Journal of Clinical and Translational Research 2022; 8(5): 403-413

Journal of Clinical and Translational Research

Journal homepage: http://www.jctres.com/en/home

REVIEW ARTICLE

High tumor burden in non-small-cell lung cancer: A review of the literature

Luis Cabezón-Gutiérrez[1]*, María Sereno[2], Raquel Cervera-Calero[3], Xabier Mielgo-Rubio[4], Oliver Higuera[5]

[1]Medical Oncology, Hospital Universitario de Torrejón. Universidad Francisco Vitoria. Madrid, Spain, [2]Medical Oncology, Sofía University Hospital; European University of Madrid. Madrid, Spain, [3]Medical Oncology. Hospital Universitario del Henares. Madrid. Spain, [4]Medical Oncology. Hospital Universitario Fundación de Alcorcón. Alcorcón. Spain, [5]Medical Oncology, Hospital Universitario La Paz. Madrid, Spain

ARTICLE INFO

Article history:
Received: May 2, 2022
Revised: July 17, 2022
Accepted: July 27, 2022
Published online: September 13, 2022

Keywords:
non-small-cell lung cancer
tumor burden
aggressive disease

**Corresponding author:*
Luis Cabezón-Gutiérrez,
Medical Oncology, Hospital Universitario de Torrejón, C/Mateo Inurria Nº1, CP 28850, Torrejón de Ardoz (Madrid), España
E-mail: lcabezon@torrejonsalud.com

ABSTRACT

Background and Aim: Lung cancer is the leading cause of cancer death worldwide and the majority of the patients have advanced/metastatic disease on presentation. In clinical practice, several biomarkers and clinical factors are taken into account when choosing the best treatment option in advanced non-small-cell lung cancer (NSCLC). One potential marker may be tumor burden (TB). However, this concept is not specifically defined in NSCLC, and usually, it is used as a synonymous for aggressive disease.
Methods: A non-systematic literature review was conducted. We searched for eligible randomized controlled trials from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials with a cutoff at February 2021. The keywords included non-small-cell lung cancer, tumor burden, aggressive disease, prognosis biomarker, predictive biomarker, and immunotherapy.
Results and Conclusions: This review addresses the definition of TB in advanced NSCLC, the pathophysiology of high TB lesions, and the role of TB as a prognosis biomarker.
Relevance for Patients: The concept of aggressive disease, as high tumor burden definition, remains poorly defined and rarely considered in clinical research or clinical practice in oncology. The identification of this subgroup of patients could be interesting for defining and optimizing a more aggressive treatment strategy.

1. Introduction

Lung cancer (LC) is the leading cause of cancer death worldwide. In 2020, a total of 19 million cancer patients were diagnosed, of which 11.4% was LC, causing 18% of all cancer deaths [1]. According to the latest information from the National Institute of Statistics provided in December 2019, corresponding to 2018, cancer was the second cause of death in Spain (26.4% of deaths), with LC being the main cause death from cancer, with some 22,133 deaths from this cause in 2018 [2].

Non-small-cell lung cancer (NSCLC) is the most common LC subtype and the majority of the patients have advanced/metastatic disease on presentation [3]. Platinum-based chemotherapy (CT) has historically been the standard treatment for these patients, although responses to these agents are generally modest, with relatively short intervals until disease progression[4]. Recently, immunotherapy (IT), especially the immune checkpoint inhibitors (ICI), has emerged as an exciting alternative treatment for patients without actionable driver mutations and it has dramatically improved the prognosis of advanced NSCLC in some patients [5-9].

Various predictive biomarkers for the response to ICIs have been previously reported, such as tumor mutation burden (TMB), mismatch repair and DNA replication genes, tumor

DOI: http://dx.doi.org/10.18053/jctres.08.202205.008

microenvironment, immune gene signature, interferon-γ-related mRNA-based signatures, peripheral blood biomarkers, myeloid-derived suppressor cells, and lactate dehydrogenase (LDH) level [10]. However, in the real-world clinical setting, biomarkers available before starting treatment are limited. One such potential marker is tumor burden (TB) [11].

