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RESEARCH ARTICLE

Costs of Target Therapy and Proportionality to Number of Purchases: Propose Using Maintenance Dose and Limited Duration

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The 2-year costs of the immune check point inhibitors (ICI) were equitable with overall survival in advanced/metastatic non-small lung cancer. Target therapy (TT) is presently continued till disease progression or toxicity. The TT 2-3-year costs were justified in view of outcome and safety. Economically, what matters most is duration of use beyond 3-years. Li et al (2022)) identified the cost burden of prolonged TT administration. Guirgis (2023) suggested using caps to limit costs. The current cost policy of continued TT is untenable, and a fresh perspective is warranted.

Objectives: 1-Focus on the deleterious cost impact of prolonged TT. 2-Propose using maintenance doses at 50% of the current recommendations and 4-year-limit.

Methods: The ICI costs were calculated as dose in mg x price x number of cycles and TT as the monthly optimal dose x 12.

Results: The 2019 Pembrolizumab, ICI prototype, was at $134,796 cost in 2018-19, increasing to $190,400 in 2023. The median cost of 5-ICI was $163,640. The 3-month $47,700 cost, if therapy extended beyond 2-years, was unnecessary due lack of further survival. The annual Osimertinib cost, TT prototype, was $229,600, the median of 5-TT. Costs multiplied with each extended year.

We reasoned that if 3000 United States patients be treated by all TT at $229,600 for 5-years, the cost would mount to $344,000,000. If used for 4-years, the cost would drop to $2,755,200,000. Treating 9000 patients in the European nations for 5-years would cost $10,332,000,000 and 4-years $8,265,600,000. Using TT dose as maintenance at 50% of the current recommendations would further cut costs.

Conclusion: Costs of TT were proportional to number of purchases. The proposed TT maintenance dose and the 4-year-limit on duration of use in advanced lung cancer would drastically cut costs. Clinical studies are warranted to ensure the safety of our proposal.

Keywords: Costs, non-small lung cell cancer, Immune check point inhibitors, Osimertinib, Targeted Therapy.

Abbreviations

Advanced/metastatic non-small lung cancer (a/m-NSCLC)
Anaplastic lymphoma kinase (ALK)
Atezolizumab (Atezo), Cemiplimab (Cemi)
c-ros oncogene 1 (ROSE1)
Epidermal growth factor receptor (EGFR)
Immune check point inhibitors, (ICI)
Neurotrophic Tropomyosin receptor kinases (NTRK)
Target therapy (TT)
Pembrolizumab (Pembro).

Introduction

Pembrolizumab (Pempro) (1-3), the 1st immune check point inhibitors (ICI) introduced, resulted in a well-documented 2-year outcome and safety in advanced/metastatic lung cancer (a/m- NSCLC). Other ICI soon followed at competitive value and cost-effectiveness. The 2-year costs of Pembro, Atezolizumab (Atezo) (4) and Cemiplimab (Cemi) (5) were equitable with overall survival in a/m-NSCLC. The 3-year target therapy (TT) costs were justifiable in view of outcome and safety (Guirgis, ESMED 2022) (6). Survival stabilized without significant changes after 4-5-years. The current TT practice recommends continued therapy till recurrence or toxicity. Li et al (2022) (7) identified the cost burden of prolonged TT administration. Guirgis (2023) (8) suggested using caps to limit costs. There have been, so far, no checks or balances to curb the mounting costs of TT unconstrained usage.

Our objectives: 1-Demonstrate the cost burden of TT prolonged duration. 2-Challenge the current status quo practice by proposing maintenance dosage at 50% of the recurrent recommendations and limit TT usage to 4-years.

Methods: The ICI costs were calculated as dose in mg x price x number of cycles and TT as the monthly optimal dose x 12.

Results

The 2018-19 Pembrolizumab cost was $134,796 increasing to $190,400 in 2023. The median cost of 5-ICI was $163,640 and shown in Table 1:

Table 1: Estimated US 2023 Drug Costs

Drugs	Annual Price
Pembro	$190,400
Durvalumab	$163,640
Atezo	$152,670
Nivolumab	$202,330
Cemi	$147,520
Average ICI	$171,313
Median	$163,640

The 3-month $47,700, cost of extended therapy beyond 2-years, was considered wasteful due lack of further survival.

The TT class of drugs interfere with tumor cell proliferation and survival. They are rather costly but considered fair in view of efficacy, safety, and limited number of eligible patients. Osimertinib (9,10), the most widely used TT, is currently prescribed as neo-adjuvant, adjuvant, in advanced, metastatic, and recurrent lung cancer at annual $229,580 cost. It targets the epidermal growth factor receptor (EGFR) with an incidence of about 15%.

Crizotinib was the 1st synthesized tyrosine kinase inhibitor of the anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1). Alectinib, another ALK inhibitor, has essentially replaced Crizotinib, at cheaper costs. Entrectinib cost, an inhibitor of ros1, ALK and the chimeric tropomyosin receptor kinases (TRK) fusion, was $210,528.

