriately handled.

His mother spoke to her son and said “You can’t put an adult head on a child’s body.”

Older parents who themselves have cancer may feel that if someone is to die, it should be them and not their adult child. However, some parents may be consciously or unconsciously angry at their adult child for having developed cancer and thereby not being available to care for the parent who expected to be cared for by the adult child in his or her later years. One middle-aged woman said that whenever she mentioned a problem, her mother interrupted to speak of a “bigger problem”. When the daughter died, the mother grieved extensively, requiring the young adult grandchildren to delay their own grief to deal with their grandmother’s needs. When the “healthy” grandmother died unexpectedly a few weeks after her daughter, the family joked that the daughter would be very upset to see her mother “on the other side”, she couldn’t even get a break from her enmeshed relationship with her mother by dying.

Adult children may want to protect their parents from knowing exactly what is going on with them. This secretiveness not only protects the parents, it keeps the adult child from needing to witness the pain that their parent might experience and feeling that they should be able to ease the parents’ pain which their illness is causing. Some older parents with dementias or major infirmities are kept totally in the dark about their children’s illnesses and may not even be told about their death. Stories are made up about why the person is not able to visit. This collusion of course causes major problems for other family members who are dealing with their own grief.

The more these issues can be discussed openly and dealt with through discussion or family counseling, the easier the period around death and bereavement will be for those remaining.

Mary Vachon, RN, PhD, is a psychotherapist in private practice and may be reached at maryvachon@sympatico.ca.

Does culture influence patients’ and families’ DNR decision-making?

By L. Andersson, RN, PhD, S. Mary Williams, RN, MH, and Nicole Bradley, BSc(C)

In a highly multicultural society we cannot avoid asking if culture plays a role in the decision-making process of whether or not a patient should be resuscitated in the event of cardiac arrest. Making this choice can challenge an individual in every dimension – physically, emotionally and spiritually. Many medical practitioners encourage patients and families to make this difficult decision immediately upon the patient’s admission to a hospital or long-term care (LTC) facility. Although the DNR status may seem an obvious choice if a patient has an irreversible, grave disease and is of advanced age, the DNR decision does not come easily for patients or families.

From July 2003 to January 2005 we conducted a pilot study of 60 family members of patients with serious incurable medical conditions from 19 different cultural backgrounds. All were recent immigrants to Canada (within two to 10 years), were chosen to have power of attorney for their relatives with advanced directives than others.
Lessons from my dad

By Karen Faith, MEd, MSc, RSW

My father is a gentle, wise and intelligent soul who in his 88th year continues to teach me lessons about life and, more recently, how one faces the last part of life’s journey.

Having been widowed 18 years ago, my father maintained a philosophical commitment to live every day to its fullest. Prior to having kidney surgery four years ago, dad discussed his wishes for care at end of life. He prefaced the discussion with “I’ve lived a good life. I have no regrets.” I knew intuitively what was coming next. He proceeded to explain that if anything should happen to him and he should be unable to make his own decisions, he wanted me to know that no aggressive life support should be used. “Let me go,” he stated simply.

Sitting there with my father, I was of two minds. One part of me remarked what a relief it was to know how to determine his best interests if I should ever be consulted by his health care team. Another part of me sat in deep sadness, not wishing to face this last precious link to feeling parented and loved as a child.

I have held many discussions with family members about best interests for an incapable patient. However it was this personal experience with my father that made me acutely aware of how ambivalent family members feel about such discussions. An important part of the ethical obligations of those responsible for an incapable person’s care decisions is to reflect on how the patient had lived his/her life, the values held and wishes stated when capable. The task is even more challenging when those close to the patient know these wishes to be different from their own.

Decision-making at end of life requires that family members or substitute decision-makers are supported to rise above their own pain or self-interest in order to support the known wishes and personal values of the patient. Whenever I witness the struggle of family members and substitute decision-makers in the twilight of a patient’s journey, I am reminded of the night I spoke with my father and the deep emotional divide I experienced as a daughter.

Karen Faith is a Clinical Ethicist at Sunnybrook and Women’s College Health Sciences Centre.

Temmy Latner Centre Update on Palliative Care

Palliative care and children

By Stephen Jenkinson, MTS, MSW, RSW

With the generous support of the Wolfe family, The Temmy Latner Centre for Palliative Care is now in the design phase of creating a paediatric palliative care centre. The centre will have a dual focus – to provide quality, home-based interdisciplinary palliative care to dying children and their families, and to provide an age-appropriate grief program for children who are living through the dying process of a family member. This affords us the rare opportunity to design a service delivery model that is informed by, and reflects faithfully, the realities of dying and death.