Therefore, because the relationship between the NSCLC, TB, and response to treatment remains unclear, the present article addresses TB in the context of NSCLC.

2. Methods

A non-systematic literature review was done. We searched for eligible randomized controlled trials (RCTs) from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials until February 2021. The keywords included non-small-cell lung cancer, tumor burden, and aggressive disease. Selection criteria were randomized, double-blind, placebo-controlled, prospective, and retrospective studies using non-small-cell lung cancer and tumor burden or aggressive disease in the title of the manuscripts. A total of 245 studies were retrieved.

We found additional studies from major conference proceedings of the American Society of Clinical Oncology, the European Society of Medical Oncology, the American Association for Cancer Research, and the World Conference on Lung Cancer (WCLC). The priority in the selection of the articles were RCTs, reviews, and meta-analyses, although, due to the paucity of RCTs that provide robust data on high tumor burden (HTB), some retrospective studies and case series were included with a small number of patients but with interesting and previously unpublished data.

3. HTB in NSCLC: Is It Possible to Define?

The concept of TB is globally defined as the number of cancer cells, the size of a tumor, or the amount of cancer in the body [12]. However, this concept in NSCLC is not specifically defined, despite the fact that HTB is a concept commonly used in real clinical practice as a poor prognostic factor.

It could be argued that HTB encompasses different aspects in itself. In the first place, HTB could substitute concepts such as TMB, grow tumor volume (GTV), and metabolic tumor burden; and in the second place, clinical characteristics related to the disease such as number of lesions, baseline sum of target lesions, metastasis location, or serum parameters that will be further discussed in this paper (Figure 1).

In general, the definition of TB most commonly used in different studies is the sum of the longest dimensions of measurable baseline target lesions [11]. In this study, Sakata *et al.* postulated that the TB measured in this way constitutes a prognostic factor for NSCLC patients receiving ICIs treatment and was associated with overall survival (OS). In another study, the same authors defined TB as the sum of the longest diameters for a maximum of five target lesions and up to two lesions per organ [13].

At present, the irruption of IT has transformed clinical oncology landscape in recent years, and the concept of TMB has taken on great importance. TMB is defined as the number of mutations per

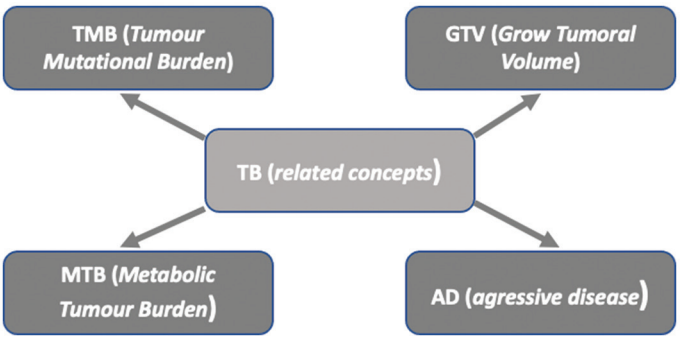

Figure 1. Different tumor burden-related concepts.

DNA megabases [14]. TMB has been described as a prognostic factor and as a predictive biomarker for ICIs efficacy in NSCLC. Hellman *et al.* examined progression-free survival (PFS) with nivolumab plus ipilimumab versus chemotherapy among patients with a high TMB (≥10 mutations per megabase). PFS was significantly longer with first-line nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high TMB, irrespective of PD-L1 expression level [15]. Rizvi *et al.* showed an association between high TMB and durable clinical benefit from ICIs in a population of advanced NSCLC patients [16]. This could be explained by the creation of neoantigens induced by mutations acquisition, increasing tumor immunogenicity, and response to ICIs. For this reason, TMB has been studied as a predictive biomarker of ICIs efficacy [17].

