Conference on Clinical Cancer Research

October 20, 2010 ~ Washington, DC

Integrating Pain Metrics into Oncologic Clinical and Regulatory Decision-Making

Charles Cleeland

MD Anderson Cancer Center

Panelists

- Charles Cleeland, Department Chair, Department of Symptom Research, MD Anderson Cancer Center
- Carole Baas, Advocate, Physical Sciences in Oncology, NCI
- Laurie Burke, Assoc. Director for Study Endpoints and Labeling Development, Office of New Drugs, CDER, FDA
- Ann O'Mara, Head of Palliative Care Research, Community Oncology and Prevention Trials Research Group, NCI
- Martin Zagari, Global Health Economics Head, Amgen

Panel Topic Introduction

- Pain is a disabling consequence of cancer and of some cancer treatments
- Pain can be best measured by self-report of patients (a patient reported outcome)
- Inclusion of effects of treatment on pain and other symptoms provides critical information about the patient's experience in clinical trials

Prevalence of Pain In Cancer

Review of 41 Studies

- After curative treatment, 33%
- During anticancer treatment: 59%
- With advanced/metastatic disease, 64%
- Pooled prevalence of pain was >50% in all cancer types
- *More than one-third graded their pain as moderate or severe.*

van den Beuken-van Everdingen Ann Oncol. 2007

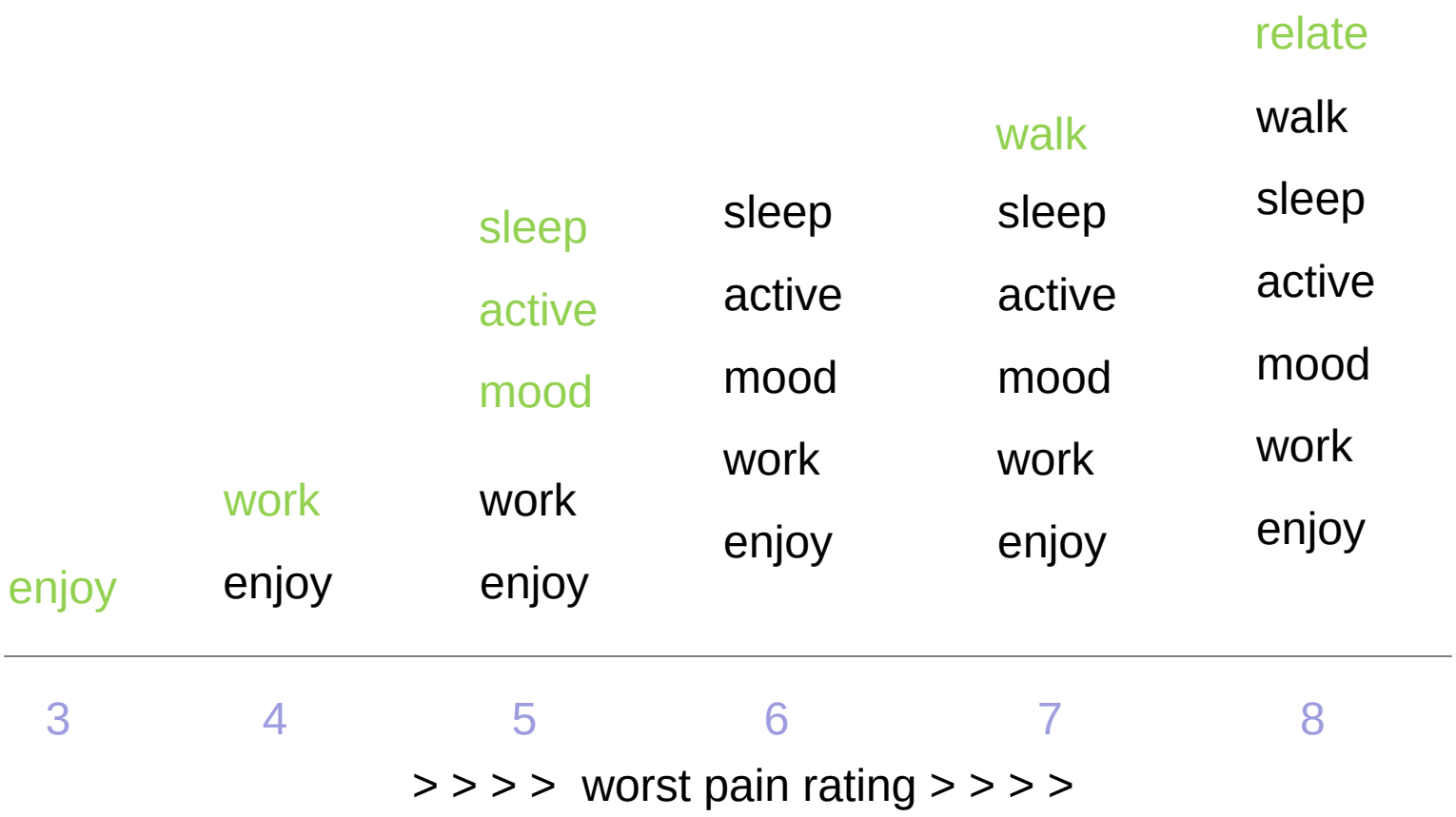
Current Cancer Pain Management

- Most disease-related pain can be controlled with opioids, BUT at a cost in side effects
- Treatment-related pain more difficult to control (especially that caused by nerve damage)
- Agents that prevent/reduce pain targeted at *mechanisms* of pain production of potentially great benefit – “opioid sparing”

