significant methodological flaws that require replication in appropriately designed, randomized studies.

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References

Authors’ Reply

Reply to the Letter to the Editor by Daniel M. Green

We are pleased to provide our perspective on the points raised by Dr. Green regarding our article, “Impact of the First Generation of Children’s Oncology Group Clinical Trials on Clinical Practice for Wilms Tumor.” Dr. Green has previously raised similar points in letters to the editor to each of which we have responded.

The first point regards our conclusion that regimen M represents a good standard of care for patients with favorable histology Wilms tumor (FWHT) and isolated lung metastases that do not respond completely to 6 weeks of chemotherapy. The AREN0533 study was designed to improve event-free survival (EFS) from 75% to 85% for patients with incomplete lung nodule response by adding cyclophosphamide/etoposide to the standard vincristine/dactinomycin/doxorubicin combination (regimen M). These EFS targets were based on outcomes according to attainment of complete response at day 70 for patients with isolated lung metastases treated on the fifth National Wilms Tumor Study (NWTS-5). Under the null hypothesis EFS of 75%, the expected event rate was 25% (30 of 120 subjects), but the observed event rate was only 12.2% (16 of 131 subjects; P=.001), leading to the firm conclusion that regimen M is beneficial for this patient group.

In a separate analysis to which Dr. Green referred, we compared the outcomes of patients with FWHT and isolated pulmonary metastases treated on AREN0533 to those treated on NWTS-5. This analysis was undertaken in response to an external review suggesting that we evaluate the totality of changes enacted for patients with isolated lung nodules on AREN0533, which included therapy reduction (omission of lung radiation therapy [RT]) for those with complete lung nodule response and therapy augmentation (regimen M) for those with incomplete lung nodule response. On NWTS-5, patients with lung nodules visible on CT scan and not chest radiograph were treated according to physician choice such that some were treated as stage IV and others were treated according to the abdominal stage. For the AREN0533 comparison, we deliberately included only patients on NWTS-5 treated as stage IV with doxorubicin and lung RT. The rationale for this was that on NWTS-4 and NWTS-5, 5-year EFS for patients with CT-only nodules who received vincristine/dactinomycin/doxorubicin was 80% compared with 56% for patients who received only vincristine/dactinomycin with or without lung RT (P=.004). Likewise, 5-year EFS was 82% in patients who received lung RT and 72% in patients who did not (P=.13). Had we included all NWTS-5 patients with lung nodules regardless of treatment, the superior EFS observed with AREN0533 would likely have been magnified.

Further regarding the comparison between AREN0533 and NWTS-5, Dr. Green points out that the number of NWTS-5 patients included did not match the number he expected based on previous published analyses. The comparison involved a new analytic dataset from NWTS-5 that met the criteria of stage IV FWHT, isolated pulmonary metastasis, and treatment as stage IV disease. We confirm that “studied” and “registered” patients were included. We do not have access to the original NWTS-5 analytic dataset to account for the 4-patient difference that Dr. Green notes, but believe that this small number is unlikely to change our conclusions.

Dr. Green raises concern that a subset of patients who enrolled on the AREN03B2 Renal Tumor Biology and Classification study did not enroll on the therapeutic studies. In contrast to NWTS-5, which was a combined therapeutic and biology study, the COG studies separated AREN03B2 from the therapeutic studies. The lack of enrollment on therapeutic studies occurred for a variety of reasons, including (1) the institution did not have the therapeutic study open, (2) the institution was unable to meet the desired timing for enrollment on the therapeutic study, or (3) the patient or their clinician declined participation in the therapeutic study. Although we do not have data on the reasons for non-enrollment, we do not believe that patients who enrolled on treatment studies had clinically or biologically different disease from those who enrolled solely on the biology study. In support of this premise, recent analyses conducted in preparation for the upcoming COG AREN2231 study indicated that patients enrolled on AREN03B2 had similar outcomes to those enrolled on the contemporaneous therapeutic studies. This was true within individual disease stages and within subgroups that received the same treatment. Based on these analyses, the statistical design for the upcoming AREN2231 study will use pooled data from AREN03B2 and the therapeutic studies to generate the historical control.
We confirm that the AREN0533 and NWTS-5 comparisons included all AREN0533 patients with isolated pulmonary metastases, including those with early progression. By contrast, patients with early progression were excluded from the analyses of therapy reduction for complete lung nodule response and therapy augmentation for incomplete lung nodule response because early progression did not fit either category and it was not possible to attribute such patients to either group. We addressed Dr. Green’s points about stage migration between NWTS-5 and AREN0532/0533 in the discussion sections of the primary manuscripts. To ensure that the excellent outcomes in patients with stage IV and combined loss of heterozygosity (LOH) at 1p and 16q were not due to preferential inclusion of patients with tiny lung nodules, we compared outcomes according to lung nodule size, and were reassured that the study results were not influenced by this group. Specifically, among patients with stage IV disease and LOH 1p/16q, EFS and overall survival (OS) estimates were similarly excellent between patients with greatest lung nodule diameter of ≥1 cm versus <1 cm. We also assessed how many NWTS-5 patients with stage I/II disease had nodules visible only on chest CT but not on chest radiograph to evaluate whether there was a significant number of patients with low-stage disease who would have been considered to have stage IV disease in the AREN0533 study. We were reassured to find that only 3 patients had CT-only nodules identified.

Dr. Green questions recommendations to augment chemotherapy when statistically significant improvements in EFS, but not OS, were identified. The philosophy of the COG Renal Tumor Committee is to use EFS as the primary endpoint for our studies because patients who require salvage therapy are at greatest risk for long-term adverse effects, relapse takes a significant psychosocial and economic toll on patients and families, and the salvage rate for relapsed FHWT is only 50% to 80%. In the case of stage I/II with LOH at 1p and 16q, 4-year OS estimates were 91.6% (95% CI, 83.6%–99.6%) for those treated without doxorubicin on NWTS-5 and 100% for those treated with doxorubicin on AREN0532 (P = .096). Although this did not reach the traditional P < .05 level of statistical significance, the result is highly suggestive that lives were saved with augmentation of therapy.

Dr. Green’s assertion that our conclusions are not based on high-quality data represents an opinion that counters a rigorous peer review process that occurred within the COG and subsequently the Journal of Clinical Oncology. Although the published studies have limitations that were outlined in the primary manuscripts, we maintain our position that the evidence to support augmentation of therapy for patients with LOH 1p and 16q and the use of regimen M for patients with incomplete lung nodule response is strong and provides a good standard of care for clinicians to follow.

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References