EDITORIAL

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Angiotensin Receptor Blockers and the Risk of Malignancy

A Note of Caution

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There have been endless attempts to link antihypertensive medications with the development of cancer, with the latest such supposed relationship coming forth with angiotensin receptor blockers (ARBs).[1] The link between cancer, hypertension and any particular antihypertensive medication has proven highly controversial to say the least. The historical association between antihypertensive medications and cancer was set in motion with reserpine and breast cancer. There, the relationship derived from case-control studies; however, this approach proved flawed and this particular cancer finding was a consequence of exclusion bias.[2] By the time the dust had settled on this debate, enthusiasm for the use of reserpine had largely faded.

Over the ensuing years, an increased risk of developing cancer was suggested but never convincingly proven with ACE inhibitors, β-blockers, diuretics and calcium channel blockers (CCBs).[3] In the case of CCBs and malignancy there was substantial debate and the suggestion that there was a cancer risk with this drug class gained considerable media coverage;[4] however, the amlodipine arm of ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) decisively laid to rest a tumorigenic potential for the CCB class.[5]

The idea that compounds that interfere with renin-angiotensin system activity might be linked to an increased risk of malignancy is by no means new. In SOLVD (Studies of Left Ventricular Dysfunction), a prospective randomized controlled trial of patients with heart failure (average duration of follow-up approximately 41 months), those who received enalapril had a slightly higher incidence of malignancy than those receiving placebo (odds ratio [OR] 1.59; 95% CI 0.90, 2.82).[6] In an additional prospective, randomized controlled trial of 583 patients with renal failure (average duration of follow-up 3 years) those who received benazepril had a slightly higher incidence of malignancy than placebo-treated patients (OR 1.52; 95% CI 0.45, 5.42).[7] Of note, in this particular study, 13 patients had cancer: eight in the benazepril group (two with bladder cancer, two with pancreatic cancer and one each with skin cancer, gastric cancer, non-Hodgkin's lymphoma and lung cancer) and five in the placebo group (one each with plasmacytoma, gastric cancer, breast cancer, anal cancer and malignant lymphoma). The incidence of cancer did not differ significantly between the placebo and benazepril arms, and the types of cancer seen were indeed exceedingly varied.

Meta-analysis of the two randomized controlled trials, including 1585 patients receiving ACE inhibitors and 1567 patients not receiving ACE inhibitors, showed an increased incidence of malignancy in those receiving ACE inhibitors, with a pooled OR of 1.57 (95% CI 0.97, 2.57). Yet, a number of other studies have shown no relationship between the use of ACE inhibitors and malignancy, and this issue was, in a fashion,

quickly over and done.[8] The issue of ACE inhibitors and cancer faded not only because there was no signal for malignancy in other large trials but also because there were those who believed that these drugs might actually decrease cancer risk.[9] In addition, at the time that this issue arose, media coverage of such a finding was not yet nearly as extensive; thus, patients would not have had ready access to such information, as would be the case in today's media-frenzied environment.

A recent meta-analysis of randomized controlled trials with ARBs has now associated use of this drug class with an increased rate of occurrence of new cancers.[1] The primary objective of this meta-analysis was to explore the effect of this drug class on new cancer occurrence rate. Secondary objectives of this meta-analysis were to determine whether ARBs affected the occurrence of specific solid-organ cancers, including lung, prostate, breast cancer, cancer deaths and cancer-related deaths. In filtering studies for inclusion in this meta-analysis, ARB studies with >100 patients, with a median or mean follow-up of at least 1 year, and that provided data on cancer, were the only ones included.

Data from nine different trials were ultimately considered for the analysis. New cancer data were available for 61 590 patients from five trials (using losartan, candesartan or telmisartan) with most patients in this meta-analysis receiving telmisartan (85.7%). The five trials with new cancer data were for telmisartan (ONTARGET [Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial], PROFESS [Prevention Regimen For Effectively avoiding Second Strokes], TRANSCEND [Telmisartan Randomized Assessment Study in ACE-intolerant Subjects With Cardiovascular Disease Regimen]); losartan (LIFE [Losartan Intervention For EndPoints]); and candesartan (CHARM-Overall [Candesartan in Heart Failure Assessment of Mortality and Morbidity Trial in Patients Taking ACE Inhibitors]). In addition, data were available for cancer deaths in LIFE and TRANSCEND, and for valsartan in VALIANT (Valsartan in Acute Myocardial Infarction trial) and Val-HeFT (Valsartan Heart Failure Trial). The ARBs irbesartan, olmesartan and eprosartan were not reported on in this meta-analysis.