The opportunity is also a demanding one. Of all the challenges facing palliative care administrators, clinical staff, and patients and families, probably the greatest is how to shift their clinical and existential orientation from treatment to palliation. Officially palliative care is typically represented as a constituent part of the ‘continuum of care’, but practically its providers know that palliative care requires a fundamental change in practice, purpose, vocabulary, and feeling tone. It is a change in kind, not degree, and almost always represents a kind of ruptured, loss-infused departure from a prior way of working and living. In a culture that continues to be heavily influenced by death phobia, ‘compassion’ typically takes the form of softening this shift to the point where it is articulated, if at all, with considerable subtlety and reluctance, accompanied with dizzying euphemisms. The general belief in the inherent benefits of remaining ‘hopeful and positive’ further argues against being overly clear with people about their prognoses. There is a widespread conviction that excessive candor in these matters is depression-inducing, and the result can often be that care providers unwittingly conspire to dull awareness of the implications of a palliative diagnosis for patients and families.

This culture views a child’s dying to be unnatural and deeply unjust, and the issues mentioned above are magnified accordingly in paediatric palliative care. Typically the patient is rarely the decision-maker in this area of practice, with the result that parents and professional teams alike struggle to find a new way of defining ‘everything possible and necessary’ in the care they propose and accept. Palliative care challenges parents deeply to find a way of parenting a child who will not outlive them.

As such, a home-based paediatric palliative care centre is obliged to reassess the typical distinction between ‘medical’ and ‘non-medical’ practice. While sound medical care will obviously be integral to the centre’s work, an ongoing willingness to reassess the essence of the work in light of the issues above is a core requirement. In that sense paediatric palliative care providers are primarily psychosocial spiritual workers, engaged in work that has far-reaching moral and cultural involvement and consequence. The Max and Beatrice Wolfe Children’s Centre at Mount Sinai Hospital’s Temmy Latner Centre represents a significant opportunity to benefit this community in one of its most vulnerable times and places.

Stephen Jenkinson is Leader, Psychosocial Team, and Director, Paediatric Palliative Care Centre, Mount Sinai Hospital.
PROG rounds are held by video and teleconference monthly between various radiation oncology centres across Canada. A synopsis of one of these monthly rounds will now be featured in Hot Spot. In this issue, Dr. Berrang tells us about a study carried out in Ottawa to assess the knowledge of community physicians and nurses about palliative radiotherapy. (For more information about PROG rounds please contact Dr. Barnes at toni.barnes@sw.ca)

Palliative Radiotherapy: Knowledge among community physicians and nurses

Palliative radiotherapy (PR) is an effective treatment modality, but is everyone who could benefit referred into the system? Many patients with advanced cancer are cared for in the community unless referred to a regional cancer centre. For patients to receive optimal care, it is important that health care workers have a basic understanding of PR.

At three continuing medical educational events in Ottawa, nurses, family physicians and family medicine residents completed 147 surveys on PR. Most of those surveyed were involved with the care of cancer patients, felt their knowledge was insufficient for their needs, and were interested in learning more about PR. Approximately 70% of respondents had a good understanding of the proportion of patients who could benefit from PR, how frequently PR is given and how long it takes to deliver a typical dose of radiotherapy. Most correctly indicated that PR is not painful and does not make patients radioactive. Side effects such as nausea, vomiting, and hair loss following PR were felt by the majority of respondents to be minor and dependent on the site treated. Bone metastases and spinal cord compression were the most recognized indications for PR, whereas less than 50% identified hemoptysis and brain metastasis as symptoms that could derive benefit from PR. Over 50% of respondents incorrectly identified hypercalcemia, diffuse liver metastasis, diffuse lung metastasis and febrile neutropenia as indications for PR. Overall, the family physicians scored significantly better than either the nurses or family medicine residents.

This survey gives us an introduction to the PR knowledge of community health care workers, but many questions still remain. Which groups of health care professionals could benefit from more education? What information regarding PR is most important and how can this best be provided?

