editorials

Cost Savings and Increased Access With Ultra-Low-Dose Immunotherapy

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In the article that accompanies this editorial, Patil et al[1] reported findings from a randomized clinical trial of nivolumab for advanced head and neck cancer. This trial found a substantial overall survival benefit from the addition of nivolumab to a regimen combining cytotoxic (methotrexate) and targeted (erlotinib) therapies. These findings are most notable not for the magnitude of clinical benefit but for the dose of nivolumab used to achieve them; at a flat dose of 20 mg once every 3 weeks, this represents a small fraction of the doses approved by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency. This trial was conducted in India, and the investigators present this alternative nivolumab dosing schedule as a viable method to substantially reduce drug costs and hence increase access to immunotherapy agents in resource-limited settings.

The nivolumab dose in this trial is approximately 6% of the FDA-approved flat dose of 240 mg once every 2 weeks. The investigators were able to reduce costs through vial sharing, administering two full 20-mg treatments from each 40-mg vial of nivolumab. The resulting treatment costs were < 10% the cost of nivolumab (or pembrolizumab) monotherapy at FDA-approved doses. This cost reduction brought treatment costs within the range that is covered by the Indian national public health insurance fund, thereby enabling patients to receive treatment with an agent which would otherwise be inaccessible because of its excessively high price. The study, therefore, represents a direct and substantial step forward within the Indian health care system and also potentially for patients with head and neck cancer treated within other health care systems that face similar budgetary constraints.

With all patients in both study arms receiving oral methotrexate 9 mg/m^2 once per week, celecoxib 200 mg twice daily, and erlotinib 150 mg once daily, the addition of nivolumab 20 mg once every 3 weeks prolonged median overall survival from 6.7 months (95% CI, 5.8 to 8.1) to 10.1 months (95% CI, 7.4 to 12.6) and increased survival at 1 year from 16.3% (95% CI, 8.0 to 27.4) to 43.4% (95% CI, 30.8 to 55.3). This is comparable with the benefit previously seen with single-agent immunotherapy for head and neck cancers, although differences in clinical setting limit direct comparison. In a platinum-refractory population, the CheckMate-141 trial found that nivolumab (at a dose of 3 mg/kg once every 2 weeks) improved median OS from 5.1 months to 7.5 months, and 1-year survival from 16.6% to 36.0%, compared with investigator's choice of methotrexate, docetaxel, or cetuximab.[2] In addition, in a platinum-refractory population, pembrolizumab improved median OS from 6.9 months to 8.4 months in the Keynote-040 trial.[3]

The fact that much lower doses of nivolumab produce clinical benefit comparable with conventional doses should come as no surprise, given what has long been known regarding the underlying pharmacokinetics of this drug.[4] Early phase I data found similar receptor occupancy and response rates with doses ranging from 0.1 mg/kg to 10 mg/kg once every 2 weeks.[5-7] For a 70 kg patient, 0.3 mg/kg per administration would work out to approximately 20 mg per administration, the flat dose used in the current study. While higher doses persist in the plasma for a greater duration of time,[5] a 3-week dosing interval appears to be sufficient to maintain therapeutic plasma concentrations even at the low dose of 0.3 mg/kg.[8] Furthermore, there has already been evidence to suggest that these pharmacokinetics translate to similar clinical outcomes for ultra-low-dose nivolumab. A randomized phase II study in advanced kidney cancer found no dose-response relationship for doses between 0.3 to 10 mg/kg once every 3 weeks in terms of progression-free survival or overall survival.[9] Further clinical examples of the efficacy of ultra-low-dose nivolumab include a study in relapsed/refractory Hodgkin disease. In this study, using a dose of 40 mg once every 2 weeks, an objective response rate of 70% was achieved.[10]

Although this study may directly improve cancer care in low- and middle-income countries, some may argue that the study should have limited direct implications in high-income countries. For the population treated in this study—metastatic or locally advanced head and neck cancer among patients who are candidates only for palliative systemic therapy—the control arm therapy of low-dose methotrexate and erlotinib would be considered nonstandard. Single-agent methotrexate is recommended as a potential palliative option,[11] although at a substantially higher dose (40 mg/m^2 intravenous once per week) than the 9 mg/m^2 once per week used in this study.[12] Erlotinib is not recommended either as a single