Larotrectinib inhibits the TRK fusion at an incidence of <1%. In 2019-20, the wholesale yearly acquisition cost (WAC) was $399,370. The annual price was lowered to $173.900 in 2023.
The 4- and 5-year TT costs (Table 2) clearly demonstrate the huge costs of prolonged therapy, doubling at 8 and 10 years.

Table 2: Estimated Costs of Target Therapy in the US

Drugs doses in mg	Annual Costs	4-year costs	5- year costs
Osimertinib 80 daily	$229,5	$818,320	$1,147,900
Alectinib 600 bid	$221,110	$884,440	$1,105,550
Crizotinib 250 bid	$226,300	$905,200	$1,131,500
Entrectinib 600 bid	$210,530	$842,120	$1,052,650
Larotrectinib 100 bid	$399,370	$1,597,480	$1,996,850
Average	$257,380	$818,320	$1,131,500
Median	$229,580	$848,440	$1,105,550

We reasoned that if 3000 patients in the United States were treated by all approved TT at $229,600 for 5-years, the cost would mount to $344,000,000 vs 4-years of $2,755,200,000. Treating 9000 patients in Europe for 5-years would cost $10,332,000,000 and 4-years $8,265,600,000. The annual cost per patient was $918,400.

Maintenance doses at 50% of the current recommendations would further cut expenses by half.

Discussion

The present work was initiated after complaints of a 65 yo Caucasian female patient of the high costs of Alectinib (Alect) (Guirgis,11). She initially presented in 2014 with NSCLC, ALK +, metastatic to brain, liver, and bones. She was started on Alect 600 mg po bid. Repeat CT scans at 3-6 months revealed significant and progressive improvements in liver and brain lesions. After lengthy discussion between patient, husband, and oncologists, it was decided to continue Alect. Adequately ensured, the patient still pays a significant out of pocket coverage. The estimated current monthly cost is $18,426 and one year $221,110. The patient is still on Alect for the last 9 years at $1,989,990 costs.

Previous attempts to control drug costs have met with minimal success including application of caps (12,13).

After the 1st introduction of ICI and TT, similar drugs followed at competitive efficacy, safety, value, and cost-effectiveness (14-16). The TT costs have not yet been thoroughly scrutinized as compared with the mounting detailed information on outcome and safety. Most of TT costs were quoted from the 2019-20 monthly wholesale acquisition cost (WAC).

NEW YORK, Dec 30 (Reuters) reported that most of the pharmaceutical companies plan to raise prices in the US on more than 350 unique drugs in early January, according to data analyzed by healthcare research firm 3 Axis Advisors.

It is generally acknowledged that comprehensive molecular profiling of NSCLC tumors is vital for proper treatment by TT drugs. Crizotinib was the 1st synthesized tyrosine kinase inhibitor of ALK and ROS1. The ALK alterations vary widely by geographic location and smoking habits. The incidence of ALK is higher in Los Angeles CA, with a higher incidence of smoking than Orange County with only 60 miles difference in distance. Alectinib, another ALK inhibitor, crosses the brain barrier at cheaper cost than Crizotinib.

Enrectinib is a multi-kinase inhibitor of ros I, ALK and TRK. Presently there have been more specific inhibitors for each alteration. The 2023 Larotrectinib $173,850 cost is justifiable in view of efficacy, CNS penetration, limited number of eligible patients, and rarity of alternatives.

The KRAS mutations occur in 25% of lung cancer and 12% in G12c. Sotorasib and Adagrasib block the KRS signaling. However, these drugs do not belong to the TT family.

Presently, in the drug synthesis arena, artificial intelligence (AI) and 3-D photography have replaced the inhumane and expensive use of mice, rats, and monkeys. The AI could make drug development simpler, faster, more direct, and probably cheaper. So far, we have not seen the fruits of such developments.

Most of the TT drugs analyzed were synthesized and used in the US at high costs. These drugs are also widely prescribed in Canada, The European nations, and the United Kingdom. But sadly, TT are unaffordable to low-income patients and countries. The cost calculus of anti-cancer drugs put a limit on TT prolonged use. The cost doctrine of proportionality with number of purchases would encompass the entire spectrum of commodities from drugs to milk and bread.

The 3rd generation TT Lorlatinib was recently reported in phase II study to be effective in central nervous system (CNS) relapse at annual $339,936

cost. The drug demonstrated higher blood-brain barrier penetration in ALK-rearrangement than the 2nd-generation Alect and Brigatinib and over the 1st-generation Crizotinib in NSCLC (17)

In conclusion, in a time of shrinking national and international economies, it is wise stewardship to avoid the financial toxicity (18) of cancer care in general and the high costs of cancer drug therapy with prolonged TT in particular. After 4-years limit on administration and using maintenance dosage at 50% of the current recommendations, costs would dramatically decrease. In case of recurrence, treatment with any of the newly developed anticancer classes e.g. antibody drug conjugate (ADC) would be considered. Clinical studies are needed to ensure the safety of maintenance dosage and test 4 - vs 5-year TT use.

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