ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Access to Novel Cancer Drugs in Low- and Middle-Income Countries

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H&O What are the biggest barriers preventing patients with cancer in India from accessing novel drugs?

AP Accessing novel cancer drugs in India remains a major challenge. For example, in a 2022 study of more than 1500 patients with head and neck cancer, fewer than 3% were able to access immunotherapy.[1]

Most of the population cannot afford novel agents because of their high cost. Geography compounds the problem because nearly 60% of India's population resides in rural areas, where access to cancer care beyond basic primary health care is extremely limited. Patients often must travel long distances to metropolitan cities such as Mumbai or Delhi to receive advanced treatments, which adds logistic and financial burdens.

Finally, institutional and policy-related barriers further delay access. At the policy level, regulatory approval timelines for new drugs are often longer in India than in many other countries. At the institutional level, academic centers tend to focus primarily on service delivery rather than clinical research, which slows the pace of innovation and the development of local clinical trials.

Despite these challenges, the potential for improvement is significant. With coordinated policy changes, infrastructure development, and expanded research capacity, India can make substantial progress in increasing equitable access to novel cancer therapies in the coming decade.

Health care services in India are steadily improving, including those related to cancer care. A major milestone was achieved in September 2018 with the launch of the Pradhan Mantri Jan Arogya Yojana (PM-JAY), the country's largest publicly funded health insurance scheme. PM-JAY provides free coverage to 120 million families (550 million beneficiaries) that make up the poorest 40% of the Indian population, effectively serving as India's version of Medicaid.

Under PM-JAY, each eligible family is entitled to coverage worth approximately US $5700 per year, which can cover many basic cancer treatments. These include surgical procedures, selected chemotherapy protocols, and even high-cost biologics such as rituximab and trastuzumab (albeit in limited doses).

Although PM-JAY has significantly expanded access to essential treatments, an unmet need for broader coverage remains, particularly for advanced therapies and long-term cancer care. An Indian version of Medicare, which extends benefits to people older than 70 years, has already begun enrolling patients. The next step would be to expand health care coverage to more people, including middle-income groups.

H&O Regarding prostate cancer, could you describe the response to the National Comprehensive Cancer Network (NCCN) recommendation from 2019 regarding low-dose abiraterone with food as an alternative treatment option to full-dose abiraterone?

AP The NCCN guidelines permit the use of abiraterone at 250 mg/d after a low-fat breakfast in patients who cannot afford the standard dose of 1000 mg/d after an overnight fast.[2] This recommendation was based in part on a phase 2 study that showed similar declines in prostate-specific antigen levels in fed patients taking a low

dose and fasted patients taking a standard dose.[3] Basically, we can decide whether to prescribe a single 250-mg tablet to be taken after a meal or four 250-mg tablets to be taken on an empty stomach. We decided to conduct a survey of Indian medical oncologists to understand their knowledge and practices regarding abiraterone. In the survey, 75% of the 118 oncologists surveyed were aware of the NCCN low-dose recommendations.[4] Approximately 7% had already switched to prescribing low-dose abiraterone with food, 55% were using the low dose in constrained settings, 29% were willing to switch to the low dose, and 9% were not willing to switch. All participants agreed that the recommendations would reduce costs, and 93% agreed that taking 1 tablet after food would improve adherence. An economic analysis revealed a cost saving of approximately $3640 per patient, which translated to $182 million per year in India in 2020.

Abiraterone is highly soluble in fat, so taking it with food allows very good absorption. Taking medication with food is also much simpler than taking medication on an empty stomach and not eating anything for the next hour, especially when a treatment lasts for 3 to 5 years. Most of my colleagues are prescribing 1 tablet after lunch, even now that a much cheaper generic version of abiraterone is available.

H&O How substantial could cost savings be with low-dose abiraterone in the United States?

AP Even in the United States, which is a wealthy country, medical bankruptcy is quite common. One study found that nearly 40% of patients with cancer in the United States declare financial insolvency after 4 years of treatment.[5] Financial insolvency is a risk factor for early mortality.[6] Our survey article was accompanied by 2 correspondences, one from the United States and one from Ireland. The US article found that adopting the single-tablet regimen would save $700 million yearly, without including commercial payers.[7] If financial toxicity and savings are of such magnitude in the United States, it is not difficult to imagine how important cost concerns are in low- and middle-income countries. Sadly, financial toxicity is rarely discussed at academic conferences.

H&O What strategies can be used to reduce costs when patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) breast cancer are being treated?

AP The 3 blockbuster cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors—palbociclib (Ibrance, Pfizer), ribociclib (Kisqali, Novartis), and abemaciclib (Verzenio, Lilly)—have changed the management of HR+/HER2– breast cancer. Initially, they were used in the second-line setting of metastatic breast cancer and were later moved to the first-line setting. What the phase 3 SONIA trial from the Netherlands showed us is that CDK4/6 inhibitors can be given in the second line with fulvestrant without compromising outcomes in comparison with first-line endocrine therapy with CDK4/6 inhibitors.[8] In fact, we can shorten the duration of CDK4/6 inhibitor treatment and reduce toxicities and cost with this approach. This finding solidified the question we asked in a 2019 article: why are we pushing these expensive drugs into the first-line setting when we know they work in the second-line setting? We can save costs and reduce toxicities by postponing their use to the second line.[9]

Taken together, these data strongly suggest that low-dose immunotherapy is effective, yet standard doses of immunotherapy remain higher than necessary.

H&O What strategies can be used to reduce costs in patients with metastatic HR+ breast cancer?