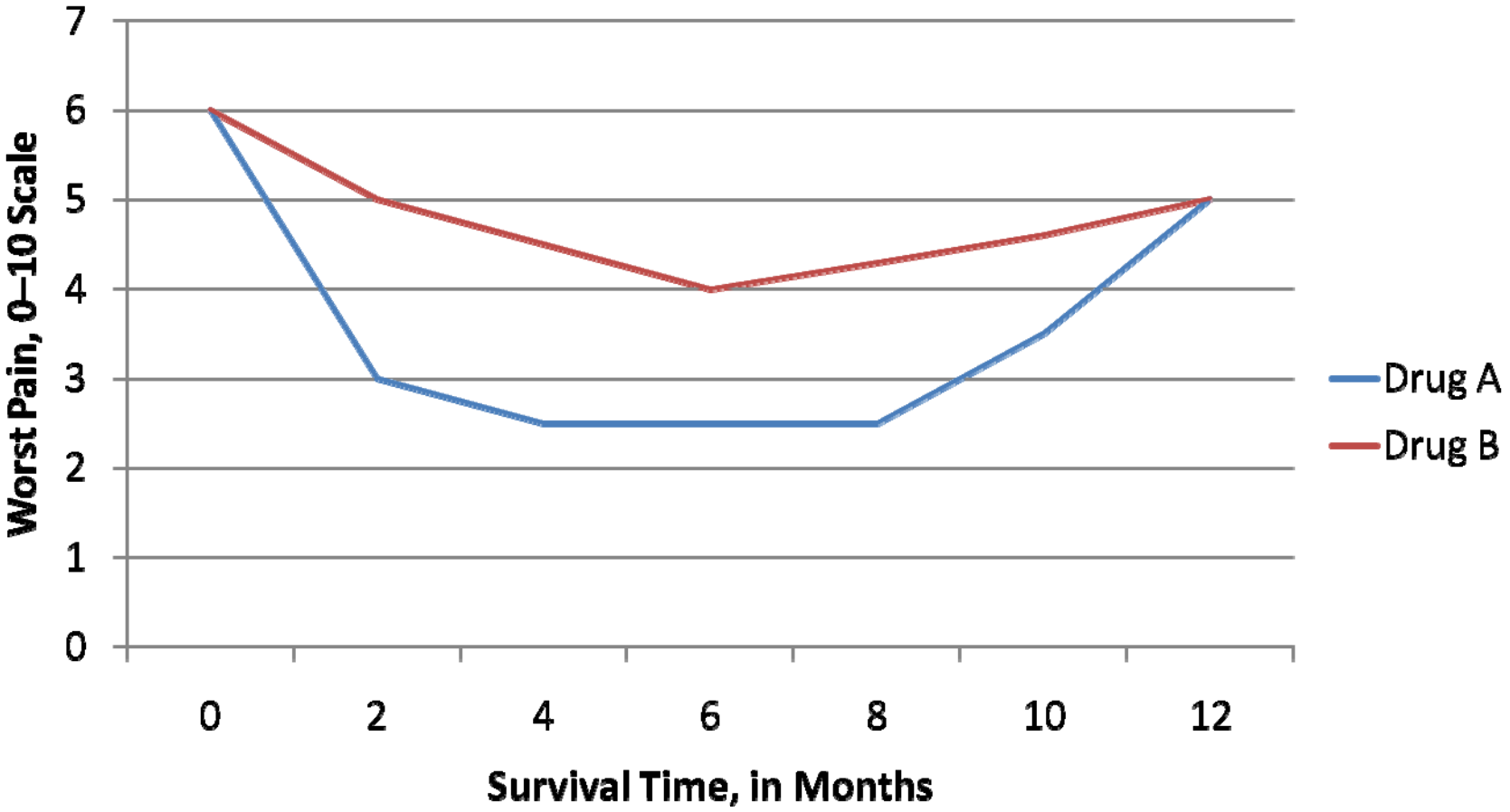
Pain “Benefit” in Cancer

- The pain benefit of a treatment is related to both
  - the reduction of pain severity/impact
  - the time of overall survival spent with no or lower severity pain.

