Title
New drugs and options can enhance patient outcomes: But can they also erode them?

Authors
Kim, Myung S
Prasad, Vinay

Publication Date
2021-09-01

DOI
10.1016/j.ejca.2021.04.047

European Journal of Cancer 154 (2021) 1–3

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

New drugs and options can enhance patient outcomes: But can they also erode them?

Myung S. Kim [a], Vinay Prasad [b,c,*]

[a] Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, USA
[b] Department of Medicine, University of California, San Francisco, San Francisco, CA, USA
[c] Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

Received 27 April 2021; accepted 30 April 2021
Available online 30 June 2021

Abstract The expanding list of treatment options available to patients with cancer is a source of excitement. Drugs with novel mechanisms of action receive attention at academic meetings and approval of novel drugs are cited as a victory of medical research. This is evidenced by the interest in number of new drug approvals each year. The Food and Drug Administration provides a yearly report of New Molecular Entities approved by the Center for Drug Evaluation and Research. High numbers of approved drugs is celebrated and equated with improvement in patient outcomes, as well as evidence of the effectiveness of regulatory agencies [1]. While more effective therapies lead to improved outcome, merely having more options may erode outcomes in unexpected ways. We discuss 3 different clinical scenarios where having more options can lead to worse outcomes.

1. A new drug displaces an older drug that is actually superior

First, new drugs are often approved and introduced into clinical practice without comparison to the current standard of care. The quality of the control arms has been investigated and suboptimal control arms are not uncommon [2]. In these cases, how the new drug compares to the actual current standard of care remains unknown. If the newly approved drug is inferior, then patients receiving that drug will have worse outcomes. This is notable in the space of multiple myeloma drug approvals. Consider the drug selinexor. Selinexor received regulatory approval in the relapsed setting in a randomised trial showing that, in combination with bortezomib and dexamethasone, the agent extended progression-free survival [3]. The control arm for this trial was unfortunately bortezomib and dexamethasone, and not a triplet, such as carfilzomib, lenalidomide and dexamethasone or daratumumab based triplets. As such, if a doctor

* *Corresponding author*. University of California, 550 16th St, San Francisco, CA, 94158, USA.
E-mail address: vinayak.prasad@ucsf.edu (V. Prasad).

https://doi.org/10.1016/j.ejca.2021.04.047
0959-8049/

prescribes a patient who progresses on VRD (bortezomib, lenalidomide, dexamethasone), SVD (selinexor, bortezomib, dexamethasone), we do not know if outcomes may be eroded compared to prescribed DRD (daratumumab, lenalidomide, dexamethasone).

A recent systemic review by Mohyuddin *et al.* identified that 14% of phase III clinical trials in multiple myeloma published in the past 10 years enrolled patients into control groups receiving known inferior regimens, of which the Boston trial was one [4]. This phenomenon may also occur with many drugs that approved without a control arm, as we do not know they are better than alternatives [5]. In fact, an article by Haslam shows that among drugs approved based on response rate, 33% had a prior drug in the same tumour type with higher response rate. When drugs with novel mechanisms or new drug combinations are approved without comparison to the current standard, it is possible that patients receiving newly approved treatments would have worse outcomes than when treated with prior standard of care.

2. New drugs for patients unfit for aggressive therapy are used in patients fit for aggressive therapy

Second, new drug approvals are based on trials with specific inclusion criteria, however once approved may be applied to a broader range of patients. Azacitidine and venetoclax is now approved as combined therapy for previously untreated acute myeloid leukaemia in adults aged 75 year or older or who have comorbidities that preclude intensive chemotherapy. The definition of comorbidities is specific in the phase III clinical trial and includes heart failure warranting treatment of with an ejection fraction of 50% or less, chronic stable angina, lung diffusing capacity of 65% or less, lung forced expiratory volume in 1 s of 65% or less or Eastern Cooperative Oncology Group performance-status score of 2 or 3 [6]. In the real world, patients with variable degrees of comorbidities may be given the azacitidine and venetoclax regimen instead of standard induction chemotherapy with cytarabine and anthracycline (7 + 3 regimen). Borderline patients that may be eligible for induction chemotherapy may receive the new regimen and have worse outcomes than if they had received standard induction chemotherapy.

