THE PEMETREXED´S LESSON

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BACKGROUND

In May 2008, the European Medicines Agency (EMA) granted authorization to Pemetrexed as a first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC), other than predominantly squamous cell (non-SC) histology patients. A phase III trial compared Pemetrexed with Gemcitabine, both in association with cisplatin, and found a similar overall survival between both groups (10.3 months). The EMA authorization was based in a subgroup analysis of this phase III trial. In late 2008, the first Gemcitabine generic drug was commercialized.

PURPOSE

Our aim was to highlight the limited evidence considered on pemetrexed's approval and the impact on it´s use.

MATERIAL AND METHODS

The literature was reviewed and a retrospective analysis of the first-line treatment options in non-SC NSCLC in our hospital was made, between July 2013 and June/2017.

http://www.eahp.eu/24-1ISG-007

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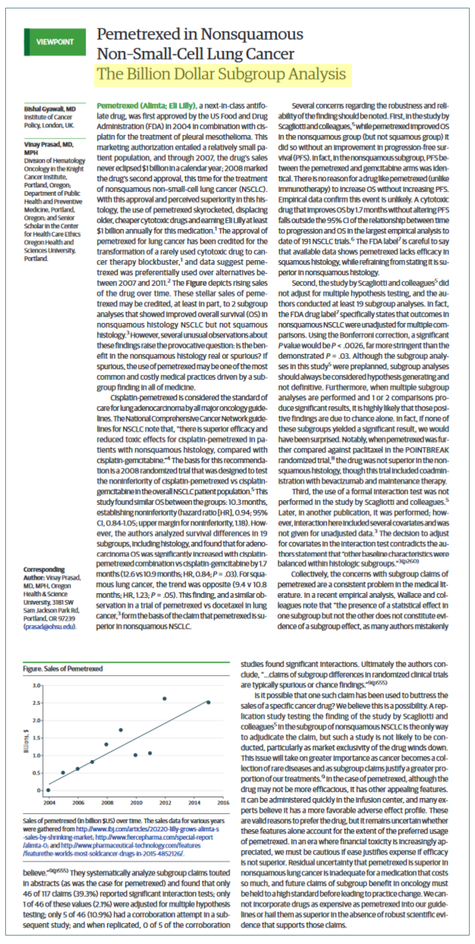
RESULTS

An opinion article was published in January 2018 in JAMA Oncology.[1] It discussed if an approval based in a subgroup analysis of a clinical trial, predefined but never tested in a phase III trial design for its validation, was strong enough to influence clinical practice.

It is well known that any data retrieved from a clinical trial subgroup analysis is indicative and non-conclusive. It is uncertain when a subgroup analysis should influence clinical practice.



VIEWPOINT

Pemetrexed in Nonsquamous Non-Small-Cell Lung Cancer
The Billion Dollar Subgroup Analysis

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Pemetrexed (Alimta; Eli Lilly), a next-in-class antifolate drug, was first approved by the US Food and Drug Administration (FDA) in 2004 in combination with cisplatin for the treatment of pleural mesothelioma. This marketing authorization entailed a relatively small patient population, and through 2007, the drug's sales never eclipsed $1 billion in a calendar year; 2008 marked the drug's second approval, this time for the treatment of nonsquamous non-small-cell lung cancer (NSCLC). With this approval and perceived superiority in this histology, the use of pemetrexed skyrocketed, displacing older, cheaper cytotoxic drugs and earning Eli Lilly at least $1 billion annually for this medication.[1] The approval of pemetrexed for lung cancer has been credited for the transformation of a rarely used cytotoxic drug to cancer therapy blockbuster,[1] and data suggest pemetrexed was preferentially used over alternatives between 2007 and 2011.[2] The Figure depicts rising sales of the drug over time. These stellar sales of pemetrexed may be credited, at least in part, to 2 subgroup analyses that showed improved overall survival (OS) in nonsquamous histology NSCLC but not squamous histology.[3] However, several unusual observations about these findings raise the provocative question: is the benefit in the nonsquamous histology real or spurious? If spurious, the use of pemetrexed may be one of the most common and costly medical practices driven by a subgroup finding in all of medicine.

Cisplatin-pemetrexed is considered the standard of care for lung adenocarcinoma by all major oncology guidelines. The National Comprehensive Cancer Network guidelines for NSCLC note that, "there is superior efficacy and reduced toxic effects for cisplatin-pemetrexed in patients with nonsquamous histology, compared with cisplatin-gemcitabine."[4] The basis for this recommendation is a 2008 randomized trial that was designed to test the noninferiority of cisplatin-pemetrexed vs cisplatin-gemcitabine in the overall NSCLC patient population.[5] This study found similar OS between the groups: 10.3 months, establishing noninferiority (hazard ratio [HR], 0.94; 95% CI, 0.84-1.05; upper margin for noninferiority, 1.18). However, the authors analyzed survival differences in 19 subgroups, including histology, and found that for adenocarcinoma OS was significantly increased with cisplatin-pemetrexed combination vs cisplatin-gemcitabine by 1.7 months (12.6 vs 10.9 months; HR, 0.84; $P = .03$). For squamous lung cancer, the trend was opposite (9.4 v 10.8 months; HR, 1.23; $P = .05$). This finding, and a similar observation in a trial of pemetrexed vs docetaxel in lung cancer,[6] form the basis of the claim that pemetrexed is superior in nonsquamous NSCLC.

