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Bevacizumab Linked to Higher Mortality Risk

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MedPage Today Action Points

- Note that in this meta-analysis, bevacizumab was associated with an excess mortality risk, particularly in patients who were also receiving platinum or taxane therapy.
- Note also that patients with prostate cancer, lung cancer, and renal cell carcinoma had the highest risk of fatal adverse events.
- Point out, however, that the authors noted that the overall risk of fatal adverse events was low and should be weighed against the potential benefits of treatment with bevacizumab.

Review

Cancer patients treated with the angiogenesis inhibitor bevacizumab (Avastin) had almost 50% more fatal adverse events compared with control groups, data from a meta-analysis of 10,000 patients showed.

The 16 studies included in the analysis had a 2.5% cumulative incidence of fatal events in bevacizumab-treated patients compared with 1.7% among patients treated with regimens that did not include the targeted agent. Hemorrhage was the most common fatal event associated with bevacizumab, investigators reported in the Feb. 2 issue of the *Journal of the American Medical Association*.

The mortality association varied significantly by the type of chemotherapeutic agent or agents paired with bevacizumab, with taxanes and platinum drugs conferring the highest risk.

The overall risk of fatal adverse events was low, the authors noted, and should be weighed against the potential benefits of treatment with bevacizumab.

"The increased risk of fatal adverse events associated with bevacizumab may vary with bevacizumab doses or tumor types," Vishal Ranpura, MD, Sanjaykumar Hapani, MD, and Shenhong Wu, MD, PhD, of Stony Brook University Medical Center in New York, wrote in conclusion.

"Further efforts are needed to reduce fatal adverse events due to hemorrhage, neutropenia, and gastrointestinal perforation in association with bevacizumab therapy. It is important for physicians and patients to recognize the risks as well as the benefits associated with bevacizumab treatment and to monitor closely to identify and treat serious adverse effects."

The analysis adds another link to a chain of unfavorable news for bevacizumab. In July an [FDA advisory committee](#) voted in favor of revoking the agent's accelerated-approval status for advanced breast cancer. Heeding the committee's advice, the [FDA in December](#) announced that the withdrawal process had begun.

In early January, [another meta-analysis](#) showed an excess incidence of heart failure among breast cancer patients treated with bevacizumab.

Bevacizumab manufacturer Roche-Genentech has requested a hearing to make a case with the FDA to keep the breast cancer indication.

The latest meta-analysis included patients involved in randomized controlled trials that evaluated bevacizumab in a variety of tumor types: prostate, pancreatic, renal cell, breast, lung, and colorectal. Altogether, the authors analyzed data on 10,217 patients.

The patients received a variety of concurrent medications, including conventional chemotherapy and biologic therapy.

The 16 trials included in the analysis consisted of four phase II studies and 12 phase III studies. The total population comprised 5,589 bevacizumab-treated patients and 4,628 patients from control groups. About half of the studies employed a bevacizumab dose of 5 mg/kg, and the rest used 2.5 mg/kg or a combination.

Overall, 148 fatal adverse events occurred in bevacizumab patients, versus 72 in the control groups. The difference translated into a relative risk of 1.46 for bevacizumab versus control therapy ($P=0.01$).

The highest incidence of fatal events in bevacizumab patients was 13.4% and occurred in a phase II trial involving patients with non-small cell lung cancer (NSCLC). The lowest incidence was 0%, which occurred in a phase III breast cancer study.

Analysis of fatal events by tumor type showed significant variation ($P=0.001$), suggesting that tumor type or associated treatment might have a major influence on the risk of fatal adverse events, the authors wrote. Patients with prostate cancer had the highest risk of fatal adverse events (RR 3.85 versus control), followed by lung cancer (RR 2.12) and renal cell carcinoma (RR 1.11).

Breast cancer patients treated with bevacizumab had a reduced risk of fatal adverse events compared with control groups (RR 0.69).