This phenomenon may also occur in metastatic oestrogen receptor-positive (ER-positive) breast cancer. Palbociclib and letrozole is widely used for metastatic ER-positive breast cancer. Another treatment option for such patients is sequential single agent chemotherapy most commonly with anthracycline or taxol class agents. In fact, with high volume visceral disease chemotherapy is recommended over endocrine therapy. Approximately a quarter of participants in the phase 3 study comparing palbociclib and letrozole to letrozole alone are without measurable disease (23.9% and 23%) which mostly coincided with patient that have bone only disease (23.2% and 21.6%) [7]. The volume of disease in patients with visceral involvement is not described however clinical trial participants are likely to have more low-volume disease that is stable. In patients with high-volume visceral disease, it is unknown if they would do better with palbociclib and letrozole compared to chemotherapy. If they receive palbociclib and letrozole they may experience progression and clinical deterioration and subsequently lose the opportunity to try chemotherapy. After approval of the combination, doctors are free to use it even in such scenarios.

3. Tissue agnostic approvals may displace better tissue specific treatments

Finally, tumour agnostic approval of drugs may lead to inferior outcomes in certain clinical situations. Pembrolizumab is now approved in patients with tumour mutational burden-high ($\geq$10 mutations/megabase) solid tumours after progressing on prior treatment. In a recent publication by Valero *et al.* high tumour mutational burden correlated with response rates to checkpoint inhibitors in some tumour types however this was not the case gastric cancer, hepatobiliary cancer, pancreatic cancer and mesothelioma when using a binary cut-off of 10 [8]. Different tumours have unique distributions of tumour mutation burden, thus even if high tumour mutation burden is associated with increased response to checkpoint inhibitors, treatment decisions based on arbitrary thresholds across a broad range of tumours may lead to worse outcomes. For example, in a patient with metastatic pancreatic cancer that has progressed on gemcitabine-based chemotherapy, irinotecan plus fluorouracil as second-line therapy improves survival [9]. If this patient happened to have a tumour mutation burden of 12, he may receive pembrolizumab although response rate to pembrolizumab is no higher in patient with score of 10 or higher. Such broad approvals are another unforeseen pathway to possible inferior outcomes.

4. More options often improve outcomes but not always

More options and new drug approvals do not always lead to enhanced outcomes and may in some cases erode outcomes. We should recognise that clinical trials with substandard control arms may lead to net harm to patients even if it leads to earlier approval of drugs. It may be inevitable that newly approved drugs are utilised beyond the strict inclusion criteria of clinical trials. However, we must also recognise that broader application of an approval risks leading to erosion of outcomes even compared to the efficacy of standard therapy before the new drug was available. Excitement about newly

approved drugs and chemotherapy free regimens may lead to overenthusiastic use of regimens that have proven efficacy only in a specific subgroup of patients with that tumour. Clinical trials should report comprehensive descriptions of patients in the trial regarding tumour burden or comorbidities for reliable application of trial results. Finally, regulatory agencies should be cautious in approving drugs for a broad range of tumour types based on imperfect biomarkers and understand the implication it may have to patient outcomes.

Funding

V.P. is funded by Arnold Ventures. Grant Number: N/A.

Contributorship

V.P. developed the concept of the article and provided critical revision and M.S.K drafted the article. Both authors approved the final article and are accountable for all aspects of the work.

Conflict of interest statement

V.P. reports receiving research funding from Arnold Ventures, royalty payments from Johns Hopkins Press, Medscape and MedPage, consultancy fees from UnitedHealthcare, speaking fees from Evicore and New Century Health, and other fees from Plenary Session podcast which has Patreon backers.

References

[1] New Drug Therapy Approvals 2019. Food and drug administration website. January 6, 2020. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2019#2019. [Accessed 15 April 2021].

[2] Hilal T, Sonbol MB, Prasad V. Analysis of control arm quality in randomized clinical trials leading to anticancer drug approval by the US food and drug administration. JAMA Oncol 2019;5(6):887–92.

[3] Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet 2020;396(10262):1563–73.

[4] Mohyuddin GR, Koehn K, Sborov D, et al. Quality of control groups in randomised trials of multiple myeloma enrolling in the USA: a systematic review. The Lancet Haematol 2021;8(4):e299–304.

[5] Haslam A, Gill J, Prasad V. The response rate of alternative treatments for drugs approved on the basis of response rate. Int J Canc 2021;148(3):713–22.

[6] DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020;383(7):617–29.

[7] Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375(20):1925–36.

[8] Valero C, Lee M, Hoen D, et al. Response rates to anti–PD-1 immunotherapy in microsatellite-stable solid tumors with 10 or more mutations per megabase. JAMA Oncol 2021 May 1;7(5):739–43. https://doi.org/10.1001/jamaoncol.2020.7684.

[9] Wang-Gillam A, Li C-P, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387(10018):545–57.