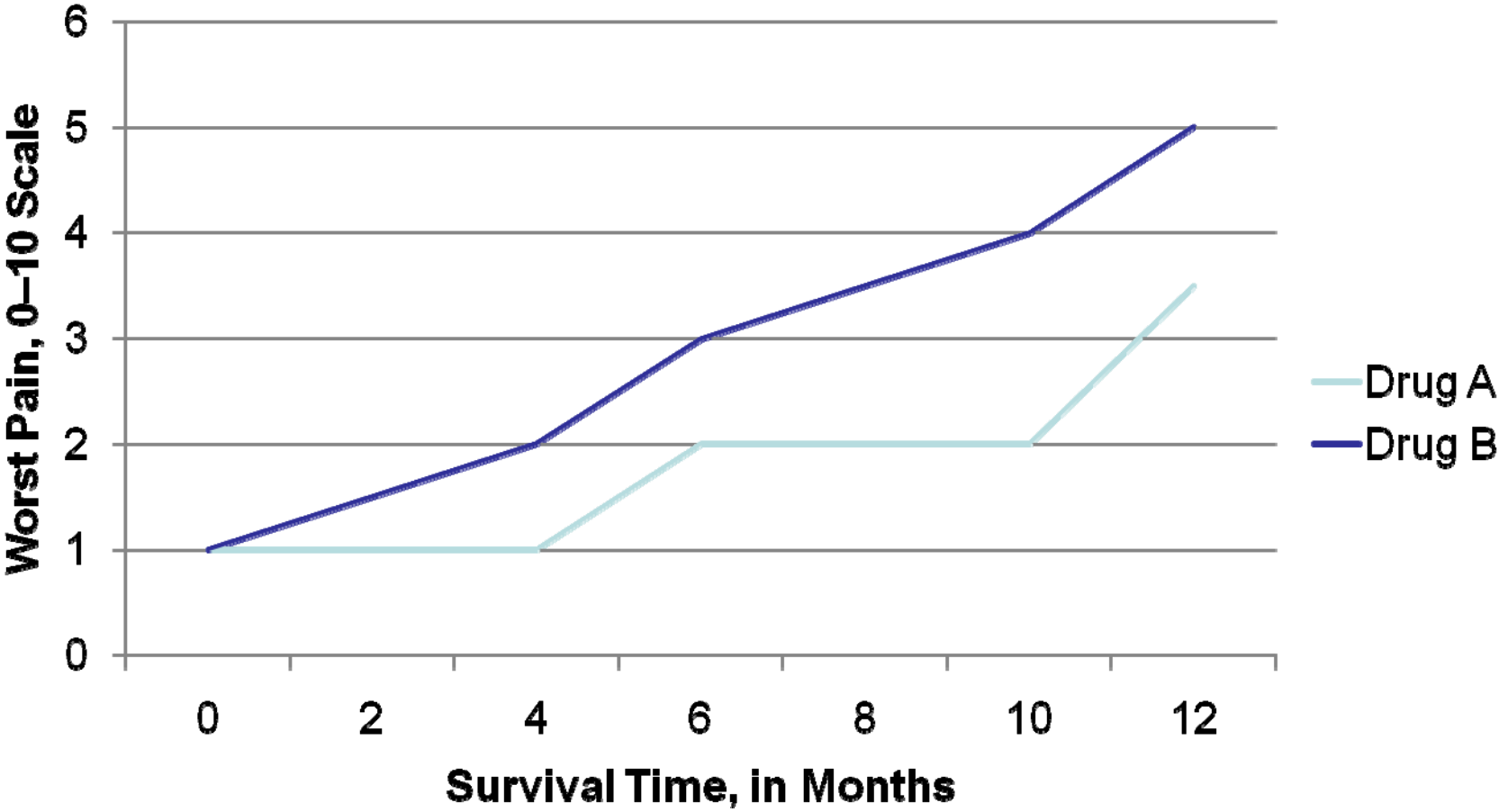
Activities Impaired by Increasing Pain



Pain Palliation as Benefit



Pain Prevention as Benefit



Challenges for Implementation

- Why or why not do sponsors include pain?
- Is pain a primary or secondary endpoint?
- How do palliation and progression endpoints differ?
- How to incorporate effects of analgesics in endpoints?
- How to separate effects of agent on pain and tumor burden?

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NCI Perspective

Ann O'Mara, PhD, RN

Head, Palliative Care Research

Division of Cancer Prevention, NCI

RTOG 9714: Short vs. Long-Course for Palliation of Painful Bone Metastasis

- 8 Gy vs. 30 Gy
- Breast or prostate cancer
- Endpoints: pain and narcotic relief
- 898 patients
- Stratified by # of painful sites, treatment site, initial worse pain score, use of bisphosphonates

Endpoint Evaluation

- At 3 months after radiation therapy:
  - Worst pain score on Brief Pain Inventory
  - Use of any narcotic pain medication
- Complete response: no pain, no narcotics
- Partial response: Pain score $\leq$2 at baseline
- Stable response: Pain +/- 1
- Progression: Pain $\geq$2

Results

- No difference between 2 arms:
  - Complete, partial, stable or progression of pain
  - Use of narcotics
  - Pathologic fracture incidence

Other Symptoms

- Early stage prostate cancer
  - What is the effect of different radiation approaches (external beam, brachytherapy, protons, fractionated stereotactic radiotherapy) on symptoms (urinary, bowel, erectile dysfunction)?

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Martin Zagari, MD

Amgen

Contemporary Drug Development Reality and Symptom Endpoints

- Drug development costs continue to escalate, research productivity is down, and payment for future innovative product increasingly uncertain
- Designing increasingly complex trials is not the primary challenge (industry and FDA are used to complexity)
- The measurement of pain or symptoms is imperfect, path to labeling and meaning of results often unclear, and risk perceived as high
  - Can't be done in time for phase 3; Unforeseen benefit in ph 2
  - Reluctance to allocate alpha for uncertain results
  - "Hard" regulatory requirements and trial "must haves" are (of course) prioritized first
  - Downside outweighs upside (efficacy requirements are very high but safety labeling is increasingly broad and inclusive)

What Would Stimulate More Pain and Symptom Research Interest?

