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Pharmacoeconomics

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Advances in cancer treatment have led to substantial improvements in survival. These include several drugs for treatment of multiple myeloma and metastatic prostate cancer, and immunotherapy with checkpoint inhibitors for treatment of nonsmall cell lung cancer, kidney cancer, melanoma, and others. Management of breast cancer has also changed substantially in the last two decades with approval of CDK4/6 inhibitors, trastuzumab, pertuzumab, TDM1, and other drugs. The pricing of these agents is set by what the market will bear but typically will be more than U.S. $12,000 (~INR 880,000) per month for approved schedules of treatment in the United States, an obscene price that brings huge profits to the pharmaceutical industry. In India, the cost of these therapies is not affordable and only a handful of patients are treated with these medications. There may be some price reduction in other countries, particularly those with a national health service that can bargain for bulk purchase. Some drugs are manufactured and sold in India at a much lower price. However, many effective drugs remain unaffordable for all but the wealthy in lower- and middle-income countries (LMIC) such as India. The majority of people with cancer who could benefit from treatment with new drugs live in LMIC. It is a hollow victory to have generated effective treatments for several types of cancer, but for these therapies, not to be available to the global majority who could benefit. And the nonavailability of life-prolonging treatment is not due to the cost of manufacturing the drugs, it is due to protection of profit at the expense of human life.

Pharmacoeconomics is a relatively new term which uses pharmacologic and pharmacodynamic properties of drugs to propose less-expensive alternatives to standard treatment.[1,2] This helps to increase access to effective therapy. Various types of evidence can be used to support the acceptance of alternative treatments relative to a standard (Food and Drug Administration [FDA]- and European Medicines Agency [EMA]-approved) treatment. Strategies for achieving near-equivalent outcomes at lower cost (and/or less toxicity) include[3] the following:

- Prescribing a lower dose if the approved dose exceeds that needed for maximal antitumor activity.
- Less frequent dosing of the drug where pharmacokinetic and pharmacodynamic data suggest that longer intervals are appropriate.
- Prescribing a shorter course of treatment.
- Improving oral drug absorption by food intake or with another agent that enhances bioavailability.
- Giving an alternative, less-expensive drug with similar efficacy.

Anticancer drugs are frequently prescribed in routine practice at lower doses than those approved by registration agencies, and knowledge of pharmacoeconomics could lead to modifications of treatment with substantial reductions in cost, with little or no loss of efficacy, and thereby increase access of effective drugs to cancer patients.

Typically, new drugs are approved for treatment of cancer following a series of clinical trials that follow preclinical evidence of efficacy. Phase-I trials evaluate tolerance in small groups of patients and define an appropriate dose and schedule to be used in further trials, phase-II trials evaluate antitumor activity against specific types of human cancer, and phase-III randomized controlled trials (RCTs) compare measures of patient benefit (ideally overall survival and also quality of life) with a current standard of care. Phase-I trials are small, and those evaluating targeted agents have changed their design minimally from those used to evaluate chemotherapy; they are designed usually on the principle that higher doses will be more effective and that substantial toxicity must be tolerated. For many molecular targeted agents, there is little evidence of a dose response around their approved doses for either target inhibition or antitumor effects, suggesting that substantially lower doses might be equally effective. Two examples are the use of abiraterone in

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management of metastatic prostate cancer and immunotherapy with pembrolizumab or nivolumab.

Abiraterone, an inhibitor of androgen synthesis, is an effective drug that has improved survival of men with various stages of prostate cancer, including castrate-resistant prostate cancer either before or after chemotherapy,[4,5] and when added to standard androgen depletion therapy (i.e., orchidectomy or an LHRH [luteinizing hormone-releasing hormone] agonist) as initial treatment of metastatic disease.[6,7] The approved dose is 1,000 mg/day fasting; however, no clear dose–response relationship at lower doses was shown in phase-I studies, and its bioavailability was increased by a factor of 5 to 7 when given after a low-fat meal.[8-11] In an RCT of 72 patients of advanced prostate cancer, 250 mg/day given after food had equal pharmacodynamic effects on its target of CYP17A as 1,000 mg/day fasting, leading to similar effects to reduce the adrenal androgen, dehydroepiandrosterone sulfate, as well as a trend toward better outcome based on PSA (prostate-specific antigen) response and duration.[12] The National Comprehensive Cancer Network (NCCN) recommended the lower dose with food as an alternative to the standard dose fasting on the basis of this study. A survey of oncologists in India highlighted that more than 90% of them either changed or were willing to change the existing practice to use lower dose abiraterone with food. Thereby access to treatment will improve for Indian patients with a projected annual cost saving of U.S. $182 million in Indian health care.[13]

