Lung Cancer 138 (2019) 139–140

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Optimization of response classification criteria for patients with malignant pleural mesothelioma, a validation study

Dear editor,

Image-based response assessment is often used as a surrogate for the efficacy of a treatment in patients. The radiological response assessment in patients with malignant pleural mesothelioma (MPM) is notoriously difficult, despite changes in the scoring system, modified Response Evaluation Criteria in Solid Tumors (modified RECIST). The current clinical method for tumor response assessment in mesothelioma is the modified RECIST guideline, which calls for two linear measurements of tumor thickness to be summed from each of three axial sections, primarily in computed tomography (CT) scans. To classify patients into response categories, progressive disease (PD) is defined as a summed measurement increase larger than 20%; partial response (PR) is a summed measurement decrease of 30% or more, and stable disease (SD) is any measurement change between -30% and +20% [1–3]. These changes occur between the scan at baseline or at best response.

Since the measurements are notoriously difficult to interpret and not always correlate with survival, an attempt was made by Labby et al to improve this [4]. He studied 78 patients with MPM and compared the change in tumor thickness measurements across serial CT scans with survival. These optimal response categories were identified by checking all of the possible classification threshold combinations and maximizing the resultant concordance (C) value. The cutoff between PR and SD was tested at each 1% increment between -100% and 0% change in modified RECIST summed tumor thickness measurement. Simultaneously, the cutoff between SD and PD was tested at each 1% increment between 0% and 100% change in summed tumor thickness measurement. The cutoff pair that yielded the highest value of C was determined to be the optimum criteria. Changing the different response category thresholds to -64% (PR) and +50% (PD) and applying them to best response or first follow up scan resulted in an improved correlation with patient survival. These numbers were assumed to be better suited to the specific morphology and growth pattern of mesothelioma [4]. Here we refer to this approach as the Optimized modified RECIST.

To evaluate this recommendation, we conducted a retrospective study in an independent mesothelioma patient cohort using these cutoffs. With the approval of the institutional review boards of the Netherlands Cancer Institute and The University of Chicago, imaging and clinical data from 65 patients from a prospective open-label randomized phase 3 trial involving maintenance therapy with thalidomide versus active supportive care in MPM patients after first-line chemotherapy (NVALT 5 study) were analyzed [5].

While the standard modified RECIST criteria (PR -30% and PD + 20%) yielded in this cohort a C statistic of 0.776 with a standard error of 0.057, the Optimized RECIST criteria (PR -64% and PD + 50%) yielded a C statistic of 0.737, which was lower than the initially reported C statistics of 0.855.

Out of curiosity, we optimized the NVALT data, the C statistic for the best linear response and this improved to 0.833 with a standard error of 0.062, when a setting of -41% (PR) and 100% (for PD) was used.

To assess the clinical utility of these results, the median survival times were evaluated based on the response categories associated with the different methodologies. Unfortunately, the low number of patients with a partial response precluded us to make a solid statement about this, but the outcome of OS in the three categories seemed to be all in the same range (Table 1).

The differences in outcome of the two mesothelioma studies may be due to the different focus of these trials. The Labby trial evaluated patients treated with chemotherapy in which the PR group seems to be the best represented. The NVALT trial was a randomized maintenance study after first line chemotherapy and patients were not expect to have a PR on the study drug/active supportive care. Therefore, many patients eventually had progressive disease and there were only a few responders. This study had a higher proportion of long survivors, due to the selection criteria. A larger, well balanced cohort to create new RECIST criteria may result in improvements, giving better tools for how long patients may be treated with the same regimen, to optimize their survival.

We need to keep searching for better and simpler ways to evaluate the response in patients with malignant mesothelioma. Although the modified and Optimized RECIST model seemed promising, it did not lead to a superior system yet. Using a larger data base, for example by using larger data sets from recent multi-center mesothelioma trials, might help us to improve the response analysis.

Table 1
Response rate, overall survival and C statistic of 3 RECIST models.

Best response model	PR	SD	PD	C statistic
Standard RECIST OS −30% +20%	21,5m	25,4m	13,8m	0.776
Labby Optimized RECIST OS −64% +50%	–	21,9m	14,8m	0.737
Optimized RECIST OS −41% +100%	21,5m	20,5m	12,9m	0.833

https://doi.org/10.1016/j.lungcan.2019.10.027
Received 16 September 2019

Funding

None.

Declaration of Competing Interest

W.A Buikhuisen: declarations of interest: none.

F. Qayyum : declarations of interest: none.

S.G. Armato receives personal fees from Aduro Biotech, Inc., for unrelated work.

P. Baas received grands from BMS and MSD for unrelated work and is related to MSD, BMS, Astra Zeneca, Boeringer Ingelheim, Tarovax and Verastem for advisorships.

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