

Harnessing Advocacy Relationships To Deal With Serious Safety Issues

Recent experience with a serious complication, osteonecrosis of the jaw (ONJ) potentially attributable to bisphosphonate use in cancer patients, illustrates how existing advocacy relationships can play a key role in early management of serious safety issues. While the gold standard in evaluating drug safety remains the prospective clinical trial, the lead time to gather such data is unacceptable when dealing with approved drugs in wide use. Advocacy organizations can leverage existing relationships to quickly gather data to help patients and their physicians make better decisions while the prospective studies proceed in parallel.

We became aware of the problem from people coming to multiple myeloma support groups or calling the International Myeloma Foundation (IMF) hotline reporting problems with their jaws. Soon thereafter, oral surgeons Marx and Ruggiero published articles reporting ONJ in over 90 patients, all of whom had been taking bisphosphonates. ONJ is a condition in which a part of the jaw bone dies, which can result in loss of teeth, death of the gums, exposed bone, bone spurs, poor healing, infection and pain. To make matters worse, some people with ONJ were being treated with surgery, including jaw replacements, which tended to make the problem worse, since bone metabolism was compromised, interfering with healing.

Most of the people reporting the problem had been taking Zometa or Aredia, bisphosphonates widely used in myeloma and other cancers to prevent or minimize bone destruction. Talking to other advocates, it was clear that this was an issue that went beyond myeloma, involving people with breast and prostate as well as other cancers.

Working with Brian Durie, chairman of the IMF and a hematologist at Cedars-Sinai Outpatient Cancer Center, we developed a web-based survey to get diagnosis and treatment histories for cancer patients with an eye towards understanding more about who was getting ONJ and what might the risk factors be. We were able to partner with Y-ME National Breast Cancer Organization and Nexcura to reach beyond the myeloma community.

In less than 30 days, we were able to gather over 1200 responses to an extensive survey that provided detailed data on cancer diagnosis and treatment, as well as specific information on ONJ symptoms and other dental problems. The data showed a clear elevated short-term risk for ONJ in patients taking Zometa, a potent bisphosphonate introduced just a few years ago. It also showed a longer-term risk for those taking Aredia, another bisphosphonate that's been available for about a decade. There was no association evident with a broad spectrum of other

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cancer treatments reported. The majority of the patients with ONJ had had dental problems and/or a major dental procedure that preceded the ONJ diagnosis.

There are many technical issues with the data, primarily because the survey was conducted anonymously via the web (to avoid HIPAA issues) and entailed patients self-reporting data. The survey could not be used for any estimates on incidence, as there was no random sampling. Despite these issues, the message for patients was clear. There is good reason to believe that taking Zometa or Aredia puts one at increased risk for developing ONJ. There are common sense precautions that should help, but can't guarantee safety (e.g., having a dental workup and fixing dental problems before beginning bisphosphonate therapy, avoiding major dental procedures while on therapy.) And, prophylactic use of bisphosphonates in patients with no overt bone disease, long a "no-brainer" in myeloma management, was no longer a "no-brainer."

While many have focused on the technical limitations inherent in an anonymous, web-based survey, the results were accepted for oral presentation at the 2004 meeting of the American Society of Hematology and were the centerpiece of an FDA Oncologic Drugs Advisory Committee hearing on the issue. Via the IMF website (<http://www.myeloma.org>) many patients and physicians have reviewed the results and used them to better inform their decisions.

Efforts are proceeding on more elaborate and rigorous retrospective and prospective studies. Unfortunately, it will be years before conclusive evidence can be assembled. As a patient who is currently being treated with bisphosphonates, I am very glad to have the information from our survey in hand to help me make better decisions today.

For more information on Osteonecrosis of the Jaw, please see <http://osteonecrosis.myeloma.org> or call the International Myeloma Foundation hotline at 800-452-2873 (818-487-7455 outside of the US and Canada.)

Submitted by Mike Katz, International Myeloma Foundation

Targeted Therapies Continue To Change Clinical Practice

You may be aware of the release of interim data from trials on the use of bevacizumab (Avastin) in metastatic breast cancer and the use of trastuzumab (Herceptin) in the treatment of adjuvant breast cancer. Details of the findings from these trials will be available at the American Society of Clinical Oncology (ASCO) in May.

The phase III study *A Randomized Phase III Trial of Paclitaxel (Taxol) vs. Paclitaxel and Bevacizumab (Avastin) as First Line Therapy for Locally Recurrent or Metastatic Breast Cancer (E2100)* met its primary efficacy endpoint of showing an improvement in progression-free survival with the use of bevacizumab and paclitaxel when compared to chemotherapy alone.