Tanya Berrang, MSc, MD, can be contacted at tberrang@ottawahospital.on.ca.
Latest advances in antiemetics for radiation therapy and chemotherapy

Background
At one time nausea and vomiting were experienced by virtually all patients who received the commonly-used chemotherapy drugs, cyclophosphamide, doxorubicin and cisplatin. In the 1980s, marked improvement was made in the control of emesis through the use of corticosteroids and 5-HT₃ receptor antagonists. Although many oncologists now feel that emesis is largely well-controlled, recent studies have shown otherwise. Despite standard antiemetic therapy, approximately one-half of patients who receive high-dose cisplatin will vomit or retch at some point during their chemotherapy treatment. The largest problem with uncontrolled emesis occurs beyond the first 24 hours.

Radiation-induced emesis has received far less emphasis than that due to chemotherapy. Approximately 100% of patients who receive total body irradiation and 50% of patients who receive radiation therapy to the upper abdomen will vomit if no antiemetics are given. Radiation to other parts of the body is associated with a substantially lower risk of emesis. As with chemotherapy, both the 5-HT₃ receptor antagonists and low-dose corticosteroids have demonstrated efficacy in randomized trials.

It has been common practice in antiemetic research to distinguish nausea and vomiting that occurs in the first 24 hours following chemotherapy (“acute phase”) from that which occurs later (“delayed phase”). Before the introduction of effective antiemetics, the major problem with emesis occurred in the first 24 hours. With the introduction of the 5-HT₃ receptor antagonists, control of emesis in the early phase of emesis improved markedly, but this drug class had little effect on delayed nausea and vomiting. As our understanding of the physiology of vomiting improved, it became clear that mediators other than serotonin (e.g. substance P) were responsible for most of the emesis that occurs beyond 24 hours.

Patients who are younger and female are more likely to vomit.

Corticosteroids
- Many randomized trials show benefit in both the acute and delayed phase.
- 15-20% absolute reduction in the likelihood of vomiting due to chemotherapy
- For agents such as 5 FU and vinorelbine, the incidence of vomiting is low enough that steroids are usually not necessary
- For cisplatin chemotherapy, 20 mg IV more effective than lower doses.
- For moderately emetogenic chemotherapy (e.g. AC or CMF), doses higher than 8 mg IV provide no additional benefit.
- To prevent emesis beyond 24 hours, guidelines recommend continued administration of corticosteroids for at least day two and day three, particularly for cisplatin-induced emesis.
- 25% absolute reduction in risk of emesis in patients receiving radiation to the upper abdomen

5-HT₃ receptor antagonists
- Most effective antiemetic class in the acute phase.
- No clear difference in efficacy amongst ondansetron, granisetron and dolasetron.
- Palonosetron, an intravenous 5-HT₃ receptor antagonist not available in Canada appears to be more effective than the others for emesis other than cisplatin.
- Commonly prescribed several days post chemotherapy, but studies suggest efficacy is little better than placebo in the delayed phase, especially when corticosteroids have been given beyond day one.
- Well-established efficacy against radiation-induced emesis.

Dopamine receptor antagonists
- PRN metoclopramide, prochlorperazine and domperidone are frequently prescribed.
- Efficacy is uncertain but suspected to be minimal.
- One non-blinded study suggested efficacy for domperidone 20 mg tid.
- Three randomized trials showed that metopimazine (not available in Canada) added to the efficacy of ondansetron.
- In radiation-induced emesis, inferior to 5-HT₃ receptor antagonists.

Cannabinoids
- More effective than conventional doses of dopamine receptor antagonists for chemotherapy.
- No studies in radiation-induced emesis.
- Use peaked in 1980s.
- Largely forgotten with introduction of 5-HT₃ receptor antagonists.
- An animal model suggests that a cannabinoid adds to the efficacy of a 5-HT₃ receptor antagonist, but no studies have been done in humans.
- Anecdotally, adding ∆9 THC or nabilone can be markedly effective if prior problems with emesis.
- CNS toxicity (particularly dysphoria) is problematic for some patients.

NK₁ receptor antagonists
- A novel class of antiemetics.
- Aprepitant is the only agent to reach phase III trials.
- Aprepitant reduced vomiting due to cisplatin or an anthracycline and cyclophosphamide in women by 20%.
- Untested for radiation-induced emesis.
- As with the 5-HT₃ RA, the efficacy against nausea is less impressive than that against retching or vomiting.
- Side effects are difficult to distinguish from placebo.
- At this time aprepitant is not available in Canada.

