

NEWS

Highlights from the latest news and research in clinical investigation

Zoledronic acid in conjunction with chemotherapy: bisphosphonate gives fresh hope for newly diagnosed multiple myeloma patients

Research presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO) demonstrate that treating newly diagnosed multiple myeloma patients with a combination of Zometa® (zoledronic acid) and first-line chemotherapy significantly improves overall and progression-free survival. Zoledronic acid is a bisphosphonate used in conjunction with chemotherapy to prevent skeletal fractures and other skeletal-related events (SREs) in the treatment of certain cancers. These results indicate that the drug has anticancer effects in addition to its effect on bone complications, “This is a very important study that provides clear-cut evidence for the first time of the antitumor effect of zoledronic acid in multiple myeloma, something that we have observed in the laboratory but have not confirmed clearly in the clinic trials until now” comments James Berenson of the Institute for Myeloma and Bone Cancer Research exclusively to *Clinical Investigation*.

“...addition of zoledronic acid to postsurgery hormonal therapy increased disease-free survival in premenopausal women, confirming earlier trial results and highlighting the potential application of the dual effects of zoledronic acid in the treatment of cancer.”

Zoledronic acid, approved in more than 100 countries and the most widely used bisphosphonate in an oncological setting,

is used to reduce or postpone SRE in multiple myeloma, a type of cancer causing bone lesions and affecting bone marrow, and for other metastatic cancers including breast, lung and solid tumors involving the bone.

The study, lead by Gareth Morgan at the Institute of Cancer Research, aimed to establish whether bisphosphonates used in an oncology setting affect the outcomes in patients with multiple myeloma beyond their effect on SREs.

Approximately 2000 patients with newly diagnosed multiple myeloma were enrolled between May 2003 and November 2007, and randomly allocated one of the following treatments: either an infusion of zoledronic acid 4 mg every 3–4 weeks or an oral dose of clodronic acid 1600 mg daily, another bisphosphonate used in an oncological setting. These treatments were both administered alongside first-line chemotherapy. The primary end points of the trial were overall survival, progression-free survival and overall response rate. Berenson explains the novelty of this trial in highlighting the effects of zoledronic acid: “Most previous studies done in multiple myeloma with these types of drugs involved patients receiving a wide variety of different antimyeloma treatments, not simply a regimen plus a weak bone drug in the same class as clodronate versus the much stronger drug zoledronic acid. This made it difficult to establish the antimyeloma effect of zoledronic acid in prior studies”.

Zoledronic acid showed a reduction in mortality of 16% versus clodronic acid as well as an extended median overall

survival of 5.5 months. These anticancer effects were in addition to the drug’s beneficial effects on SREs. Zoledronic acid also outperformed clodronate in the prevention of SREs associated with multiple myeloma, showing a reduction in risk of 24% more than clodronate. Both bisphosphonates displayed similar response rates, patient tolerance and occurrence of adverse events related to bisphosphonate treatment.

The findings complement other data on zoledronic acid, also presented at the ASCO annual meeting as part of the 5-year follow-up analysis of the Phase III Austrian Breast and Colorectal Cancer Study Group-12 (ABCSG-12) trial. These results demonstrate that addition of zoledronic acid to postsurgery hormonal therapy increased disease-free survival in premenopausal women, confirming earlier trial results and highlighting the potential application of the dual effects of zoledronic acid in the treatment of cancer.

Summarizing the trial results, Berenson says “This study opens the door to looking at these drugs (bisphosphonates) and newer analogs in terms of not only their antitumor effects but also their potential to change the course of patients’ disease and most importantly extend their overall survival.”

Sources: Morgan GJ, Davies FE, Gregory WM *et al*. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet* 376(9757), 1989–1999 (2010); Newly diagnosed multiple myeloma patients - Zometa® added to chemotherapy shown to considerably improve survival: www.medicalnewstoday.com/articles/191631.php

Paliperidone extended-release: first antipsychotic treatment for schizoaffective disorder to receive approval in the EU

Paliperidone extended-release (INVEGA®), an antipsychotic developed by Janssen–Cilag International, has received approval in the EU for use in the treatment of schizoaffective disorder. The approval followed a recommendation of the treatment, an extended-release formulation of the antipsychotic paliperidone, by the Committee for Medicinal Products for Human Use (CHMP), the scientific committee serving the European Medicines Agency.

Schizoaffective disorder is characterized by expressions of both schizophrenia and other major mood disorders such as depression or bipolar disorder. Symptoms such as hallucinations or delusions as well as mania and/or depression make schizoaffective disorder a highly disabling mental illness.