In the meta-analysis, patients randomly assigned to receive ARBs had a significantly increased risk of new cancer occurrence, compared with those in the control groups (7.2% vs 6.0%; risk ratio [RR] 1.08; 95% CI 1.01, 1.15; p = 0.016). When the analysis was limited to trials where cancer was a pre-specified endpoint, the RR rose slightly to 1.11 (95% CI 1.04, 1.18; p = 0.001). Lung, breast and prostate cancers were examined for and only new lung-cancer occurrence was significantly higher in those randomly assigned to ARBs compared with control subjects (0.9% vs 0.7%; RR 1.25; 95% CI 1.05, 1.49; p = 0.01). There was no significant difference in cancer deaths observed in this meta-analysis between those who took ARBs and control subjects (1.8% vs 1.6%; RR 1.07; 95% CI 0.97, 1.18; p = 0.183).

The researchers note that "In this analysis, the increased cancer occurrence did not result in a significant excess in cancer deaths, although oncogenesis, tumor growth and treatment failure followed by death is typically a slow process. Therefore, with the present trials, it is not possible to make conclusions regarding the effect of ARBs on cancer-related deaths." The authors further offer that "Given the limited data, it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug."[1] Unfortunately, the genie has been let out of the bottle with this analysis requiring that manufacturers assume a defensive posture and regulatory bodies rapidly address this issue.[10-12]

The limitations of this meta-analysis are many and are well recognized by Sipahi et al.[1] First, there is no real biological plausibility offered for the observation. Indeed, most oncologists would view as far-fetched the notion that malignancies would develop and become clinically detectable in such a short time period – 2 to 4 years. The trials in question were not designed to explore cancer outcomes and the cancer diagnoses were not adjudicated in a standardized fashion. Most importantly, the analysis did not include individual patient data for any of the trials; thus, the effect of sex, age, smoking or other known risk factors for malignancies was noticeably absent from this

analysis. The study populations in these studies also were vastly different, including those with heart failure and hypertension, as well as hypertension and vascular disease. This level of patient heterogeneity alone could seriously confound the findings of this meta-analysis.

Of the several issues with this meta-analysis there are two additional points worthy of comment. First, this meta-analysis pooled data for telmisartan and telmisartan/ramipril from the ONTARGET trial. It was only in so doing that the results reached statistical significance; otherwise, there was not a statistically significant risk for new cancers for telmisartan alone. Second, the data from the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial[13] was not included in this meta-analysis. In VALUE, there were 81 fewer cancers in the valsartan arm than in the CCB arm. If the cancer cases from VALUE are added to the equation, any cancer signal with ARBs is abolished with a new cancer diagnosis rate of 7.7% in the ARB monotherapy group versus 7.7% with other drugs.[13,14] The exclusion of VALUE from this meta-analysis leads one to wonder if a suddenly 'negative' finding would ever have been published in the first place.

In summary, we are once again faced with the daunting task of confirming the safety of a drug class, which heretofore has been shown to be remarkably safe. The well reasoned physician can most times identify when a clinical finding is unreasonably slanted and then share this thought process with a patient. Unfortunately, the considerable press coverage of scientific findings in the lay media leaves interpretation and continuation of a medication at the discretion of the patient. This is just one of the several dangers that are a consequence of the release of such arguable data. Moreover, it is just a matter of time before the malpractice community seizes upon this finding as to the issue of product liability, which would only further kindle the issue. The unfortunate aspect of drug use in the current era is that the noise level on a negative finding is oftentimes far greater than the true relevance of the finding to patient safety. Responsible researchers and journalists must balance the public's need to be informed against the possibility that countless patients will be pointlessly upset by news of a finding that may have small personal consequences.

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