Supplement to Hot Spot, the newsletter of the Rapid Response Radiotherapy Program of Toronto Sunnybrook Regional Cancer Centre - May 2005
Recommended dose of 5-HT\textsubscript{3} receptor antagonists

- Ondansetron 8 mg IV* or 24 mg PO (for moderately emetogenic, 8 mg PO x 2)
- Granisetron 1 mg IV* or 2 mg PO
- Dolasetron 100 mg PO or 100 mg IV*

* when equivalent doses are used, the route of administration is unimportant

Note: Palonosetron 0.25 mg IV day one may be more effective than other 5-HT\textsubscript{3} RA for moderately emetogenic chemotherapy but is not available in Canada

Recommended antiemetic regimens

Chemotherapy-induced emesis

Highly emetogenic chemotherapy

- Dexamethasone 20 mg IV or PO day one then 8 mg bid x 2-4 days PLUS
- 5-HT\textsubscript{3} receptor antagonist day one only

Note: Aprepitant 125 mg PO day one and 80 mg PO days two-three has been shown to reduce emesis when added to standard therapy but at the time of this issue is not available in Canada. If aprepitant is used, the dose of oral dexamethasone is reduced by approximately one-half.

Mildly emetogenic chemotherapy

- Nothing or dexamethasone 8 mg IV or PO emesis refractory to standard antiemetic therapy
- Add a 5-HT\textsubscript{3} receptor antagonist or steroid if not previously given
- Consider switching to another 5-HT\textsubscript{3} receptor antagonist
- Consider adding a cannabinoid (\(\Delta 9\) THC 2.5- 5 mg tid or nabilone 1 mg bid)

Radiation-induced emesis

Total body irradiation

- 5-HT\textsubscript{3} receptor antagonist + dexamethasone e.g. 8 mg PO/IV*

Upper abdominal irradiation

- 5-HT\textsubscript{3} receptor antagonist or dexamethasone 2 mg tid PO*

* the optimal duration of administration is unknown – the risk of emesis is generally highest in the first week

Emetogenicity of commonly-used chemotherapy drugs

<table>
<thead>
<tr>
<th>Level</th>
<th>Drugs</th>
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<tr>
<td>High</td>
<td>Cisplatin, Cyclophosphamide, Dacarbazine</td>
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<tr>
<td>Moderate</td>
<td>Oxaliplatin, Cytarabine &gt; 1 g/m\textsuperscript{2}, Cyclophosphamide &lt;1500 m/m\textsuperscript{2}, Carboplatin, Ifosfamide, Anthracyclines*, Irinotecan</td>
</tr>
<tr>
<td>Low</td>
<td>Docetaxel, Gemcitabine, Etoposide, Vinorelbine</td>
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*In women who receive an anthracycline plus cyclophosphamide, the risk of emesis is considered to be high
Novel therapeutics for management of multiple myeloma

- Myeloma is a clinically heterogeneous disease defined by genetically variable subsets
- Therapy is tailored to age
- Younger patients benefit from high-dose melphalan and stem cell transplant
- Novel therapeutic agents including Bortezomib (Velcade), Thalidomide, Revlimid are now available or in clinical trials.
- Comprehensive care requires supportive therapy for anemia, renal failure, bone disease, infection risk and appreciation of potential emergent conditions e.g. hypercalcemia, cord compression, deep venous thrombosis.

Myeloma basics
- Multiple myeloma is a malignancy of bone marrow plasma cells that produce an immunoglobulin, also referred to as a monoclonal protein (M-protein), which can be detected in blood, urine or both
- Median age is 65 years and less than 2% of patients are under age 40
- Multiple myeloma often begins with the relatively common monoclonal gammopathy of unknown significance (MGUS) and terminates with marrow failure and extra-medullary disease
- Multiple myeloma affects 15,000 new individuals each year in North America and has a prevalence of 50,000 cases which comprises approximately 1% of all malignant disease and 10% of hematological malignancies

Treatment of myeloma
The disease may remain indolent for years in many patients, particularly in those with low level M-protein (<30 g/L) and absent bony lesions. As there is no evidence that early treatment prolongs survival, therapy should be reserved for patients with symptoms.

Induction chemotherapy
Therapies vary widely for younger, healthier patients who pursue an aggressive intervention versus elderly, less well, or disinclined patients who choose a more conservative approach. Indeed, it is recommended that all myeloma patients be considered for clinical trials as this disease remains incurable and newer therapeutic agents and a better understanding of molecular events triggering the disease have ushered in an era of risk adapted therapy.