Patients who received the higher dose of bevacizumab had more than a twofold higher incidence of fatal adverse events compared with control group (2.7% versus 1.1%, $P=0.001$). The rate of fatal events did not differ significantly between the lower bevacizumab dose and control therapies.

Analysis of fatal events by concurrent chemotherapy revealed significant interaction ($P=0.045$). Bevacizumab plus a taxane or platinum agent had the highest risk of fatal events (RR 3.49, $P<0.001$), whereas bevacizumab paired with nonplatinum and nontaxane agents was not associated with an excess mortality hazard (RR 0.85).

The authors found that the cause of death was not specified in 54.7% of bevacizumab groups. Among all of the remaining cases, hemorrhage accounted for

23% of deaths, followed by neutropenia (12.2%), gastrointestinal perforation (7.1%), pulmonary embolism (5.1%), and cerebrovascular accident (5.1%).

In an accompanying editorial, University of Michigan oncologist Daniel F. Hayes, MD, said key to striking a risk-benefit balance with bevacizumab will be the identification of patients who are most likely to benefit from treatment.

"Careful review of response rates to bevacizumab suggest that bevacizumab works well, but only in selected patients," Hayes wrote.

"Even though more than 10,000 patients have been enrolled in randomized clinical trials of bevacizumab, few insights are available about specific subgroups of patients who may benefit," he added.

"Thus, oncologists are forced to dilute the potential effects of bevacizumab by exposing all treated patients, and society, to enormous costs and occasional life-threatening toxic effects," Hayes continued. "These unfortunate circumstances are sad for those who pay the bills -- and sadder for patients with solid tumors."

An investigator in one of the trials included in the analysis said the findings, for the most part, confirm what was already known about the risks associated with bevacizumab.

"We have known for a long period of time that bevacizumab can increase the risk of heart attack or stroke, can increase the risk of perforation of the gut, and we certainly know that such events can be fatal," Leonard Saltz, MD, a colorectal cancer specialist at Memorial Sloan-Kettering Cancer Center in New York, told *MedPage Today*.

"An analysis that shows us there is an increase in fatal events with bevacizumab is consistent with the data we already had ... This is not something that should change the routine use of the drug," he added.

Treating cancer is risky, regardless of the treatment used, Saltz continued. The results of the analysis should be considered with that in mind.

"It's important to look at absolute numbers, not percentages," he said. "If you look at the absolute numbers, it's a 1.7% to 2.5% difference. I think that gives you the proper perspective. You could say, well, that's a 50% increase, which sounds a lot scarier, but I'm not sure that's the most appropriate way of looking at it."

Nonetheless, the higher mortality risk with bevacizumab does provide reason for concern, particularly for non-oncologists. Cancer specialists have been aware of the risk associated with the drug, said Saltz, but other physicians might not have recognized the association with potentially serious, and even fatal, adverse events.

Responding to the current analysis, Genentech officials said the findings are not new and pointed out that the analysis included tumor sites for which bevacizumab does not have approval in the U.S.: prostate cancer, pancreatic cancer, and advanced squamous-cell NSCLC.

"For three of the FDA-approved cancer types (advanced colorectal, renal cell, and breast cancers), the incidence of treatment-related deaths reported in this analysis was similar between the Avastin and the control groups," company officials said in a statement. "The higher incidence in NSCLC is known; however, the incidence

reported in this analysis is greater than previously reported due to the fact that the analysis included patients with advanced squamous cell NSCLC, for which Avastin is not indicated.

"Overall, the authors note that 'the absolute risk of treatment-related mortality is low' and the data should be considered in the context of potential benefit with Avastin."

Wu disclosed relationships with Onyx, Novartis, Pfizer, Amgen, and Genentech.

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Ranpura V, et al "Treatment-related mortality with bevacizumab in cancer patients. A meta-analysis" *JAMA* 2011; 305: 487-494.

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Source reference:

Hayes DF "Bevacizumab treatment for solid tumors. Boon or bust?" *JAMA* 2011; 305: 506-508.

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