Another concept related to TB is the GTV, or macroscopic volume, used in the planning of radiotherapy treatment, and defined as the sum of the macroscopic volumes of the primary tumor and the lymph nodes involved as determined by imaging, usually CT (computed tomography). In a meta-analysis, Yang et al. suggested that GTV strongly influences prognosis of NSCLC after 3D-CRT and GTV may have a prognostic and predictive value of OS in patients with NSCLC [18].

Since the use of positron emission tomography (PET) is the gold standard in the staging of lung cancer, the concept of metabolic tumor burden has become increasingly important. It is defined us total body tumor burden reflected by the volume of tumor tissue demonstrating increased FDG uptake on PET or metabolic tumor volume (MTV). Percy *et al.* evaluated the prognostic value of tumor burden measured by 18F-fluorodeoxyglucose (FDG)-PET images. In this study, HTB assessed by PET, MTV is an independent poor prognostic feature in LC, independent of other established prognostics factors, namely, stage, treatment intent, age, weight loss, and performance status [19].

Finally, we highlight the similarity that may exist in real-world clinical practice between the concept of HTB and aggressive disease. Differences between both concepts (HTB vs. aggressive disease) will be discussed in the next paragraph.

4. Aggressive Disease in NSCLC: What Does it Mean?

The concept of aggressive disease, as a TB definition, remains poorly defined and rarely considered in clinical research or clinical

DOI: http://dx.doi.org/10.18053/jctres.08.202205.008

practice in oncology. In cancer, the term aggressive is broadly used to describe tumors that develop, progress, or metastasize faster [12]. Therefore, aggressive disease behavior is expected to result in poor clinical outcomes, such as lack of response or disease control and a shorter duration of time to PFS or OS. At present, there is no consensus on the definition of aggressive disease. Winfree *et al.* conducted a systematic literature review to explore the definitions of aggressive disease. They identify 14 RCTs reporting the efficacy of select second-line treatments in patients with advanced NSCLC possessing attributes associated with aggressive disease. They conclude that definitions of aggressive disease vary and that a more standard definition is necessary to allow us to make indirect treatment comparisons in this subgroup of LC [20].

In general, when we refer to advanced NSCLC with characteristics associated with aggressive disease, these characteristics include the following: Refractory and/or progressive disease following prior treatment; rapid progression; previous treatment was short; HTB or size; short time between the first- and second-line treatments; and high symptom burden.

Aggressive disease is not synonymous with HTB. When we refer to advanced NSCLC with characteristics associated with aggressive disease, these characteristics include different concepts related to the time to progression to a first line of treatment and the type of response to this treatment. In the different clinical trials, investigators have utilized operational definition of aggressive NSCLC to capture early progression on or after platinum-based chemotherapy. Two time-based measures have been implemented: time since start of first-line therapy (TSFLT) and time since end of first-line therapy (TELFT) [21]. In NSCLC, TSFLT cutoff points of <3 months, ≤5 months, and <9 months have been explored in clinical datasets [22], with TSFLT with <9 months as the most commonly used cutoff point in prognosis and predictive analyses [23]. For TEFLT, a cutoff of <3 and ≤6 months has been evaluated. Curiously, cutoffs of <3 months correspond to the definition of platinum resistance used in small-cell lung cancer (SCLC) [24]. Aggressive disease has also been defined by lack of disease control during initial treatment, as indicated by progression of disease (PD) as best response to first-line therapy (PD-FLT). PD-FLT is a more restrictive concept because it excludes patients who attain even short-lived responses. Refractory disease is another concept related to aggressive disease and has been used variously to refer to PD-FLT; TSFLT ≤ 5 months and TEFLT ≤ 6 months.

Clinically, the concept of "aggressive disease" may be useful for identifying a subset of patients with unfavorable clinical course of disease (prognostic relevance) and/or those patients that may derive particular benefit from specific therapeutic approaches (predictive relevance) [25].

