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Authors

Gill, Jennifer
Prasad, Vinay

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VIEWPOINT

Pembrolizumab for Non–Muscle-Invasive Bladder Cancer—A Costly Therapy in Search of Evidence

Jennifer Gill, MS
Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco.

Vinay Prasad, MD, MPH
Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco.

In January 2020, the US Food and Drug Administration approved pembrolizumab to treat patients with bacillus Calmette-Guerin (BCG)–unresponsive, high-risk, non–muscle-invasive bladder cancer (NMIBC) with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.[1] Approval was based on KEYNOTE-057 (NCT02625961), a single-arm trial that found a 41% complete response rate and 16.2-month median duration of response. The **Figure** shows the probability of sustained clinical response based on these data.

Pembrolizumab is presented as a promising alternative therapy to surgery.[1] Yet there is danger in viewing pembrolizumab as a superior alternative to cystectomy for those eligible for surgery and a better solution compared with continued BCG treatment for those who are not eligible for surgery. There is a critical distinction between patients who are ineligible for cystectomy vs patients who refuse to undergo surgery. The lack of distinction in this study and approval[1] allows for broad use of pembrolizumab without strong evidence. Without data from randomized clinical trials comparing pembrolizumab with standard of care (SOC) in BCG-unresponsive, high-risk patients with NMIBC, both eligible and ineligible for surgery, we cannot know if pembrolizumab is improving or worsening survival and quality of life (QOL) in this population.

Current SOC for NMIBC

Approximately 70% of new urothelial bladder cancer cases are found to be NMIBC, and 40% to 80% of those treated will experience recurrence within a year.[2] Initial treatment includes transurethral resection of all visible bladder tumor, which is followed by observation or intravesical therapy depending on the stage, grade, and risk factors. The BCG vaccine is the recommended intravesical therapy for high-risk NMIBC, along with frequent surveillance through cystoscopy.[3] For those unresponsive to BCG, there is a high risk of local and distant progression. The SOC for BCG-unresponsive patients with high-grade NMIBC is radical cystectomy. Those deemed medically unfit for cystectomy are treated with salvage intravesical therapy.[3,4]

Pembrolizumab is currently approved for 2 distinct groups of BCG-unresponsive patients with MNIBC: those who are ineligible for surgery, and those who refuse surgery.[1] To determine the safety and efficacy of this drug, we must consider its role in each group.

Patients Who Are Ineligible for Radical Cystectomy

Those ineligible for cystectomy are likely an older population with greater illness severity. In KEYNOTE-057, 97.1% of patients had at least 1 adverse event, with 29.4% of patients experiencing grade 3 to 5 adverse events. Treatment was discontinued in 11% of patients because of adverse reactions.[1] Treating surgery-ineligible patients with pembrolizumab on the basis of a single-arm study based on response rate does not ensure improved survival or QOL. Moreover, high rates of adverse events among patients in the trial suggest that treatment with this drug may be detrimental to QOL. To justify treating this population with an aggressive, expensive drug, data must show that pembrolizumab improves mortality over SOC and does not cause a substantial decline in QOL. We suggest that a trial be conducted that randomizes patients who are ineligible for cystectomy to pembrolizumab vs SOC (intravesical therapy, if appropriate, or observation) with overall survival as the primary end point and rate of muscle-invasive bladder cancer and QOL as secondary end points. Without evidence from such a trial, patients may be taking an expensive, aggressive drug with little benefit to their longevity or well-being.

