ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Reducing Drug Toxicity and Costs Through Off-Label Dosing

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H&O What is wrong with the way doses are currently determined for oncology drugs?

MR The US Food and Drug Administration (FDA) has approved many oncology drugs at doses that appear excessive. For example, in May 2021, the FDA approved a 960-mg dose of sotorasib (Lumakras, Amgen) for use in patients with non–small cell lung cancer harboring a *KRAS* mutation. Approval was based on the fact that the overall response rate was numerically higher with the 960-mg dose than with the 240-mg dose, at 33% (95% CI, 24%-47%) vs 25% (95% CI, 17%-34%), respectively, although no improvement in progression-free survival (PFS) was observed.[1] The FDA authors also noted a non-significant increase in overall survival (OS) with the higher dose.[2] However, the higher dose was associated with a significant increase in grade 3 or higher treatment-related adverse events.[1,3] The FDA has introduced Project Optimus to require dose optimization for oncology drugs before approval, although its authority to require dose optimization of approved drugs, particularly those that have received traditional (full) approval, is limited.

H&O What other oncology drugs could be used at lower doses?

MR The absorption of many oral oncology drugs is increased with food, but they are labeled to be taken under fasting conditions. For example, the absorption of lapatinib is increased more than 3-fold when it is taken with a high-fat meal. Despite this finding, the package insert states that the drug should be taken "at least one hour before or one hour after a meal."[4] The fact that lapatinib is taken with capecitabine, which must be taken with food, makes the regimen more complicated than it needs to be, as well as more expensive.[5]

Another example is abiraterone, whose area under the curve was initially reported to be 5-fold higher when it was administered with a low-fat meal rather than on an empty stomach.[6] Nonetheless, the package insert states, "Do not eat food 2 hours before and 1 hour after" taking this medication.[7]

The approved drug with the largest food effect is sonidegib (Odomzo, Sun), which is approved for locally advanced basal cell carcinoma. The absorption of this agent is increased more than 7-fold when it is taken with a high-fat meal rather than as labeled, on an empty stomach.[8]

We also have ample evidence that nivolumab (Opdivo, Bristol Myers Squibb) can be used at much lower doses than are typically administered. In a study of metastatic renal cell carcinoma, PFS and OS were not statistically different regardless of the dose of nivolumab: 10, 2, or 0.3 mg/kg administered every 3 weeks.[9] In addition, in a phase 3 study from India, low-dose intravenous nivolumab—20 mg every 3 weeks—was an effective treatment for patients with head and neck cancer who were unable to access full-dose treatment because of cost.[10] According to *News 18* in India, the lower dose would bring the cost down from 6,200,000 to 350,000 in Indian rupees,[11] which translates to roughly $74,700 vs $4,217 in US dollars. The original regimen would be considered affordable to fewer than 3% of patients in India, whereas the lower-dose regimen is affordable to more than 75% of patients.

Nivolumab is available in a variety of vials of different sizes, so that it easy to use a lower dose. We have every

reason to think that lower doses would work just as well for pembrolizumab (Keytruda, Merck), but pembrolizumab is not available in smaller vials, and sharing vials is not legal in the United States. What we might do with pembrolizumab is give it less frequently, which is what we have been studying (NCT04295863).

If the government is looking for an effective way to reduce the toxicities of marketed drugs and reduce costs, this is an ideal place to start—a way to make America healthy again through rational clinical trials.

H&O What steps do you recommend when the approved dose is too high?

MR In the United States, we do not currently have the proper incentives to use (or even study) lower doses of these drugs, unlike in low- and middle-income countries such as India, where lower doses are embraced because they markedly increase access.[12] In this country, we may be blessed with the resources to use more medication, but sometimes that means that our patients receive worse care, and nobody is pushing back. I would like to see the federal government push back through the Centers for Medicare & Medicaid Services (CMS). If the government is looking for an effective way to reduce the toxicities of marketed drugs and reduce costs, this is an ideal place to start—a way to make America healthy again through rational clinical trials. If CMS did due diligence and made an evidence-based determination that a dose of a drug was not reasonable or necessary, it could limit coverage to the minimum reasonable and necessary dose. CMS is obligated to cover oncology drugs for approved (or compendia-listed) indications, but that does not necessarily mean it is required to cover the FDA-approved dosage. For example, CMS could limit sotorasib prescriptions to an average daily dose of 240 mg. For 240-mg tablets of sotorasib—120 per bottle—refills would be limited to once every 4 months.

If we can assume that CMS has the legal authority and the political will to make this change, the next step would be for it to hire additional staff and/or form an advisory committee to review the literature regarding doses of approved drugs and propose trials as needed to generate additional evidence. Although CMS does not currently fund clinical trials, it is certainly feasible for CMS, the National Cancer Institute, and the FDA to design, fund, and execute jointly appropriate post-marketing dose optimization trials.[13] Notably, this was explicitly recommended by the 117th Congress in its FDA fiscal year 2023 appropriations.[14]

There are also opportunities to reduce costs by substituting one formulation for another, or even by splitting packs of marketed oncology products.[15] For example, cabozantinib is sold as both capsules (for medullary thyroid cancer) and tablets (for kidney and hepatocellular cancer). The capsules cost $5.93/mg and the tablets are $25.58/mg, so one way to reduce costs is to prescribe the capsules instead of the tablets.[16]

H&O How effective are guidelines at promoting the use of lower doses?