- For patients who do not want or cannot tolerate aggressive therapy, oral melphalan (Alkeran) 9 mg/m² and prednisone 100 mg (MP) daily for four days given at four to six week intervals is used. Treatment is continued until maximal reduction in the M-protein has occurred and a plateau reached for a minimum of four months (generally one year of treatment)
- Maintenance therapy should be used, as two large randomized studies have now demonstrated benefit to maintenance with prednisone (50 mg orally alternate days) or Dexamethasone 40 mg for four days each month.

- Adding Thalidomide to MP has been shown to increase response rates to 90% and complete responses to greater than 20%, however the incidence of complications including deep venous thrombosis is high and randomized trials are required before the routine use of Thalidomide is recommended in newly-diagnosed elderly patients
- In younger patients destined for high-dose therapy with stem cell support the most common regimens are VAD or Dexamethasone used as a single agent
- Recently the combination of Thalidomide and Dexamethasone in younger patients has been shown to confer a higher response rate than Dexamethasone alone, albeit at the cost of higher toxicity rates and without evidence of longer term benefit. Other new agents such as Velcade and Revlimid are only now being examined in newly-diagnosed patients. Velcade appears very active in this setting but should only be used in the context of clinical trials

Myeloma is a clinically heterogeneous disease defined by genetically variable subsets.
High-dose melphalan with autologous stem cell support

Use of high dose melphalan with stem cell support is presently the standard of care in patients with symptomatic myeloma under age 70 years. Induction regimens as described above using non-alkylating agents (eg. VAD, Dexamethasone and Thalidomide or Dexamethasone alone) are specifically chosen to avoid damage to stem cells. High-dose melphalan (Alkeran)(200 mg/m$^2$) is the most common transplant regimen used. Mortality from transplant toxicity is low at 1-3% hence it is relatively safe. In a landmark, randomized trial in myeloma patients under age 65, the transplant procedure led to improved progression-free survival of 52% at five years versus 12% in patients treated with conventional chemotherapy alone. Unfortunately, most patients following transplantation will continue to have evidence of the disease and all will eventually relapse. Another approach is to intensify HDT with double (or tandem) transplants which in some but not all studies has proven to be of further benefit, particularly to those not obtaining a complete remission after the first round of high-dose therapy. One study has suggested a benefit to use of Thalidomide as maintenance therapy in this setting but several large trials are nearing completion.

Relapse after chemotherapy

Generally within one to three years of discontinuation of therapy, disease will recur. Options include:
- An alkylating agent such as cyclophosphamide and steroids
- Dexamethasone alone or in combination with Thalidomide may be efficacious and is particularly useful in patients with cytopenias and in those reluctant to continue intravenous therapy
- In a large randomized trial, Velcade has recently been shown to confer a disease-free (eight versus 5.6 months) and overall survival (80% versus 66% at one year) benefit in relapsed patients when compared to Dexamethasone alone
- In a second large randomized trial Revlimid and Dexamethasone have also recently shown superiority to Dexamethasone alone

Refractory myeloma

Nowadays patients will progress through use of alkylating agents – high or conventional dose, high dose corticosteroids, Thalidomide and Velcade – before being declared refractory. Median survivals of five to six years are the norm in younger patients. Having exhausted these options, patients may still qualify for one of numerous possible investigational therapies including targeted small molecule approaches, monoclonal antibodies or targeted radiotherapies. Clinical trials should be actively pursued in this population.

Novel agents in myeloma

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<tr>
<th>Agent</th>
<th>Response rate single agent</th>
<th>Use</th>
<th>Dosing</th>
<th>Major toxicity</th>
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<tbody>
<tr>
<td>Velcade</td>
<td>35-50%</td>
<td>First or later relapse</td>
<td>1.3mg/m$^2$ IV twice weekly</td>
<td>Neuropathy</td>
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<td>Fatigue</td>
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<td>Thrombocytopenia</td>
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<td>Thalidomide (unapproved - available through special access)</td>
<td>25-35%</td>
<td>Up-front, maintenance or relapse (usually with steroids)</td>
<td>100-200mg daily p.o.</td>
<td>Sedation</td>
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<td>DVT</td>
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<td>Revlimid (not yet approved)</td>
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<td>Relapse/ refractory</td>
<td>15-25mg daily p.o.</td>
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