Understanding the Paclitaxel Dose Effect

Answers to key questions about the paclitaxel controversy, including why the dose-response effect discussion is important and the impact of improved patient-level data collection.

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The recent developments regarding paclitaxel and mortality have been unparalleled in terms of interest, discussion, and controversy, culminating in an FDA panel meeting in June 2019. One of the key issues is whether or not there is a paclitaxel dose effect on mortality. In this article, I'd like to answer five key questions that will hopefully be of interest and move the discussion forward.

1 What did the original *Journal of the American Heart Association (JAHA)* article[1] say about dose?

The meta-analysis published in *JAHA* in late 2018 reported a significant increase in all-cause mortality at 2 and 5 years in patients treated for femoropopliteal disease with paclitaxel-coated devices compared with controls who were not exposed to the drug.[1] The authors postulated that the excess mortality was caused by paclitaxel, using the Bradford Hill criteria[2] to justify causation. For a drug to cause an adverse event, there must be consistency and temporality between the drug exposure and the adverse event. There must also be evidence of a biologic gradient or dose-response relationship. The authors reported a positive dose response at 2 and 5 years using a metaregression analysis and an exposure equation that included device paclitaxel dose, vessel diameter and length, and time.

The meta-analysis methodology is sound, but the assumptions around causation and the dose-response relationship have been criticized. The authors only had access to summary-level data using study-level estimates of lesion length and vessel diameter rather than the exact number, diameter, and length of devices used in each patient. They also miscalculated the paclitaxel dose that patients were exposed to with drug-eluting stents (DESs).

2 Why is the dose-response effect discussion so important?

The presence or absence of a paclitaxel dose relationship to mortality is a key issue. A dose-response relationship is considered proof of causation and is used by regulatory bodies to guide drug safety and efficacy. Although radiation exposure may result in random side effects where severity is unrelated to dose, pharmacologic side effects are deterministic or dose related. Therefore, if no dose-response relationship can be proven, it is likely that the relationship between elevated mortality and paclitaxel exposure reported in the meta-analysis is one of association, not causation. Many possible reasons for this association have been proposed, including forms of trial bias.

An interesting question is if there is a safe dose of paclitaxel. It has been suggested by some physicians and industry partners that using lower-dose paclitaxel devices in femoropopliteal interventions may protect patients from mortality risk. There is no evidence that this is the case. Interestingly, no late mortality relationship has been shown with very low paclitaxel doses used in coronary stents or with much higher doses used in oncology applications.

3 What has been the impact of improved patient-level data collection on the dose discussion?

The FDA released a letter to health care providers in March 2019, noting a significant increase in crude risk of death for paclitaxel-coated devices versus control devices in three pivotal premarket trials evaluating these devices for the treatment of peripheral artery disease. Interestingly, the definition of mortality was not consistent in these studies, and when a single "proportional" method was used to define mortality, there was an inverse relationship between dose and mortality. The highest mortality was associated with the lowest-dose device.[3] The FDA noted that there were considerable missing data on patient vital status, limiting the validity of the findings.

Since that time, trial sponsors have made exhaustive efforts to track the vital status of trial patients, and these data were presented at the FDA panel meeting in June 2019. The result of these efforts is that in almost all trials, the mortality signal has reduced in amplitude

or disappeared. There is also a lack of consistency in the signal. For example, in the IN.PACT Global trials that used the In.Pact Admiral drug-coated balloon (DCB; Medtronic) in the femoral artery, no mortality signal was seen in Europe or Japan, but a signal persists in the United States. The FDA noted after the panel meeting that not only was there no plausible mechanism of action for paclitaxel to cause increased late mortality, there was also no proven dose effect.

A limitation of trial analysis is that this has been performed on an "intention-to-treat" basis. This is a valid approach to assess device efficacy, but it is not appropriate to address a severe safety issue such as mortality, particularly if there is significant crossover in the trial. This is most relevant in Cook Medical's Zilver PTX randomized controlled trial (RCT) performed in the United States and Europe. The trial design allowed opportunities to cross into the DES arm at several time points, and 40% of patients in the plain angioplasty balloon arm crossed over to the paclitaxel device in the first year. When the Zilver PTX RCT is analyzed on an "as-treated" basis, there is no significant paclitaxel mortality effect.

4 Is there evidence of a dose effect in applications outside the femoropopliteal segment?

As previously mentioned, no relationship between paclitaxel dose and mortality has been seen in doses smaller or larger than those used in peripheral vascular interventions. These devices have been used in other vascular territories—most notably in tibial artery and dialysis access interventions. The published experience with paclitaxel devices in tibial arteries is small and follow-up is limited, but no mortality signal has been reported. The value of DCBs in the dialysis access circuit has gained interest in recent years, and more data have been accumulated. A recent meta-analysis showed no evidence of increased mortality with interventions involving a paclitaxel-coated balloon versus plain balloon technologies.[4]

An interesting issue in both critical limb and dialysis access interventions is the significantly different life expectancy in patients with these conditions compared with claudicants. For example, the 2-year mortality of patients on hemodialysis is 33.2%,[5] which is at least twice that of claudicants. This calls into question the relevance of the mortality discussion for these indications.

5 What is the implication for other antirestenotic drugs, and what is the way forward?

The safety issue with paclitaxel has been seen by some as an opportunity to promote other antirestenotic drugs, such as the limus group. This should be interpreted with some caution. First, it is well known that paclitaxel has a cytostatic effect rather than a cytotoxic effect when used in the doses seen in peripheral vascular devices. In addition, any new device trials using limus-based drugs would need large numbers and prolonged follow-up to confirm any safety advantage over paclitaxel.

The FDA has provided recommendations on the ongoing use of paclitaxel devices, including patient consent and close clinical follow-up. Geographic variations in the use of these devices will likely be driven more by local regulatory and legal concerns than patient efficacy and safety data. Future well-designed trials will hopefully provide final clarity on this issue. ■

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