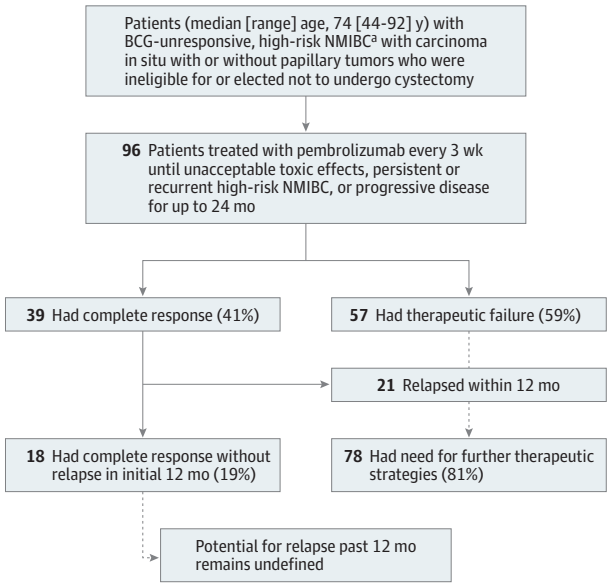
Patients Who Refuse Surgery

For patients healthy enough to undergo a cystectomy, knowledge and access to pembrolizumab may cause inadvertent harm by shaping treatment decisions. Patients refuse surgery for many reasons. Some will never agree to radical cystectomy, while others seek to try all other options before acquiescing to surgery. Patients who may have once agreed to cystectomy after NMIBC recurrence may refuse later because they believe there is a less invasive, comparable treatment (ie, pembrolizumab). By approving pembrolizumab for patients who refuse to undergo cystectomy, the US Food and Drug Administration is essentially approving the drug for all high-risk, BCG-unresponsive patients.[1]

In KEYNOTE-057, 41% of participants had a complete response, and 46% of those patients had a response of 12 months or longer.[1] That leaves more than 80% of patients with recurrence who may subsequently opt for a cystectomy. The potential for relapse past 12 months remains undefined, leaving the possibility that even more patients would need further treatment. Delays in cystectomy among patients who are unresponsive to BCG treatment are associated with worse survival compared with those who underwent surgery immediately after recurrence.[5] With the knowledge that delaying cystectomy may lead to worse outcomes, it is essential that we compare pembrolizumab with cystectomy after recurrence with immediate cystectomy. We suggest randomizing BCG-unresponsive patients with NMIBC to these 2 treatment regimens and measuring overall survival and QOL. Radical cystectomies are

Corresponding Author: Vinay Prasad, MD, MPH, University of California, San Francisco, 550 16th St, 2nd Floor, San Francisco, CA 94158 (vinayak.prasad@ucsf.edu).

Figure. Flowchart of KEYNOTE-057 Results That Led to US Food and Drug Administration Approval[1] of Pembrolizumab for Patients With Bacillus Calmette-Guerin (BCG)–Unresponsive, High-Risk Non–Muscle-Invasive Bladder Cancer (NMIBC)



[a] Bacillus Calmette-Guerin–unresponsive, high-risk NMIBC was defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG therapy was defined as administration of at least 5 of 6 doses of an initial induction course plus either at least 2 of 3 doses of maintenance therapy or 2 of 6 doses of a second induction course.

lengthy surgeries with high rates of morbidity and a small risk of mortality, and they are associated with a reduction in QOL. If pembrolizumab is able to offer similar overall survival with improved QOL, it should be considered a new SOC. Conversely, if patients treated with pembrolizumab inevitably go through cystectomy and have poorer overall survival, we would be harming patients by offering pembrolizumab as an alternative treatment.

Financial Burden of Bladder Cancer

Bladder cancer has the highest lifetime treatment costs per patient among all cancer types.[6] This is partially because of the high costs of transurethral resection of all visible bladder tumor and frequent monitoring through invasive procedures, treatments, and systemic-related complications, and it is exacerbated by high rates of recurrence, progression, and ineffective treatments. It costs approximately $300 000 to treat a BCG-unresponsive patient with NMIBC with a full course of pembrolizumab and $200 000 based on the average duration of response.[7] Comparatively, BCG costs about $2000 per patient, and the median total charges for radical cystectomies are approximately $53 000.[6] Adding a prohibitively expensive treatment to patients' regimens without proof of efficacy burdens patients, their families, and our health care system. We cannot determine the cost-effectiveness of pembrolizumab without first determining its efficacy compared with SOC.

Conclusions

Without randomized trials to determine the survival and QOL benefits of pembrolizumab in BCG-unresponsive, high-risk patients with NMIBC, we may be causing more harm to this vulnerable patient population. For patients who are ineligible for surgery, pembrolizumab may cause toxicity without elongating survival. For patients who are eligible for surgery, pembrolizumab may delay treatment with cystectomy and thereby worsen survival rates. For all patients with NMIBC, pembrolizumab will add considerable financial burden. Further clinical trials are warranted, and we encourage clinicians and patients to enroll.

ARTICLE INFORMATION

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