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Original Article

Cost-effectiveness analysis of nivolumab compared to pembrolizumab in the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck

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Abstract: Pembrolizumab and nivolumab are anti-PD-1 immunotherapy agents approved for the treatment of metastatic or recurrent head and neck squamous cell carcinoma (HNSCC) with demonstrated benefit as shown by the CheckMate 141 and KEYNOTE-040 clinical trials. Increasing costs of anticancer drugs in particular may influence the choice of treatment. There are limited data and mixed results on the cost-effectiveness of these immunotherapy agents when used in the setting of recurrent or metastatic HNSCC. This study compares the cost-effectiveness of pembrolizumab and nivolumab in this setting. Data published from the CheckMate 141 and KEYNOTE-040 studies were used to generate a model estimating treatment costs and overall survival benefit. Cost of treatment of toxicity-related events were obtained from previous literature and incorporated into calculated costs. Data from both experimental arms and both standard of care arms in the two studies were used for cost estimation in the model. An adjusted standard of care arm was derived from existing data as a common comparator for nivolumab and pembrolizumab. The initial incremental cost-effectiveness ratio (ICER) for nivolumab was $409,000 per quality-adjusted life year (QALY). The initial ICER for pembrolizumab was $1,137,595/QALY. Comparison to adjusted standard of care arm resulted in ICERs of $484,000/QALY and $856,173/QALY, for nivolumab and pembrolizumab, respectively. Nivolumab appears to have a lower cost per QALY and may be more cost-effective than pembrolizumab. Neither drug would be considered a cost-effective treatment option at a threshold of $100,000/QALY for patients in this setting. Outcomes of improved long-term survival have yet to be reported as these agents are relatively new; incorporation of this future data would likely improve the cost-effectiveness of these drugs.

Keywords: Nivolumab, pembrolizumab, head and neck cancer, ICER, cost-effectiveness

Introduction

There are more than 650,000 new cases of head and neck cancer worldwide yearly [1]. Squamous cell carcinomas make up more than 90% of these cancers [2]. Even though multimodal approaches to therapy are used to treat locoregionally advanced squamous cell carcinoma, many of these patients experience recurrence of their disease or develop metastasis [3, 4]. For recurrent or metastatic disease, traditional systemic therapy was limited to platinum-based chemotherapy or targeted agents, such as cetuximab, alongside chemotherapy. In recent years, immunotherapy-based regimens have shown promise in in the treatment of head and neck squamous cell carcinoma (HNSCC), and as a result, have been incorporated into treatment algorithms for the disease [4]. In the setting of recurrent or metastatic HNSCC after failed initial therapy, two agents have emerged as the preferred choice for immunotherapy: the PD-1 inhibitors nivolumab (Bristol-Myers Squibb) and pembrolizumab (Merck). The role of nivolumab for recurrent or metastatic HNSCC after platinum-based chemotherapy was established by the CheckMate 141 study. In this study, nivolumab was compared against the standard of care (either single-agent methotrexate, docetaxel, or cetuximab), and nivolumab was demonstrated to increase both overall survival and progression-free survival [5]. Fewer patients experienced serious treat-

ment-related adverse events on nivolumab than on standard therapy [5].

Similar results were obtained with pembrolizumab for recurrent or metastatic HNSCC after platinum-based chemotherapy in the KEYNOTE-040 study. Pembrolizumab was compared against the same agents in the standard arm of CheckMate 141. Patients assigned to pembrolizumab had longer median overall survival along with decreased incidence of serious treatment-related adverse events compared to the standard of care [6].

It is clear that these anti-PD-1 immunotherapies are efficacious and confer survival benefit over traditional chemotherapy [5, 6]. However, the high cost of these newer agents may create a financial burden, both on an individual basis for patients and in a societal context [7]. The increasing cost of anticancer drugs in particular highlights the need to define the value and cost-effectiveness of these medications [8]. Cost-effectiveness analyses of nivolumab in recurrent or metastatic HNSCC have yielded mixed results about whether nivolumab is a cost-effective option in this setting [9, 10]. The cost-effectiveness of pembrolizumab has not been studied extensively but has been reported to be cost-effective at a threshold of $50,000/quality-adjusted life year (QALY) [11].

There is strong data supporting the use of these PD-1 inhibitors to improve overall survival in these patients, and somewhat limited data supporting their use from a cost-effectiveness perspective compared to standard systemic therapy. However, there is no clinical trial directly comparing the efficacy of these two agents and there is also no cost-effective analysis comparing nivolumab to pembrolizumab in these patients. In situations, where neither agent has a survival benefit or preferred adverse effect profile, cost may influence decision-making. This analysis aims to compare the cost-effectiveness of nivolumab and pembrolizumab in the setting of recurrent and metastatic HSNCC.