Both RCTs and observational studies indicate that aggressive disease during first-line therapy has a negative prognostic impact on outcomes in subsequent treatment lines. Weiss *et al.* analyzed the impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced NSCLC [26]. They showed that patients with prior PD-FLT had significantly shorter median OS (4.6 months) than patients with prior stable disease (10.5 months) or partial response (15.8 months) in univariate and multivariate analyses: 4.6, 10.5, and 15.8 months, respectively (both $P < 0.001$). Median OS was also shorter in patients with a TEFLT of ≤ 3 months (6.9 months) than in patients with a TEFLT of 3–6 months (9.2 months) or a TEFLT of ≥ 6 months: 6.9, 9.2, and 9.3 months, respectively (univariate analysis, p = 0.001), although this was not significant after adjustment ($P = 0.183$). A retrospective German study demonstrated a significant negative prognostic impact on OS of both PD-FLT and a TSFLT of <9 months [27]. Another finding related to the concept of aggressive disease, probably the most clinically relevant, is its role as a predictive potential surrogate for second-line therapies. The predictive relevance of aggressive disease was first highlighted in a systematic evaluation of LUME-Lung 2, which identified a TSLFT of <9 months as a potential positive predictive marker for nintedanib in combination with second-line chemotherapy. A TSFLT of <9 months was subsequently confirmed to predict the treatment effect of second-line nintedanib plus docetaxel versus placebo plus docetaxel in a pre-specified analysis of OS in patients with adenocarcinoma histology in LUME-Lung 1. Exploratory analyses also showed a more marked OS benefit of nintedanib in other aggressive disease subgroups, including patients with PD-FLT. Exploratory analyses indicate this positive predictive relevance may similarly apply for other anti-angiogenic therapies such as ramucirumab and bevacizumab. These data suggest that neoangiogenesis plays a more important role in more rapidly progressing or aggressive lung cancers [22].

5. Physiopathology of Tumors with ACT

Along the next lines, we will try to decipher the possible pathophysiological basis underlying NSCLC cases with HTB. Ki-67 protein is a cell proliferation marker that is directly associated with cell proliferation and is used to determine the growth fraction of a given cell population [28], which usually correlates with the clinical course of cancer, with a prognostic value for survival in different tumor subtypes (a higher Ki-67 expression index is associated with worse prognosis) [29].

In NSCLC, Ki-67 expression has been associated with tumor size, lymph node stage, and shortened OS in patients with adenocarcinoma [30]. In a retrospective study with 112 patients, the relationship between Ki-67 expression and response to chemotherapy and PFS in patients with advanced NSCLC was analyzed, finding a linear correlation between Ki-67 expression levels and tumor stage ($r = 0.341$, $P = 0.001$) and a negative association with objective response rate (ORR) and PFS [31]. In a meta-analysis of 108 studies and 14,732 patients with NSCLC, a positive correlation was found between Ki-67 expression and worse differentiation, larger tumors, and more advanced pathological stages, in addition to a higher probability of metastatic lymph node involvement and more advanced TNM tumor stages [32].

Therefore, a characteristic associated with HTB could be a rapid tumor growth, which can lead to a hostile tumor

DOI: http://dx.doi.org/10.18053/jctres.08.202205.008

microenvironment encompassing prevalent hypoxia. Hypoxia has been associated with aggressive behavior of tumors and, although it could limit tumor growth due to a decreased supply of nutrients, hypoxia can also favor cellular adaptation mechanisms that facilitate tumor progression, such as an upregulation of angiogenic factors (vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF], and fibroblast growth factor [FGF]) that facilitate the formation of new peritumoral vasculature [32]. On the other hand, the overexpression of VEGF can have an immunosuppressive effect on the tumor microenvironment, by inhibiting the maturation of lymphoid precursor cells of dendritic cells, macrophages, and granulocytes, and the inhibition of the recruitment of M2 macrophages. These effects worsen the response to immunotherapy, which could also be reversed, at least in theory, by adding antiangiogenic treatment. In addition, a situation of severe and sustained hypoxia could promote significant selective pressure and genomic instability that lead to more aggressive tumor phenotypes that include resistance to chemotherapy and elevated propensity to metastasize [33].