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THE TAKEAWAY

In the article that accompanies this editorial, Patil et al[1] reported results from a randomized clinical trial that demonstrates a significant and clinically meaningful benefit from incorporating ultra-low-dose nivolumab into the treatment of patients with advanced head and neck cancer. By using a small fraction of the nivolumab dose approved in the United States and Europe, this treatment regimen dramatically reduces the financial cost of immunotherapy, with the potential to increase access and improve patient outcomes in low- and middle-income countries.

agent or in combination; the alternative epidermal growth factor receptor inhibitor afatinib is a recommended, although nonpreferred, option in the post-platinum setting.[11] The role for addition of low-dose nivolumab and the potential magnitude of benefit in settings where low-dose methotrexate plus epidermal growth factor receptor–tyrosine kinase inhibitor does not represent a baseline standard-of-care, therefore, remain unclear.

These findings point us strongly toward additional clinical questions in immuno-oncology. Is the ultra-low-dose of 0.3 mg/kg equivalent to currently approved doses? Can these findings be extrapolated to other tumor types? Besides nivolumab, would similar dose reductions be possible for the other anti–programmed cell death protein 1/programmed death-ligand 1 monoclonal antibodies? It is evident that similar, ultra-low dosing of atezolizumab is also possible.[13] Given the substantial reductions in health care costs with ultra-low-dose immunotherapy, there is an urgent need for near-equivalence studies to further investigate the clinical outcomes associated with dose de-escalation.[14] This could greatly increase access to such therapies in resource-poor settings.[15]

To reduce costs and increase access to immunotherapy, there are fundamentally two strategies: reduce the cost per unit of drug or reduce the amount of drug per patient. To reduce the unit price on an individual drug, a strong negotiating position would be required on the side of the health care payer. Alternately, in cases where multiple, substitutable agents are available, prices could be driven down by competition among agents. Effective price competition may be difficult to achieve, however, as studies have suggested that cancer drug prices often fail to respond to new competition.[16-19] The potential for price competition among the programmed cell death protein 1/programmed death-ligand 1 class was further diminished by the FDA decision not to approve sintilimab, which was studied in a phase III trial (ORIENT-11) trial conducted in a Chinese population, citing standards for clinical end points, control arm therapies, and degree of unmet clinical need, which it commonly does not apply to drugs tested in the US setting.[20] The drug's manufacturer had previously stated plans to price sintilimab at approximately 40% below other drugs in the class.[21] With limited prospects for lowering the unit prices of immunotherapy drugs, reducing the amount of drug per patient—whether by using lower doses, reduced frequency, or reduced duration of treatment—may be the more immediately accessible option. The current study of ultra-low dose nivolumab is, therefore, an important step toward realizing this strategy.

This study's importance extends beyond head and neck cancer and beyond nivolumab. It demonstrates the potential to successfully execute de-escalation studies despite findings that may run counter to the financial interest of the pharmaceutical industry. Although much has been written in recent years regarding the extraordinary high cost of cancer drugs, very few viable solutions have been provided. In most countries, after vigorous lobbying, the status quo has been maintained, and prices remain high. Here, a very viable solution has been demonstrated and will have significant impact for some patients—saving lives as a direct result of achieving lower drug costs. Many similar opportunities for dose de-escalation exist for other cancer drugs. Dose reduction is now well-established as a solution to improve access to abiraterone acetate, a prostate cancer drug.[22] These examples should be used as a springboard to assess the opportunities for dose de-escalation across cancer types and pharmaceutical agents.

In many ways, the current state of cancer immunotherapy is analogous to that of HIV medications two decades ago. At that time, highly effective medications were available only in wealthy countries. In Africa, where disease prevalence was high, the drug prices were too high to be widely accessible, and patients continued to die as a result. Similarly, immunotherapy is highly effective for some cancers, yet it is out of reach for most patients in poor countries. With lower doses and lower costs, many deaths could be prevented. Perhaps ultra-low dosing of cancer drugs will provide the much-needed solution for these patients.

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