MR Updating guidelines generally does not solve the problem. For example, the current National Comprehensive Cancer Network (NCCN) guidelines[17] provide the option of prescribing abiraterone at 250 mg/d, to be taken following a low-fat breakfast, "in patients who will not take or cannot afford the standard dose of 1000 mg/d after an overnight fast." The guidelines note that a noninferiority study[18] showed that the primary endpoint of log change in prostate-specific antigen (PSA) favored the lower dose, as did the PSA response rate. PFS was equal in the 2 arms. The guidelines state that the "cost savings may reduce financial toxicity and improve adherence." Nonetheless, physicians continue to prescribe the higher dose, patients continue to take it, and payers continue to pay for it. Physicians may be reluctant to prescribe a reduced dose because they are concerned about being sued if the patient experiences a recurrence, and patients are unlikely to be aware that they can reduce their risk of side effects by taking a lower dose. That leaves payers as the ones who can change prescribing patterns, and the federal government is in the best position to make this change.

This is not just about saving money. Patients who take the full 960-mg dose of sotorasib have a 42% rate of any-grade diarrhea, but the package insert does not recommend reducing the dose unless the diarrhea is grade 3 or 4 despite antidiarrheal therapy.[19] The fact is that someone with grade 2 diarrhea, which is technically "moderate," is experiencing 5 to 7 more bowel movements per day over their baseline number, which is extremely

disruptive to their ability to lead any resemblance of a normal life. The FDA may be okay with that, but I find it to be unacceptable.

Disclosures

Dr Ratain serves as a patent litigation consultant and has testified as an expert witness on behalf of multiple generic pharmaceutical companies. He has consulted for the following healthcare companies in the past 24 months: T3 Pharma (Data and Safety Monitoring Board), EQRx, Astellas, Cerona Therapeutics, Oscotec, Revolution Medicines, and Nurix Therapeutics. He receives royalties from Mayo Clinic Laboratories related to UGT1A1 *genotyping for irinotecan. He is also the board chair (uncompensated) of the Optimal Cancer Care Alliance, a Michigan nonprofit corporation.*

References

1. Popat S, Ratain MJ. Dose optimization of sotorasib: has the burden of proof for the labeled dose been met? *Eur J Cancer*. 2024;212:115044.
2. Singh H, Vellanki PJ, Pazdur R. The retrofit: lessons from sotorasib's dosing conundrum. *J Clin Oncol*. 2025;43(3):248-250.
3. Hochmair MJ, Vermaelen K, Mountzios G, et al. Sotorasib (960 mg or 240 mg) once daily in patients with previously treated KRAS G12C-mutated advanced NSCLC. *Eur J Cancer*. 2024;208:114204.
4. Tykerb [package insert]. East Hanover, NJ: Novartis; 2024. https://www.novartis.com/us-en/sites/novartis_us/files/tykerb.pdf.
5. Ratain MJ, Cohen EE. The value meal: how to save $1,700 per month or more on lapatinib. *J Clin Oncol*. 2007;25(23):3397-3398.
6. Ratain MJ. Flushing oral oncology drugs down the toilet. *J Clin Oncol*. 2011;29(30):3958-3959.
7. Zytiga [package insert]. Horsham, PA: Janssen; 2024. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ZYTIGA-pi.pdf.
8. Odomzo. Macquarie Park NSW: Novartis Pharmaceuticals Australia; 2015. https://www.tga.gov.au/sites/default/files/auspar-odomzo-191127-pi.pdf.
9. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol*. 2015;33(13):1430-1437.
10. Patil VM, Noronha V, Menon N, et al. Low-dose immunotherapy in head and neck cancer: a randomized study. *J Clin Oncol*. 2023;41(2):222-232.
11. Chandna H. Just what doctor ordered: hope for head & neck cancer patients, therapy cost down from Rs 60L to Rs 3L. *News 18*. November 25, 2022. Accessed May 21, 2025. https://www.news18.com/news/india/just-what-the-doctor-ordered-hope-for-head-neck-cancer-patients-therapy-cost-down-from-rs-60-l-to-rs-3-l-6464203.html.
12. Tannock IF, de Vries EGE, Fojo A, Buyse M, Moja L. Dose optimisation to improve access to effective cancer medicines. *Lancet Oncol*. 2025;26(3):e171-e180.
13. Strohbehn GW, Lichter AS, Ratain MJ. US government payer-funded trials to address oncology's drug-dosing conundrum: a congressional call to action? *J Clin Oncol*. 2023;41(14):2488-2492.
14. United States Committee on Appropriations. Explanatory Statement for Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2023. https://www.appropriations.senate.gov/imo/media/doc/AGFY23RPT.PDF
15. Harvey RD, Ratain MJ. A cost-focused alternative cancer medication dispensing strategy-"pack splitting". *JAMA Oncol*. 2019;5(12):1691-1692.
16. Wesevich A, Stadler WM, Ratain MJ. Formulation-based cost savings with cabozantinib capsules [published online April 3, 2025]. *JAMA Oncol*. doi:10.1001/jamaoncol.2025.0175.
17. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®). Prostate Cancer. Version 2.2025. Updated April 16, 2025. Accessed May 21, 2025. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
18. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol*. 2018;36:1389-1395.
19. Lumakras [package insert]. Thousand Oaks, CA: Amgen; 2025. https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Lumakras/lumakras_pi_hcp_english.pdf.