ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Weight-Based Dosing vs Fixed Dosing of Pembrolizumab: an Economic Analysis

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H&O When were the first checkpoint inhibitors approved by the FDA?

DG Immunotherapy has been an important breakthrough of the past few years. The cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb) was the first checkpoint inhibitor approved by the US Food and Drug Administration (FDA). Ipilimumab was approved in 2011 for the treatment of unresectable or metastatic melanoma. Since that time, several other checkpoint inhibitors have been approved, such as pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), and avelumab (Bavencio, EMD Serono/Pfizer), which are inhibitors of programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1). The initial FDA approvals of checkpoint inhibitors were mainly in melanoma. Approvals followed in other malignancies, such as lung cancer, kidney cancer, and bladder cancer. There are also approvals of agents for wider indications, such as cancers with microsatellite instability.

H&O How have dosing recommendations evolved for the PD-1/PD-L1 inhibitors?

DG The early approvals by the FDA were based on results of trials that used weight-based doses. With pembrolizumab, 2 weight-based doses—2 mg/kg and 10 mg/kg—were used in the initial trials in melanoma and lung cancer. An equivalency study in lung cancer showed that 2 mg/kg and 10 mg/kg were equally effective. This finding led to a change in the dosing policy by Merck. Subsequent trials with pembrolizumab used a fixed dose of 200 mg for all patients, regardless of their weight.

The average weight of an American adult is approximately 75 kg. If the dose were 2 kg/mg, then the dose for a 75-kg patient would be 150 mg. Therefore, one could argue that a dose of 150 mg every 3 weeks, instead of 200 mg every 3 weeks, would be sufficient—as we know that 2 mg/kg has equivalent efficacy to 10 mg/kg. The financial impact of this difference is significant, with potential savings of approximately $2000 per dose. The difference becomes many thousands of dollars throughout the course of treatment for a single patient. From the societal perspective, the difference is substantial.

The KEYNOTE-024 trial (Study of Pembrolizumab [MK-3475] Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer) of pembrolizumab as a first-line therapy in PD-L1–positive (>50%) non–small cell lung cancer (NSCLC) evaluated a dose of 200 mg every 3 weeks. The results of this trial led to the approval of pembrolizumab at 200 mg, and this dose is therefore recommended for patients. After this approval, the company was able to retroactively change the earlier approved weight-based doses, so that the fixed dose of 200 mg was approved for all indications of pembrolizumab.

H&O How did you evaluate the cost difference between weight-based dosing and fixed dosing?

DG My colleagues and I designed a study to calculate

the budget impact difference of administering pembrolizumab at a personalized dose of 2 mg/kg instead of 200 mg among patients with treatment-naive, metastatic, PD-L1–positive NSCLC on the population level in the United States. We estimated the number of patients who would receive pembrolizumab as a first-line treatment of NSCLC. At the time of the study design, pembrolizumab was approved for patients whose tumors express PD-L1 in at least 50% of cells, so only those patients were included in our analysis. We excluded patients who were ineligible for pembrolizumab, such as those with small cell lung cancer, those with mutations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK), and those who were too sick or frail for systemic therapy. From Medicare data, we captured the number of patients who die annually of lung cancer each year, and subtracted these subsets of patients. We estimated that nearly 20,000 patients each year would be treated with pembrolizumab in this setting. To calculate the cost savings, we used several different variables, such as the cost of the drug and the duration of treatment in clinical trials. We showed that the use of weight-based dosing had the potential to save approximately 0.8 billion dollars annually, without any reduction in the level of efficacy.

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Since our analysis, the KEYNOTE-021 study (A Study of Pembrolizumab [MK-3475] in Combination With Chemotherapy or Immunotherapy in Participants With Non-Small Cell Lung Cancer) has led to the approval of pembrolizumab in combination with chemotherapy in the first-line treatment of NSCLC, regardless of the patient's PD-L1 status. One could therefore argue that our published estimation is now a significant underestimate. It appears that pembrolizumab is becoming the standard of care for most patients in the first-line setting of NSCLC. Pembrolizumab is also used in other malignancies, such as bladder cancer and melanoma. Thus, this estimate of $0.8 billion will rise if we consider all additional indications.

H&O Are there any barriers to the implementation of a weight-based dosing strategy?

DG There are challenges based on the size of the available vials. Originally, vials of pembrolizumab were available in 2 sizes: 50 mg and 100 mg. A few years ago, the 50-mg vials were removed from the marketplace in the United States, making it more difficult to give lower doses. With only 100-mg vials available, if a patient requires a dose of 150 mg, then 50 mg of the drug will be left over. Reaching the cost savings found by our study would require careful management to share vials of the drug among patients. Some patients may be unwilling to share drug vials.

Reimbursement policies pose another challenge. The Centers for Medicare & Medicaid Services reimburse hospitals for leftover drug in a vial. There is no financial incentive for hospitals to use the leftover drug in another patient instead of discarding it.

H&O Does the weight-based dosing strategy impact clinical outcome?

DG Data from previously published studies suggest that weight-based dosing and fixed dosing are associated with similar levels of efficacy and side effects. The KEYNOTE-001 trial (Study of Pembrolizumab [MK-3475] in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-Small Cell Lung Carcinoma) compared pembrolizumab at doses of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks. The levels of efficacy were similar.

H&O Are there other strategies to optimize dosing?

DG We spend huge amounts of money on cancer drugs right now, and sometimes the dosing may be higher than what is needed. An interesting study led by Dr Russell Szmulewitz evaluated the dosing of abiraterone acetate in prostate cancer. In the pivotal clinical trials, abiraterone acetate was administered to patients who were fasting. The study by Dr Szmulewitz compared pharmacodynamics and clinical outcome when abiraterone acetate was administered to patients who had eaten a low-fat meal or who were fasting. The study found equivalent efficacy with 1 tablet (250 mg) given on a full stomach compared with 4 tablets (1000 mg) given on an empty stomach. There is thepotential for substantial cost savings with this strategy.

There is the potential that other drugs could be effective at lower dosages. Other types of de-escalation strategies should be evaluated in subsequent studies. Benefits may be especially prominent in resource-poor settings, where it is not possible to fund a certain drug in the first place. A decrease in the cost of a drug may allow funding of it.

H&O Do you have any other insights to share regarding the cost of drugs?

DG As a society, it is necessary to face the fact that we are spending significant amounts of public and private resources at the end of life, which has far-reaching impact. Both the cost and the benefit should be considered when making decisions about treatments for individual patients and larger populations in regard to pharmaceutical drugs, as well as other costly interventions, such as hospitalizations and diagnostics.

Disclosure

Dr Goldstein has no real or apparent conflicts of interest to report.

Suggested Readings

Bach PB, Conti RM, Muller RJ, Schnorr GC, Saltz LB. Overspending driven by oversized single dose vials of cancer drugs. *BMJ*. 2016;352:i788.

Garon EB, Rizvi NA, Hui R, et al; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028.

Goldstein DA, Gordon N, Davidescu M, et al. A phamacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in firstline PD-L1-positive non-small cell lung cancer. *J Natl Cancer Inst*. 2017;109(11).

Reck M, Rodríguez-Abreu D, Robinson AG; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823-1833.

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(14):1389-1395.