Following the results of two clinical trials, it was concluded that paliperidone extended-release can provide a significant clinical benefit to sufferers of schizoaffective disorder and is the only antipsychotic approved for treatment of the disorder in the EU. Christophe Tessier at Janssen–Cilag International highlights the importance of the approval “We are proud to be able to bring to market the first antipsychotic treatment for schizoaffective disorder in Europe – a difficult-to-diagnose condition associated with a high rate of hospitalizations and suicidal behavior”.

Both trials were randomized, 6-week, double-blind, placebo-controlled studies. The first, from October 2006 through to February 2008, involved 316 patients with schizoaffective disorder as measured by the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS) and/or Hamilton

Depression Rating Scale (HDRS). A high (12 mg) and low (6 mg) dose of paliperidone extended-release was investigated, the outcome of treatment with the higher dose showed significant improvement compared with the placebo, however, treatment with the lower dose did not.

The second trial, which involved 311 patients diagnosed with schizoaffective disorder as measured by the YMRS, investigated the effect of extended-release paliperidone in both 6 mg and flexible doses as a monotherapy or in conjunction with mood stabilizers and/or antidepressants. Paliperidone extended-release improved symptoms both as a monotherapy as well as an adjuvant, and had the greatest effect on those who displayed prominent manic or depressive symptoms prior to treatment.

These two complementary studies constitute the first program for antipsychotic treatment in schizoaffective disorder. Lead investigator Carla Canuso comments “These two studies combined represent the largest set of prospective data in patients with schizoaffective disorder and provide important insights into this understudied disease. INVEGA was proven to be effective both as a monotherapy and as an adjunctive therapy in reducing psychotic and manic symptoms and provides a welcome treatment option for this debilitating condition.”

Sources: Canuso CM, Lindenmayer JP, Kosik-Gonzalez C *et al.* A randomized, double-blind, placebo-controlled study of 2 dose ranges of paliperidone extended-release in the treatment of subjects with schizoaffective disorder. *J. Clin. Psychiatry* 1(5), 587–598 (2010); Canuso CM, Schooler N, Carothers J *et al.* Paliperidone extended-release in schizoaffective disorder: a randomized, controlled study comparing a flexible dose with placebo in patients treated with and without antidepressants and/or mood stabilizers. *J. Clin. Psychopharmacol.* 30(5), 487–495 (2010); INVEGA® approved as first and only antipsychotic treatment for schizoaffective disorder in the European Union: www.jnj.com/connect/news/all/invega-approved-as-first-and-only-antipsychotic-treatment-for-schizoaffective-disorder-in-the-european-union; Janssen’s INVEGA has become the first drug to be licensed in Europe to treat schizoaffective disorder: www.inpharm.com/news/110106/janssen-invega-paliperidone-schizoaffective-approval-europe

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact:

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Arctic Front® catheter system approved for atrial fibrillation

Medtronic have announced the US FDA approval of its Arctic Front® Cardiac CryoAblation Catheter System, making it the first and only cryoballoon in the USA indicated for the treatment of drug refractory paroxysmal atrial fibrillation. This novel technology uses a balloon-based technology delivered through a catheter with a coolant rather than heat, creating circumferential lesions around the pulmonary vein to block the conduction of arterial fibrillation in cardiac tissues.

This freezing technology also allows for greater catheter stability as the catheter is able to adhere to the tissue during ablation. “This technology represents a significant improvement over currently used focal ablation treatment for atrial fibrillation” enthused Vivek Reddy, Director of Electrophysiology Laboratories at The Mount Sinai Medical Center.

The FDA approval of the Arctic Front system was based on results from the pivotal

Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial, which were presented at the American College of Cardiology 2010 Scientific Sessions last year. Investigators of the trial enrolled 245 patients with paroxysmal arterial fibrillation at 26 centers with the purpose of comparing the cryoballoon ablation technique with antiarrhythmic drug therapy.

“This unique ablation approach ... [provides] a straightforward and efficient approach to pulmonary vein isolation, while giving patients a new, minimally invasive treatment approach proven to be safe and effective...”

The results demonstrated that 69.9% of patients treated with the Arctic Front system were free from atrial fibrillation at year

one, compared to 7.3% of patients treated with drug therapy only.

The device also had a good safety profile with limited procedure-related adverse events (3.1%) and patients enrolled in the study displayed a significant reduction of symptoms, a decrease in the use of drug therapy and substantial improvements in both physical and mental quality-of-life factors.