AP Fulvestrant is an expensive drug that is used in treating patients with metastatic HR+ breast cancer. The standard dose of fulvestrant in India since 2010 has been 500 mg on days 1, 14, and 28 and then monthly, at a cost of $290 per dose, which is more than the national per-capita income. Before 2010, the initial dose was 250 mg monthly after a loading dose of 500 mg. Pharmacokinetic data show that the 250-mg dose steadily maintains adequate levels after 3 to 6 doses. Trials that have compared the 2 doses have produced mixed results, with the higher dose producing either no significant benefit or only marginal progression-free survival benefit. Another advantage of the lower dose is that the patient can receive a single intramuscular injection rather than 2 injections. These are intramuscular gluteal injections that are very painful. I think that a reasonable approach in low-income

settings is a loading dose of 500 mg followed by 250 mg at days 14 and 28 and then 250 mg monthly.

What is interesting to me is that we received an email from a physician in Switzerland saying that our commentary on fulvestrant dosing from *JCO Global Oncology*[10] was going to be discussed with the medical oncology residents in that country. So, this is an approach that can make sense even in a wealthy country.

H&O Could you describe your 2023 research on reducing the dose of pegylated granulocyte colony–stimulating factor (peg-G-CSF) in breast cancer?

AP We have been using peg-G-CSF in patients with cancer for a long time. The conventional standard dose is 6 mg, although a lower dose of 3.6 mg is used in Japan. In a phase 1 pharmacokinetic study of peg-G-CSF, dosing of 60 µg/kg was equivalent to 100 µg/kg. We wanted to learn whether dosing at 3 mg would be effective for Indian patients. We designed a phase 1/2 study of 36 patients with breast cancer in which we used peg-G-CSF at 3 mg in a dose-dense protocol.[11] The first 6 patients were evaluated for total leukocyte response at 1, 6, and 24 hours after chemotherapy. The 24-hour post-chemotherapy cohort was expanded to 30 patients. We found that 97% of the patients were able to maintain dose density. We concluded that 3 mg of peg-G-CSF 24 hours after chemotherapy maintains dose density and prevents febrile neutropenia in Indian patients. The next step is to conduct a phase 3 trial of this dose.

The average Indian patient with cancer weighs approximately 45 to 50 kg, whereas the average US patient weighs approximately 70 to 75 kg. That is a large difference, and an important one. Peg-G-CSF is associated with fever and severe back pain in some patients, and lowering the dose might reduce these side effects. Of interest, dose-finding studies in Japan concluded that 3.6 mg of peg-G-CSF is the desired dose in that country.

I am currently using the 3-mg dose in my clinic. During a recent 2-week observation period at MD Anderson Cancer Center in Texas, I saw that their protocol calls for weight-based dosing of peg-G-CSF: 6 mg for patients weighing more than 45 kg, 4 mg for those weighing 31 to 45 kg, 2.5 mg for those weighing 21 to 30 kg, 1.5 mg for those weighing 10 to 20 kg, and 0.1 mg/kg for pediatric patients weighing less than 10 kg. If that is the standard at MD Anderson, why not in other parts of world? We certainly do not want to use a 6-mg dose in a 45-kg patient at our center. Because peg-G-CSF is used in nearly every type of cancer when chemotherapy is given, our findings have a very wide application.

H&O What steps can be taken to reduce the dosing of immune checkpoint inhibitors in low- and middle-income countries?

AP I, along with Daniel Goldstein and Ian Tannock, have written about improving access to immunotherapy worldwide by using lower doses.[12] A lower dosage of nivolumab (Opdivo, Bristol Myers Squibb) or pembrolizumab (Keytruda, Merck) is successful at blocking the programmed death 1 receptor and may remain effective for a longer time.[13,14] Clinical evidence comes from a phase 2 randomized study of renal cell carcinoma showing that lower doses of nivolumab maintain efficacy.[14] The first real-world evidence supporting this approach came from South Korea, where it was demonstrated that both 20- and 40-mg doses of nivolumab are effective.[15] In the Netherlands, the phase 3 NVALT-30/DEDICATION-1 trial is currently comparing the standard 200-mg dose of pembrolizumab with a 100-mg dose in non–small cell lung cancer (NCT04909684).

Taken together, these data strongly suggest that low-dose immunotherapy is effective, yet standard doses of immunotherapy remain higher than necessary. This is because immunotherapy drugs were developed following the traditional paradigm used for chemotherapy—determining the maximum tolerated dose. However, this approach is not biologically required for immune checkpoint inhibitors because their therapeutic effect depends simply on T-cell activation, which can often be achieved at much lower doses. Key opinion leaders should be vocal about this issue when discussing immunotherapy, as dose optimization could dramatically expand access globally. We need to raise our voices on this matter.

In support of this concept, a phase 3 trial of low-dose nivolumab (20 mg every 3 weeks) combined with triple metronomic oral therapy showed a median overall survival of 10.1 months in patients with recurrent or metastatic head and neck cancer.[16] The KEYNOTE-048 trial, which used a flat dose of 200 mg of pembrolizumab plus chemotherapy, reported an overall survival of 11.5 months in the first-line treatment of recurrent/metastatic head and neck cancer.[17] These results suggest that lower-dose immunotherapy can improve access without compromising patient outcomes.

H&O Is there anything you would like to add?

AP The systematic review by Jiménez-Labaig and colleagues, from London, of more than 2000 patients on low-dose immunotherapy has underscored the worldwide interest in improving access and the genuine efforts by fellows, researchers, and clinicians to accomplish this.[18] Although we need more phase 3 trials, these efforts must

be continued to reach the last patient who can be saved with scientific prudence and the pragmatic use of effective anticancer therapies. Although the 2018 Nobel Prize was awarded to the scientists who discovered immunotherapy drugs, access sadly remains accessible to only a few wealthy countries. We need to unite with the goal of improving access to novel anticancer drugs for most of the world's population.

Disclosures

Dr Patel has no disclosures.

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