Several concerns regarding the robustness and reliability of the finding should be noted. First, in the study by Scagliotti and colleagues,[5] while pemetrexed improved OS in the nonsquamous group (but not squamous group) it did so without an improvement in progression-free survival (PFS). In fact, in the nonsquamous subgroup, PFS between the pemetrexed and gemcitabine arms was identical. There is no reason for a drug like pemetrexed (unlike immunotherapy) to increase OS without increasing PFS. Empirical data confirm this event is unlikely. A cytotoxic drug that improves OS by 1.7 months without altering PFS falls outside the 95% CI of the relationship between time to progression and OS in the largest empirical analysis to date of 991 NSCLC trials.[7] The FDA label[8] is careful to say that available data shows pemetrexed lacks efficacy in squamous histology, while refraining from stating it is superior in nonsquamous histology.

Second, the study by Scagliotti and colleagues[5] did not adjust for multiple hypothesis testing, and the authors conducted at least 19 subgroup analyses. In fact, the FDA drug label[8] specifically states that outcomes in nonsquamous NSCLC were unadjusted for multiple comparisons. Using the Bonferroni correction, a significant P value would be $P < .0026$, far more stringent than the demonstrated $P = .03$. Although the subgroup analyses in this study[5] were preplanned, subgroup analyses should always be considered hypothesis generating and not definitive. Furthermore, when multiple subgroup analyses are performed and 1 or 2 comparisons produce significant results, it is highly likely that those positive findings are due to chance alone. In fact, if none of these subgroups yielded a significant result, we would have been surprised. Notably, when pemetrexed was further compared against paclitaxel in the POINTBREAK randomized trial,[9] the drug was not superior in the nonsquamous histology, though this trial included coadministration with bevacizumab and maintenance therapy.

Third, the use of a formal interaction test was not performed in the study by Scagliotti and colleagues.[5] Later, in another publication, it was performed; however, interaction here included several covariates and was not given for unadjusted data.[3] The decision to adjust for covariates in the interaction test contradicts the authors statement that "other baseline characteristics were balanced within histologic subgroups."[5(p2539)]

Collectively, the concerns with subgroup claims of pemetrexed are a consistent problem in the medical literature. In a recent empirical analysis, Wallace and colleagues note that "the presence of a statistical effect in one subgroup but not the other does not constitute evidence of a subgroup effect, as many authors mistakenly

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Figure. Sales of Pemetrexed

Sales of pemetrexed (in billion $US) over time. The sales data for various years were gathered from http://www.fiercepharma.com/special-report/alimta-q, and http://www.pharmaceutical-technology.com/features/featurethe-worlds-most-soldcancer-drugs-in-2015-4852126/.

believe,"[10(p1422)] they systematically analyze subgroup claims touted in abstracts (as was the case for pemetrexed) and found that only 46 of 117 claims (39.3%) reported significant interaction tests; only 1 of 46 of these values (2.1%) were adjusted for multiple hypothesis testing; only 5 of 46 (10.9%) had a corroboration attempt in a subsequent study; and when replicated, 0 of 5 of the corroboration studies found significant interactions. Ultimately the authors conclude, "...claims of subgroup differences in randomized clinical trials are typically spurious or chance findings."[10(p1422)]

Is it possible that one such claim has been used to buttress the sales of a specific cancer drug? We believe this is a possibility. A replication study testing the finding of the study by Scagliotti and colleagues[5] in the subgroup of nonsquamous NSCLC is the only way to adjudicate the claim, but such a study is not likely to be conducted, particularly as market exclusivity of the drug winds down. This issue will take on greater importance as cancer becomes a collection of rare diseases and as subgroup claims justify a greater proportion of our treatments.[11] In the case of pemetrexed, although the drug may not be more efficacious, it has other appealing features. It can be administered quickly in the infusion center, and many experts believe it has a more favorable adverse effect profile. These are valid reasons to prefer the drug, but it remains uncertain whether these features alone account for the extent of the preferred usage of pemetrexed. In an era where financial toxicity is increasingly appreciated, we must be cautious if ease justifies expense if efficacy is not superior. Residual uncertainty that pemetrexed is superior in nonsquamous lung cancer is inadequate for a medication that costs so much, and future claims of subgroup benefit in oncology must be held to a high standard before leading to practice change. We cannot incorporate drugs as expensive as pemetrexed into our guidelines or hail them as superior in the absence of robust scientific evidence that supports those claims.

(1) JAMA Oncol. 2018;4(1):17–18

Almost at the same time Gemcitabine generic drug was arriving the market, all the non-SC NSCLC treatment guidelines replace Gemcitabine for Pemetrexed as a first option, with evidence level II, using efficacy and not safety as a reason, which could be an argument.
In Portugal, Pemetrexed was considered cost-effective compared with Gemcitbine, based on the same limited efficacy data, and considering the cost of the original gemcitabine drug, instead of the generic drug.

In our hospital, in the 4 years analysed, 71 non-small cell lung cancer, patients, with non-squamous cell histology, were treated with Pemetrexed, whereas 22 were treated with Gemcitabine, both associated with platin. The cost difference per patient (six cycles considered) was 10.554€ , with a direct budget impact of 749.334€ for the 71 patients.

CONCLUSION

Pemetrexed was preferred to Gemcitabine as a first-line treatment of non-SC NSCLC, beside its limited evidence quality. A change in clinical practice should require better evidence levels. In our hospital, this change in clinical practice had a relevant economic impact.

REFERENCES

1. JAMA Oncol 2018;4:17–8. doi:10.1001/jamaoncol.2017.1944
2. J Clin Oncol 26:3543–51. doi:10.1200/JCO.2007.15.0375