Multiplicity and the marginal benefits of bevacizumab in malignant solid tumours

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Although clinical trials of novel medications have historically been individually interpreted, there is increasing recognition that trials should be considered to be part of a broader clinical trials agenda or portfolio. If a single drug is tested in many tumour types, the interpretation of any single trial result must account for the number of times that the agent is trialled. Drugs tested extensively might benefit from a portfolio-level analysis.

Bevacizumab, a vascular endothelial growth factor antibody, gained U.S. Food and Drug Administration approval in 2004 in metastatic colon cancer. Since then, bevacizumab has been tested in multiple tumour types, gaining U.S. Food and Drug Administration approval in advanced non-small-cell lung cancer, glioblastoma multiforme, metastatic renal cell carcinoma, and metastatic cervical cancer.

To better understand the effect of the entire bevacizumab trials portfolio, we conducted a systematic review of cancer trials involving bevacizumab. We sought to adjust individual trial results for the number of trials reported.

METHODS

We queried Medline for “solid tumor,” “bevacizumab,” and “meta-analysis” on 2 February 2018. We included all meta-analyses published in the preceding 10 years about the efficacy of bevacizumab when added to a chemotherapy backbone or supportive care in solid tumours.

For each meta-analysis, we extracted all included randomized controlled trials, their reported improvements in median progression-free survival (pfs) and overall survival (os), and the accompanying p values. Time to progression was treated equivalently to pfs. When multiple arms included varying doses of bevacizumab, we chose the arm with the strongest result.

We investigated the percentage of individual studies that met the traditional nominal statistical significance for pfs and os, and the percentage that retained significance after adjustment for multiplicity using the Bonferroni correction, a frequently used, albeit stringent, method to adjust for multiplicity.

RESULTS

Our search identified three meta-analyses that included 48 randomized trials (detailed in the supplementary table). One trial lacked pfs data, and another lacked os data; those trials were excluded from calculations pertaining to their respective missing outcome. Of the 48 trials, 8 (16.7%) were phase ii studies; the remaining 40 (83.3%) were phase iii studies. In the 48 trials, the most common tumour types were colorectal cancer (14 trials, 29.2%), breast cancer (9 trials, 18.8%), non-small-cell lung cancer (7 trials, 14.6%), and ovarian cancer (4 trials, 8.3%).

A statistically significant pfs benefit (using p < 0.05 as the cut-off) was reported in 30 of 47 assessable trials (63.8%). After using the Bonferroni correction to adjust the p value for multiplicity (p < 0.0010), 21 trials had reported statistically significant improvements in pfs associated with bevacizumab (43.8%).

A statistically significant os benefit (using p < 0.05) was reported in 8 of 47 assessable trials (17.0%). After using the Bonferroni correction to adjust the p value for multiplicity (p < 0.0010), 1 trial (2.1%) reported a statistically significant improvement in os associated with bevacizumab. Figure 1 shows the number of significant trials before and after adjustment.

CONCLUSIONS

We found that the number of statistically significant studies of bevacizumab is reduced when a correction for multiplicity is performed. Although 21 of 30 trials (70.0%) reporting a statistically significant pfs retained that claim after the Bonferroni correction, only 1 of 8 (12.5%) maintained its os benefit. Our findings suggest that current analytic plans might overestimate clinical benefit and might profit from being accompanied by a portfolio-based analysis such as ours.

One limitation of our study is that we used a stringent correction for multiplicity; other procedures to correct for false discovery might provide more optimistic results.

The clinical benefit associated with drugs tested repeatedly requires appropriate adjustment for the portfolio of trials conducted. To increase the practicality of portfolio-based drug analysis, companies should, alongside the
Submission of clinical trial results for novel agents, report the total number of trials completed and ongoing.

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CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: VP has received royalties from his book Ending Medical Reversal; his work is funded by Arnold Ventures; he has received honoraria for Grand Rounds or lectures from several universities, medical centres, nonprofit groups, and professional societies; and he is a writer for Medscape. VP is also host of the Plenary Session podcast, which is partially supported by contributions from the Patreon platform. NG and DT have no conflicts to disclose.

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