Methods

Clinical data

Published data from the CheckMate 141 and KEYNOTE-040 studies were used in modeling the nivolumab and pembrolizumab groups, respectively [5, 6]. In CheckMate 141, patients were randomly assigned in a 2:1 ratio of nivolumab to standard of care, with a total of 240 patients assigned to nivolumab and 121 to standard therapy. Patients assigned to nivolumab received treatment every two weeks at a dosage of 3 mg/kg. Patients assigned to standard therapy were given investigator's choice of single drug regimen, either docetaxel (30-40 mg/m^2 weekly), methotrexate (40-60 mg/m^2 weekly), or cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly). Relative distribution of patients on each standard therapy drug (47% on docetaxel, 41% on methotrexate, 12% cetuximab) was accounted for. Kaplan-Meier curves from CheckMate 141 were used to extrapolate survival rate of patients on nivolumab and standard of care. In KEYNOTE-040, patients were randomly assigned to pembrolizumab and standard of care in a 1:1 ratio (247 to pembrolizumab and 248 to standard of care). Pembrolizumab was given once every 3 weeks. The standard of care arm was structured similarly to that of CheckMate 141, with the only differences being the dosing of docetaxel (75 mg/m^2 once every 3 weeks) and the distribution of patients in the standard arm (44% docetaxel, 26% methotrexate, 29% cetuximab). The Kaplan-Meier curves from KEYNOTE-040 were used to extrapolate the survival rate of pembrolizumab and standard of care arms. Statistical significance was determined using chi square test.

Costs: The cost assigned to each therapy included in the analysis was obtained through the average wholesale price. The cost of therapy was calculated per cycle. For weight- and body surface area-dependent dosing, calculations assumed 70 kg body weight and 1.7 m^2 total body surface area. Prevalence of treatment-related adverse events were obtained from CheckMate 141 and KEYNOTE-040 and costs of the most frequent grade 3 and 4 toxicities (> 1%) in each study were obtained from literature and adjusted for inflation [12-18]. The costs of these serious adverse events were incorporated into the model. Costs of drugs and adverse events are listed in **Table 1**.

Outcomes and analysis: Survival data from CheckMate 141 and KEYNOTE-040 were used to derive benefit of treatment measured in

Table 1. Parameters for cost-effectiveness model

Parameter	Value ($)	Citation
Drug costs (per cycle)		
Nivolumab	6807	Average wholesale price [29]
Pembrolizumab	11496	Average wholesale price [30]
Methotrexate	9	Average wholesale price [31]
Cetuximab (cycle 1)	11704	Average wholesale price [32]
Cetuximab (after cycle 1)	9754	Average wholesale price [32]
Docetaxel (CM141 dosing)	568	Average wholesale price [33]
Docetaxel (KN-040 dosing)	473	Average wholesale price [33]
Drug Toxicity Costs (per event)		
Fatigue	1047	Niraula et al., 2014 [16]
Diarrhea	3635	Niraula et al., 2014 [16]
Asthenia	156	Hornberger et al., 2015 [14]
Anemia	3817	Smith et al., 2002 [17]
Mucosal inflammation	2973	Elting et al., 2007 [13]
Stomatitis	827	Niraula et al., 2014 [16]
Neutropenia	16144	Hornberger et al., 2015 [14]
Alopecia	1174	van den Hurk et al., 2013 [18]

Abbreviations: CM141 = CheckMate 141, KN-040 = KEYNOTE-040.

QALYs. For calculations in this analysis, all patients in the two studies were initially assigned the same health utility score, and their utility score would decrease to 0 upon discontinuation from the study, whether due to death or progression. The average QALY gained per patient and average cost per patient from a third-party payer perspective was calculated for both immunotherapy arms and both standard arms. The incremental cost-effectiveness ratio (ICER) was calculated for each immunotherapy arm against its respective standard comparator arm. The two standard arms from CheckMate 141 and KEYNOTE-040 were normalized to each other and new ICERs were calculated for nivolumab and pembrolizumab using the normalized standard arm.

Results

Base case

In our analysis of CheckMate 141, nivolumab increased effectiveness of treatment by 0.32 QALYs, from 0.56 QALYs to 0.88 QALYs. Average incurred cost per patient on the nivolumab arm was $143,300 compared to $14,300 in the standard arm. The ICER for nivolumab compared to standard of care was $409,000/QALY. KEYNOTE-040 analysis resulted in an increase of 0.11 QALYs (from 0.68 to 0.79 QALYs) on pembrolizumab compared to the standard arm. Average cost per patient was $159,300 for pembrolizumab and $38,000 for standard of care. The ICER for pembrolizumab compared to standard therapy was $1,137,595/QALY. A combined standard of care (S_C) arm was modeled from the standard of care arms in CheckMate 141 and KEYNOTE-040. The S_C arm yielded 0.63 QALYs and a cost of $25,881 per patient. The ICERs of nivolumab and pembrolizumab calculated using S_C were $484,184/QALY and $856,173/QALY respectively.