Reck *et al.* related an aggressive behavior of the disease with factors associated with primary resistance to chemotherapy, such as low expression of the copper transporter-1 that limits the arrival of the drug to the cell, a greater intracellular lavage due to an increase in glutathione-S-transferase activity; in addition to increased expression or polymorphisms of ERCC1, BRCA1, and RRM1 that could be related to resistance to platinum-based chemotherapy [25].

More recently, PD-L1 expression has been studied in patients with NSCLC and it seems to be associated with greater tumor proliferation and aggressiveness with higher Ki-67, higher histological grade, greater lymphatic involvement (pN), and worse OS [34,35].

This fact could be explained by the biological basis of the promotion of tumor growth and progression by PD-L1 through the activation of the WIP and β-catenin signaling cascades (PD-L1/Akt/β-catenin/WIP axis). PD-L1 promotes the expression of p-S6 through the PI3K/AKT/mTOR signaling pathway and also increases the expression of 10-catenin through the phosphorylation of GSK-3β. On the other hand, β-catenin binds to the WIP promoter and activates its expression in LC cells, ultimately favoring cell proliferation and migration, as well as protein synthesis and tumor genesis [36]. Mutations in KRAS and LKB1 can alter the patient's metabolism with activation of the KEAP1/NRF2 signaling pathway, and tumors with both mutations are highly aggressive and generally resistant to PD-L1 inhibitors, which may also be a feature of some aggressive patients with HTB [37,38].

Therefore, according to what has been described, we could say that LC with HTB could have a pathophysiological rationale based on the overexpression of markers related to cell proliferation (Ki-67, through PI3K/AKT/mTOR), upregulation of pro-angiogenic factors (VEGF, PDGF, and FGF), activation of cell growth signal activating pathways and resistance to anti-PD-1/PDL1 (KEAP1/NRF2), and loss of cell adhesion (through WIP/β-catenin). However, all these data come from translational research studies and there is no clear pathological-molecular characterization of this type of patients who present in the clinic with HTB, beyond the purely clinical and radiological criteria that underlie in this population (Figure 2).

6. Prevalence of ACT Tumor in NSCLC

At present, there is no clear evidence about the prevalence of patients presenting with a HTB in the context of NSCLC. One explanation could be that there is no definition of this concept among the community of medical oncologists that allow patient inclusion in this category and, therefore, have an approximate idea of its real prevalence in NSCLC.

Classically, several authors have considered the number of metastatic sites as an important factor involved in LC HTB definition [39,40]. Different databases have analyzed the prognosis of patients according to the number of metastatic sites. The Swedish Family Cancer Database demonstrated that around 38% of all deceased patients with LC had one metastatic site, and 19% had two or more metastases [39]. However, in the present study, ~63.8% of all metastatic cohorts exhibited metastasis to one site. Ren *et al.* reported that the most common combination for two-site metastases for adenocarcinoma was bone and brain (11.4%), and that for squamous carcinoma (SQCC), the metastatic sites were mainly bone and the liver (11.8%) [41].

Liver metastasis (LM) has been considered a possible condition for HTB and its prevalence in non-oncogene-addicted advanced NSCLC varies depending on the series. In a separate analysis of 1542 patients with metastatic NSCLC, 13% had LM [42]. Xu *et al.* described 5.8% of patients with LM as the only location in a Chinese cohort with more than 8000 patients [43].