“This unique ablation approach fills an unmet need in arterial fibrillation ablation by providing a straightforward and efficient approach to pulmonary vein isolation, while giving patients a new, minimally invasive treatment approach proven to be safe and effective” concluded Reddy.

Source: Medtronic receives FDA approval for first and only cryoballoon ablation treatment in the US for paroxysmal atrial fibrillation: www.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1292604350495&lang=en_US

Heart failure risk associated with bevacizumab used in the treatment of breast cancer, study suggests

Bevacizumab, a chemotherapy agent used in the treatment of metastatic cancers, has been implicated in an increased risk of heart failure in those receiving treatment by a new study published in the *Journal of Clinical Oncology*. The study, led by Toni Choueiri, associated the drug with a five-fold increased risk of congestive heart failure (CHF) in patients receiving treatment for metastatic breast cancer. An editorial by Nitin Verma and Sandra Swain of the Washington Cancer Institute, published alongside the study, advised ‘extreme caution’ in the interpretation of these result. This comes on top of a recent announcement from the FDA that it was seeking to remove market approval of the drug in the treatment of metastatic breast cancer, saying it does not prolong overall survival and comes with severe toxicity risks.

Bevacizumab is a humanized monoclonal antibody, used in the treatment of cancer, it recognizes and blocks VEGF A

and is associated with risks of high blood pressure and hemorrhage. The published study by Choueiri involved a meta-analysis of five trials on bevacizumab in the treatment of breast cancer, which were selected from a PubMed search of articles between 1966 to March 2010 and data presented at the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium annual meetings. The analysis aimed to establish if the therapy carried an associated risk of CHF in patients.

The selected trials consisted of 3784 subjects – patients with uncontrolled hypertension, CHF, vascular disease, angina and a recent history myocardial infarction were excluded. However, the trials did include patients previously treated with anthracyclines, known to cause irreversible damage to heart cells.

Results of the analysis showed that, incidence of CHF was significantly higher in the bevacizumab-treated group when

compared to the placebo group. In further analyses, no significant differences were observed in CHF risk between patients treated with low versus high doses of bevacizumab or those treated with different bevacizumab regimens. The authors state that “this is the first comprehensive report to show that bevacizumab is associated with an increased risk of significant heart failure in patients with breast cancer.”

However, the accompanying editorial criticized these results, stating a number of limitations – previous anthracycline use among some selected patients being the major one. In the report, anthracycline exposure among patients in the five trials was from 30 to 100%. “Patients with previous anthracyclines already have a damaged heart, so it is possible that the bevacizumab could add to that. Or, it could just be related to the anthracyclines, period, and not at all related to the bevacizumab,” comments Swain. Lack of

patient information such as a history of diabetes or cumulative exposure to some chemotherapy agents, both of which could cause a predisposition to heart failure were not presented in the report, meaning that the analysis ignores the individual, points out Swain in her editorial. Further to this, the editorial highlighted that randomized trials of bevacizumab in the treatment of other metastatic cancers, such as colorectal, lung and renal cell cancer have not reported any cases of heart failure.

Swain does not rule out the possibility that bevacizumab is a cardiotoxin, especially in light of its proven effect on blood pressure “Bevacizumab does confer a significant risk of hypertension, and there is no controversy about that. That is very clear, and the hypertension could contribute to heart failure”; however, she points out that caution must be advised when interpreting the results.

Swain suggests in her editorial that judgement on bevacizumab should be withheld until the results of three ongoing trials: BEATRICE,

E5103 and BEST, which will assess bevacizumab in an adjuvant role, “These trials will really give us the data because those patients are evaluated prospectively with different heart imaging. We should really wait for those trials before we pass sentence on bevacizumab with regard to heart failure. There are certainly reasons why it can occur, and it obviously did occur in some patients. The question is: is it related to the bevacizumab or is it the anthracycline, or is it the combination of both these things, or is it because the patients had left-sided radiation? There are a lot of questions.”

Sources: Choueiri TK, Mayer EL, Je Y *et al.* Congestive heart failure risk in patients with breast cancer treated with bevacizumab. *J. Clin. Oncol.* doi: 10.1200/JCO.2010.31.9129 (2011) (Epub ahead of print); Verma N, Swain SM. Bevacizumab and heart failure risk in patients with breast cancer: a thorn in the side? *J. Clin. Oncol.* doi: 10.1200/JCO.2010.31.9129 (2011) (Epub ahead of print); FDA says Avastin does not work for breast cancer: www.google.com/hostednews/afp/article/ALeqM5gOiIsdz9zLSJ-0J3I6LG44Ui7SMw?docId=CNG.a03843bc6289f00ba74faca28ff52cf9.491