- Ability to qualify instruments (or more instruments qualified)
- More Pathways to Labeling or Provider Access to Pain Outcome Results (“Appropriate but Attainable”)
- Consistency in Interpretation (and understanding) of Results by DACs, Medical Review Divisions, and SEALD
- Guidance from FDA on Oncology-Related Pain Assessment Methodology
- Development and Qualification of Enabling Technologies

Could Labeling Provide More Clinical and Outcomes Information?

- Can we accelerate instrument qualification (C-PATH as a path)?
- After a drug is shown to have an effect, are noteworthy secondary pain findings as important as safety results in helping physicians and patients make a balanced risk-benefit decision?
- Could there be a US equivalent of the Pharmacodynamic section of the European SmPC* where noteworthy trial results (including pain or other outcomes) are considered for listing even if alpha is not allocated?

*Summary of Product Characteristics

Can We Reduce Uncertainty in the Review Process?

- How do we reach agreement on a meaningful difference for a secondary pain outcome (i.e. what do we power for)?
  - Sponsors and FDA may not agree on a meaningful change
  - Is it necessary to spend alpha or are some *pain* differences important enough to be “self evident”? What are they?
- Does a secondary cancer pain treatment effect need to be as large as might be required for an analgesic?
- Are advisory committees and other review groups well versed enough in assessment of these outcomes?

Could FDA Develop Guidance for Oncology-Specific Pain Measurement and Analysis?

- Could industry and FDA develop endpoints for analgesia-sparing, or conventions for adjusting pain results for analgesia use?
- Can standards be agreed (or shared) for:
  - Acceptable drop out rate and missing data handling
  - Event-driven assessment and modeling (e.g. time varying techniques)
  - Non-inferiority margin for additive (supportive) treatments

How can Technology be Deployed More Effectively?

- Real-time, mobile devices could allow for collection of vastly more pain or functional impact information but costs and qualification in time for cancer trials is a challenge (many tumor types)
  - What would it take to create a cross-oncology platform?
- Is there an opportunity for functional endpoints such as Patient Activity Monitoring (PAM)?
- When are “smart” mobile devices ready for prime time?

Trial Scenarios

	Scenario 1	Scenario 2	Scenario 3
Type of compound	Anti neoplastic NME with new MOA	Similar MOA with similar survival	Pain molecule
Potential benefit	Pain palliation in addition to treatment of mCRPC	Similar survival in mCRPC but decreased painful neuropathy	Novel pain modifying agent may decrease time to cancer pain progression when added to second line
Instruments	Would qualification be required for both palliation *and* reduction in progression?		
Analgesia use and treatment benefit	How much reduction in pain is meaningful? How much reduction in analgesia is meaningful?	How is onset defined? Time to analgesic use? Interaction of analgesia with pain?	
Endpoint	Composite pain and analgesia? Time to pain or analgesia use? AUC, vs “worst pain” ?		
Alpha	Is there ever a magnitude of benefit where pre-specification would not be required for labeling?		Would non-inferiority be required and would it vary with pain effect?
Rescue			How would one approach rescue for pain?
Technology	Are some preferred technologies emerging that enable richer patient input?		

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Carole Baas, PhD

Patient Advocate

"In cancer patients, pain is one of the most feared and burdensome symptoms."

van den Beuken-van Everdingen. Ann Oncol. 2007

"Pain occurs in approximately one quarter of patients with newly diagnosed malignancies, one third of patients undergoing treatment, and three quarters of patients with advanced disease, and is one of the symptoms patients fear most."

Swarm R, et al. Adult Cancer Pain. J Natl Compr Canc Netw. 2010

"Despite the clear WHO recommendations, cancer pain is still a major problem. The increasing number of cancer survivors who live to an advanced age means that it is of paramount importance to reduce the prevalence of pain at all stages of the disease process."