However, in the majority of the situations, LM was associated with other locations such as bone, brain, or lung. The prevalence of different metastatic combinations was analyzed by Xu *et al.* on the basis of histology. They found that in adenocarcinoma, the most common pattern of metastasis combination is located in bone/brain/lung and supposed 30% of total and also bone/brain/liver in around 30% of patients included. In squamous tumor, bone/

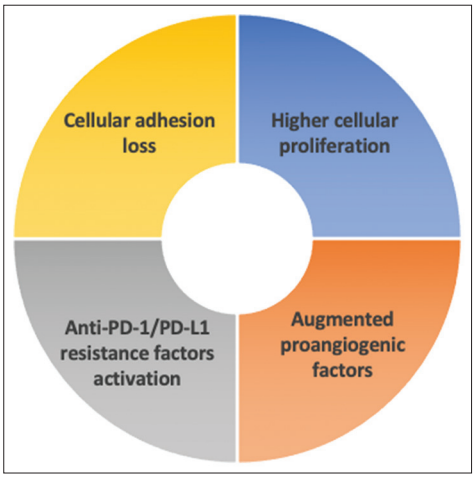

Figure 2. Potential factors associated with high tumor burden.

DOI: http://dx.doi.org/10.18053/jctres.08.202205.008

liver/lung metastasis was presented in more than 40% of patients and same combination was more common in adenosquamous and large cell carcinoma [43].

According to different authors, HTB in NSCLC could be considered three or more than 3 site metastasis locations, with a clearly poor prognosis compared to those with less than this number of different organ metastasis [43,44].

LM site, itself, could be also considered HTB according to results of different series that compared to isolated liver involvement to other combinations of metastasis locations [45,46].

Finally, we could say that the prevalence of HTB in LC is difficult to define. It varies from 19% to 38% considering the number of sites metastasis and their locations. Next section will describe more specifically, clinical profile of these kinds of patients.

7. Clinical Characteristics of HTB and Its Role as a Prognosis Factor

As we previously mentioned, HTB could be defined by several features such as number and location of lesions, sum of diameters of target lesions, and different serum markers. In this section, we briefly will describe the impact of all these concepts in HTB.

One of the parameters features postulated as important when defining TB is the number of tumor lesions. Zhang *et al.* [47] conducted a retrospective review of the medical records of 140 patients with histologically proven NSCLC and baseline 2-deoxy-2-(18F)fluoro-D-glucose (18F-FDG) PET scan before therapy. The total number of tumors (TTn) in the whole body, the number of primary tumors (Tn), positive lymph nodes (Nn), and distant metastases (Mn), along with the maximum standardized uptake values (SUVmax) of the tumors, were measured. The total number of tumors (TTn) and positive lymph nodes (Nn) were strong prognostic factors of NSCLC patients' OS. Patients with a TTn ≤ 4 (cut point based on median value) had a median OS of 15.2 months compared with 9.0 months for those with TTn > 4.

Several studies of the association between TB and survival have used the baseline sum of the target lesions' longest diameters (BSLDs) as a surrogate marker for the TB [11,48,49].

Miyamaki *et al.* [48] reported in 2020 a single-center retrospective study evaluated 163 patients with advanced NSCLC who had received (PD-L1) inhibitor monotherapy during 3 years and the clinical TB was estimated using the BSLDs, measured according to the Response Evaluation Criteria for Solid Tumors (RECIST criteria), and the baseline number of metastatic lesions (BNMLs). Multivariable analysis revealed that low BSLD, low BNML, non-squamous histologic type, and a PD-L1 tumor proportion score of using the BSLDs, measured according to the Response E.

Sakata *et al.* [11] retrospectively evaluated 83 NSCLC patients with ICIs. TB, defined as the sum of the unidimensional diameters of up to five target lesions, was a prognostic factor for OS. The optimal TB cutoff for predicting OS was 12 cm and they showed that the low TB group achieved significantly longer OS than the high TB group (median OS: 18.5 months, [95% confidence interval (CI) = 11.7-not reached] vs. 2.3 months [95% CI = 1.3–2.9], $P < 0.001$).