Avastin is a monoclonal antibody that targets the vascular endothelial growth factor (VEGF) and stops or slows angiogenesis in tumors. It has shown efficacy in the first and second line treatment of metastatic colorectal cancer, first line treatment in metastatic NSCLC and now in first line treatment of metastatic breast cancer. There are studies that are looking at the use of Avastin in other solid tumor cancers. Avastin appears to work across cancers because it targets a process necessary for all solid tumor cancers to grow, angiogenesis. Angiogenesis in cancer is the creation of new blood vessels that can bring nourishment to the tumor. Without this source of nourishment tumors could not grow large enough to endanger lives.

The question of whether Herceptin is safe and effective in the adjuvant treatment of breast cancer finally seems to have an answer. The interim analysis of two studies (*NSABP-B-31: Phase III Randomized Study of Doxorubicin and Cyclophosphamide Followed By Paclitaxel With or Without Trastuzumab (Herceptin) in Women With Node-Positive Breast Cancer That Overexpresses HER2* and *NCCTG-N9831: Phase III Randomized Study of Doxorubicin Plus Cyclophosphamide Followed By Paclitaxel With or Without Trastuzumab (Herceptin®) in Women With HER-2-Overexpressing Node-Positive or High-Risk Node-Negative Breast Cancer*) showed that improvement in overall survival was statistically significant for women receiving a combination of chemotherapy and trastuzumab. Women in both studies were carefully monitored for cardiac toxicity. Chemo-

therapy of the type given in these studies has a risk of congestive heart failure (weakening of the heart muscle) of less than 1 percent. In these studies, the likelihood of congestive heart failure in women receiving the combination of chemotherapy and trastuzumab was increased to 3% to 4%. While this increase is of concern, it must be weighed against the fact that HER2 positive breast cancer is very aggressive with a high rate of recurrence.

Expect to continue to hear more about targeted therapies. They will play a significant role in the treatment of all cancer in the future.

<http://www.cancer.gov/newscenter/pressreleases/HerceptinCombination2005>

<http://cancer.gov/newscenter/pressreleases/AvastinBreast>

Call for Registration and Disclosure of Results of Clinical Studies

The call for an international registration of all clinical study protocols and the results of those studies has been gaining support due to selective reporting of clinical trial results that affect public health. An excellent example is the non-disclosure of results of studies of selective serotonin reuptake inhibitors for childhood depression.

Advocates that want to follow this issue might be interested in what has become known as the Ottawa Statement. Canadian Institutes of Health Research hosted an open meeting on October 4, 2004 in Ottawa, Canada, to foster international consensus on trial registration. The assembled group discussed a set of guiding principles for the development of trial registers. These principles have been published as the Ottawa Statement, Part 1. <http://ottawagroup.ohri.ca/statement.html>

Summary points of the Ottawa Statement are:

- Registration and early public release of accurate information about all trials is necessary to fulfill an ethical obligation to participants
- Although protection of commercial and other interests is important, the social contract with participants should take precedence
- All trial results should be registered and publicly available, along with sufficient protocol information to enable critical assessment of their validity

Advocates who wish to contribute further to the Ottawa statement are invited to become involved (<http://www.ottawagroup.ohri.ca>). The group will meet in Portland, Oregon, on May 22, 2005 during the 26th annual meeting of the Society for Clinical Trials to discuss how these principles can be put into practice.

Calendar-What is Research Advocacy Network Doing?

March 2005

Sun	Mon	Tue	Wed	Thu	Fri	Sat
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

- **March 16-17** -University of North Carolina, School of Public Health, Health Advocacy Conference
- **March 18**—ECOG Developmental Therapeutics Committee Retreat

April 2005

Sun	Mon	Tue	Wed	Thu	Fri	Sat
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
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- **April 11-** UCSF Breast SPORE External Advisory Board
- **April 14-15** NCI Understanding SEER Data Conference
- **April 16-20** American Association of Cancer Research Annual Meeting
- **April 18-** Public Affairs Network Presentation
- **April 18-21**—NCCTG Patient Advisory Working Group
- **April 30-** Indiana University Center of Excellence Breast Cancer Advocate's Symposium

May 2005

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

- **May 1-5** American Society of Colon and Rectal Surgeons
- **May 1-2** National Comprehensive Cancer Network Breast Adjuvant Committee
- **May 13-17th** American Society of Clinical Oncology Annual Meeting
- **May**—Focus on Research Course

Watch Research Advocacy Network website for ISSUES section:

<http://www.researchadvocacy.org>

- Clinical Trials Working Group
- Funding Crisis in Translational Research
- Letter about Silicone Breast Implant

Research Advocacy Network

Advancing Patient-Focused Research

Network News

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