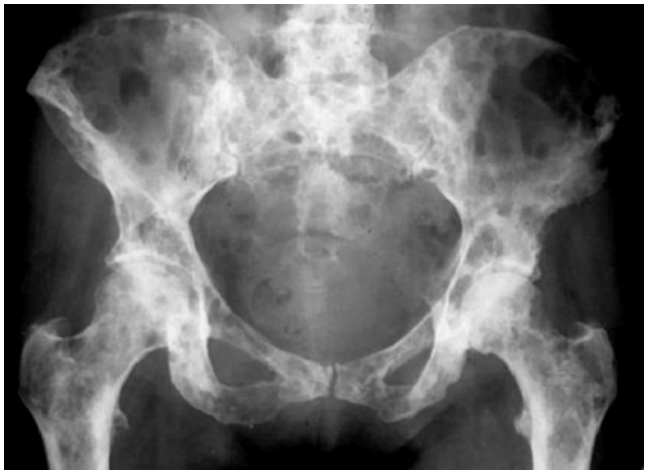
van den Beuken-van Everdingen. Ann Oncol. 2007

Why Pain Management in Patients with Metastatic Cancer?

- Pain is usually what gets patients with advanced cancer to the doctor
- Pain is usually associated with poor quality of life
- Physical pain is associated with psychological pain and spiritual pain
- Other symptoms are diagnosed and causes of the pain are identified
- Control of pain will help patients focus on getting their cancer under control

Case Study and Pain Management 1

- A 58 year old African American male is presented to the multi-disciplinary prostate cancer clinic with a PSA of 1200. His biopsy results were Gleason score of 10 (T4); advanced prostate cancer.



•CT scans and bone scan indicate extensive and aggressive cancer in hips, spinal region and shoulders.

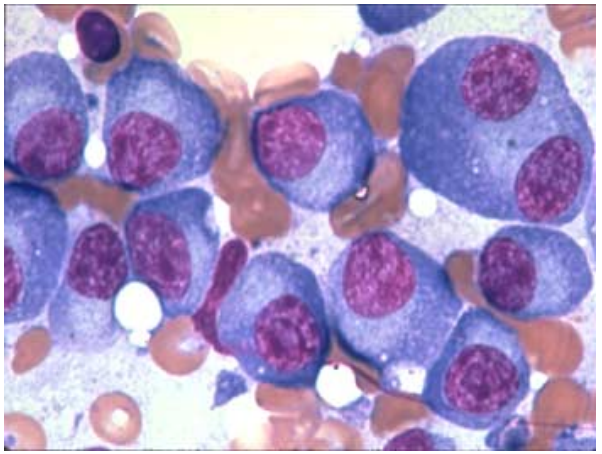
•Arrives in wheelchair and is physically unable to stand due to a tremendous amount of back and hip pain.

Pain Management & Quality of Life

- Patient was given a hormone injection (3 month LUPRON) to halt the onset of the cancer
- Patient also was scheduled for treatments with ZOMETA and EBRT (external beam radiation therapy)
- Patient returned to clinic in one month with reduced PSA score and walked into clinic with the use of walking cane (still unsteady)
- Patient and family reported significant reduction in pain and subsequently patient was able to resume walking
- Patient quality of life improved with pain management

Case Study and Pain Management 2

- 55 year old man is diagnosed with Stage 1 multiple myeloma
- Treated with steroids, chemotherapy, thalidomide and bone marrow transplant



- Relapsed 1 year later, treated with the corticosteroid dexamethasone (Decadron) and Lenalidomide (Revlimid)
- Now at Year 5: Experiencing progressive neuropathy in feet and hands

Pain Management & Quality of Life

- Patient has numbness in hands and feet
- Patient is a critical care physician: *“Working is who I am and what I do. I’m not ready to quit. I don’t want to lose function, particularly in my hands.”*
- Treatment-induced neuropathy has had a significant impact on patient’s quality of life and ability to function and work
- *“There’s a gap in practitioners’ understanding of the real treatment course. They understand the disease but not the side effects of treatment.”*

Oncology patients are interested in:

- achieving clinically meaningful beneficial effects on disease-related symptoms
- ability to carry out normal activities
- overall survival

Fleming TR, Rothmann MD, Lu HL. J Clin Oncol. 2009

"…pain management is not only for end-of-life care… There is a new population of patients who have essentially been cured or who can expect long-term survival but have been left with serious pain issues as a result of treatment."

Sherman C. Oncology Nurse Advisor 2010