The approved doses and schedules for immunotherapy drugs, like nivolumab and pembrolizumab, exceed substantially what is needed for effective treatment. A (n = 296) phase-I trial of nivolumab demonstrated no trends to differences in response rate, target binding, or survival at doses ranging from 0.1 to 10 mg/kg every 2 weeks,[14,15] and a phase-II RCT in patients with metastatic renal cell cancer revealed no dose–response relationship for progression free survival (PFS) which was the primary outcome measure at 0.3, 2.0, and 10 mg/kg every 3 weeks.[16] Still the dose and schedule in the registration trial for metastatic renal cell cancer was 3 mg/kg every 2 weeks which is at least 15 times the minimal effective dose.[17] There is evidence that patients with nonsmall cell lung cancer respond to a lower fixed dose of 20 or 100 mg every 3 weeks.[18] Moreover, the serum half-life of nivolumab is 2 to 3 weeks, and pharmacodynamic studies have shown sustained target occupancy of >70% on T-cells which lasts for at least 2 months.[19] Similarly, pharmacodynamic studies of pembrolizumab in early-phase trials suggest maximum target occupation at 1 mg/kg or greater and no increased target inhibition at doses up to 10 mg/kg.[20] Other clinical trials found no trends to differences in antitumor activity (or toxicity) for pembrolizumab given at 2 or 10 mg/kg every 3 weeks for treatment of nonsmall cell lung cancer or melanoma.[21-23] Pembrolizumab is given at a fixed dose of 200 mg every 3 weeks, and the FDA has approved recently a dose of 400 mg every 6 weeks. However, the activity of nivolumab and pembrolizumab would likely be maintained at substantially lower doses with less frequent injections, with a possible reduction in immune-related toxicities. Clinical trials are underway to compare the approved dose and schedule with less-intensive treatment and mounting such a trial would be highly appropriate for the Indian trials network. Funding such a trial will need to come from public or charitable sources, since it would not be supported by the pharmaceutical industry, as it might lead to reduced profits. Pharmaceutical companies might also increase the price of the drugs to offset a reduced dose and modified schedule, but this will be difficult for drugs that are in liquid format where vials can be shared.

There are many other anticancer drugs where reduced dosage or schedule or administration with food or other medications to improve bioavailability could lead to good outcomes with substantially less physical and financial toxicity.[1,2,24] Cost effectiveness of therapies can be measured by the cost per life-year gained, which is the added cost of a new therapy compared with the previous standard divided by the mean added life years (or quality-adjusted life years [QALYs]) gained.[25] A recent cost-effective analysis of 1-year of adjuvant treatment of trastuzumab in breast cancer in India showed that the cost per life-year gained was in the range of INR 130,000 to 180,000.[26] In 2019, the mean monthly household income in India was approximately INR 13,150,[27] and 1 year of adjuvant trastuzumab is neither cost-effective nor affordable for most Indian women with HER2+ breast cancer. However, the cost of treatment can be reduced by approximately 75% by (1) prescribing adjuvant trastuzumab for 6 months with outcomes that are similar to 1-year of treatment,[28,29] and (2) using a trastuzumab biosimilar.[30] The Finnish protocol using 9 weeks of adjuvant trastuzumab can be used to decrease cost further and is a better alternative than foregoing anti-HER2 treatment, but there is likely some loss of efficacy compared with 6 to 12 month regimens.[31]

We encourage oncologists to increase their knowledge of pharmacoeconomic strategies and to apply them to improve access of their patients to drugs that can improve survival. Large cost savings can be achieved for many drugs and specific examples are given in this article.[2] Use of these principles implies off-label prescribing, that is, giving a lower dose or different schedule than that approved by registration agencies, but this is done commonly in clinical practice to mitigate toxicity, and here the goal is again to reduce (financial) toxicity and to improve access to effective treatments. Consenting patients to receive such treatment should always provide an explicit statement that a different dose or schedule is being used than that approved for marketing. Ideally, these strategies should be evaluated in randomized trials comparing reduced with standard treatment. We encourage the Indian trials network to seek funding from nonpharmaceutical agencies to undertake such trials which will not be supported by the pharmaceutical industry. Such trials have the potential to generate pharmacogenomic data which might be substantially different from that of Caucasians.

Finally, as a specific example of use of pharmacoeconomics, if an oncologist is faced with a patient with a type of cancer for which immunotherapy with a checkpoint inhibitor has shown substantial probability of survival benefit, and the patient can afford up to 10% of the cost of treatment with the approved dose and schedule, what should (s)he do? In

our opinion, after obtaining informed consent, it would be appropriate to prescribe 20% of the approved dosage at twice the approved interval (i.e., every 6–8 weeks), recognizing that sharing of vials will be necessary to achieve cost saving.

Conflict of Interest
None declared.

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