Discussion

This analysis estimated the cost-effectiveness of nivolumab and pembrolizumab compared against their respective standard of care arms in CheckMate 141 and KEYNOTE-040 and allowed for an indirect comparison of the two agents through a common combined standard. The average cost per patient and QALYs gained were similar in nivolumab and pembrolizumab; however, when compared to a common standard, nivolumab was almost twice as cost-effective. It is important to note, based on our analysis, that neither drug meets the commonly accepted cost-effectiveness threshold of $100,000/QALY [19]. One previous cost-effective analysis of nivolumab in this setting published an ICER of $294,000/QALY, which is also above the cost-effective threshold [10]. For pembrolizumab, there is recent data from Liu et al. supporting its use as a cost-effective agent with an ICER of $11,900/QALY for recurrent or metastatic HSNCC [11]. This discrepancy can be explained by the high QALY values attained by pembrolizumab in their analysis. The ICER of pembrolizumab in other malignancies such as non-small cell lung cancer and bladder cancer has been reported to be as high as $122,557-$184,000 [20, 21]. The results from our analysis are most likely an underestimate of the true cost-effectiveness of both nivolumab and pembrolizumab. QALYs were only calculated during the study duration of 24 months, so any additional QALYs accumulated after the end of the study were not included. There is a growing body of evidence that suggests improved long-

term outcomes of patients on anti-PD-1 and anti-PD-L1 immunotherapy in multiple cancer types, indicating that the cost-effectiveness of these agents would likely increase if analyzed over a longer specified timeframe [22]. In addition, the costs of end-of-life care (i.e. palliative care, hospice) was not included in the model. It would be reasonable to expect that these costs would disproportionally affect the standard of care arms over this 18-24 month period due to lower survival relative to the immunotherapy arms.

The difference in cost-effectiveness of nivolumab and pembrolizumab is also likely not as pronounced as the apparent difference in ICERs may suggest. Initial ICER of pembrolizumab obtained from our analysis of KEYNOTE-040 was higher than findings from literature as mentioned previously. This is due to the relatively small improvement in QALYs achieved by pembrolizumab compared to the standard of care from KEYNOTE-040. Our model heavily weighted survival benefit in calculating QALYs, which scales inversely with ICER. It is not surprising that pembrolizumab had a smaller improvement against the standard of care compared to nivolumab, as KEYNOTE-040 did not meet their primary endpoint of overall survival in the initial analysis [23]. As a result, a smaller demonstrated survival benefit in patients on pembrolizumab would heavily impact the final ICER calculation. The differences in demonstrated survival benefit in CheckMate 141 and KEYNOTE-040 is thought to be due to the differences in overall survival in the standard of care arms, rather than the superior efficacy of nivolumab or pembrolizumab [24]. The median overall survival of the standard of care arms in and CheckMate 141 and KEYNOTE-040 were 5.1 and 6.9 months, which set a higher biostatistical threshold to demonstrate a positive outcome in KEYNOTE-040.

The main limitation of our analysis stems from the underlying differences between CheckMate 141 and KEYNOTE-040. These differences contribute to the differences in overall survival of the standard of care arms as well as our analysis of the cost-effectiveness of their use. One key difference in patient selection between the two studies was that KEYNOTE-040 excluded patients who recurred or progressed within 3 months of previous platinum-based therapy, and only 1% of patients had received ≥ 3 prior lines of therapy, as opposed to 20% in CheckMate 141 [24]. As a result, the patient population of KEYNOTE-040 was likely healthier with less aggressive disease. Another difference between the two studies can be found in the distribution of patients in the standard of care arm, particularly those receiving methotrexate (41% in CheckMate 141 and 26% in KEYNOTE-040) and cetuximab (12% and 29%, respectively). The higher cost of cetuximab relative to the other two standard therapies and greater proportion of patients receiving cetuximab in KEYNOTE-040 increased the cost of standard of care in KEYNOTE-040. However, the survival data of each individual therapy in the standard arm was not reported, so differences in survival between the standard arms of CheckMate 141 and KEYNOTE-040 attributed to the investigator's choice of standard regimen had to be estimated based on previous data [25-27]. While docetaxel treatment regimen was different in the studies, it has been reported that weekly versus every-3-week dosing results in similar overall survival [28]. The impact of docetaxel dosing on our analysis is likely minimal. In summary, the accuracy of our analysis relies on several assumptions and hence we propose that this analysis should be used a s a starting point for further investigation using markov chain modeling rather than be used to draw conclusions regarding a comparison of cost effectiveness between nivolumab and pembrolizumab.

Conclusions

Neither nivolumab nor pembrolizumab are cost-effective at a threshold of $100,000/QALY when compared against the standard of care in CheckMate 141 and KEYNOTE-040, respectively. When analyzed using a standardized comparator derived from the control arms of each study, nivolumab appeared to be more cost-effective than pembrolizumab. As more data on the long-term outcomes of patients on immunotherapy are published and as future cost-effectiveness analyses included markov chain modeling, it can more realistically estimate the value gained by these immunotherapy agents.

Disclosure of conflict of interest

None.

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