Gerber *et al.* [49] retrospectively evaluated data from the E4599 trial of paclitaxel-carboplatin ± bevacizumab. Associations between (RECIST) baseline sum longest diameter (BSLD), response rate, PFS, and OS were evaluated. BSLD predicted OS (hazard ratio (HR) 1.41; $P < 0.001$) and had a trend toward association with PFS (hazard ratio [HR] = 1.14; $P = 0.08$). The median OS was 12.6 months for patients with BSLD < 7.5 cm compared with 9.5 months for BSLD ≥ 7.5 cm.

Hopkins *et al.* [50] reviewed this association in LC using data from 1461 patients with a diagnosis of advanced NSCLC enrolled in the OAK, POPLAR, BIRCH, and FIR trials and treated with atezolizumab. Data were pooled and analyzed, identifying the baseline tumor size as an independent prognostic factor of worse OS and PFS.

Therefore, it could be concluded that BSLD in different retrospective studies of NSCLC is a prognostic factor, so it should be taken into account when planning the therapeutic strategy.

Another possible factors involved in TB are the location of metastases. There are multiple studies that show a different prognosis depending on the location of the metastatic disease. Oh *et al.* [51] analyzed OS in 1284 patients newly presenting with metastatic NSCLC by number of metastatic organ sites and the presence of brain metastases. Brain metastases conferred an inferior OS (median of 7 months vs. 9 months; 95% confidence interval, 7–8 months vs. 8-10 months [$P = 0.002$]). In patients with brain metastases, OS was found to be correlated inversely with the volume of all metastases or the largest lesion (hazard ratio, 1.04 or 1.03, respectively; $P = 0.01$). For patients with lung metastases, OS was better for those with a maximum tumor size below the median of 40 mm ($P = 0.0004$).

Bates *et al.* [52] included 39,910 patients from the SEER database treated for M1b NSCLC from 2010 to 2013. Patients with disease coded as in the brain without other disease in the lung, liver, or bone had improved OS relative to all other comers with M1b disease (HR = 0.84, 95% CI: 0.84–0.90, $P < 0.001$). Likewise, patients with disease coded as in the bone without other disease in the lung, liver, or brain had improved OS relative to all other comers with M1b disease (HR = 0.89, 95% CI: 0.86–0.92, $P < 0.001$).

Multiple serum markers have been evaluated as possible poor prognostic factors in NSCLC. LDH is one of the most studied. Rotenberg *et al.* [53] determined the values for total LDH activity in serum and their isoenzymes at diagnosis in 273 patients with NSCLC and they concluded that total LDH in serum may be a direct indicator of clinical stage and HTB in patients with NSCLC.

Different studies have found experimental serum markers that could be associated HTB and poor prognosis. One of these is serum miR-185 [54], serum transthyretin [55], and serum periostin [56]. However, all these data are preliminary and need a further confirmation in prospective studies. Table 1 summarizes the main studies defining TB and HTB in NSCLC.

DOI: http://dx.doi.org/10.18053/jctres.08.202205.008

Table 1. Summary of the main studies defining tumor burden and high tumor burden in non-small-cell lung cáncer.

Burden	Definition	References
TB	The sum of the longest dimensions of measurable baseline target lesions	Miyawaki *et al.* [48]
TB	The sum of the longest diameters for a maximum of five target lesions and up to two lesions per organ	Sakata *et al.* [13]
HTB	It could be considered three or more than 3 site metastasis locations	Xu *et al.*[43] Paralkar *et al.* [44]
HTB	It could be considered HTB isolated liver involvement	Milovanovic *et al.*[45] Gibson *et al.* [46]
HTB	TB, defined as the sum of the unidimensional diameters of up to five target lesions and the optimal TB cutoff for predicting OS was 12 cm	Sakata *et al.* [11]
HTB	HTB defined as baseline sum longest diameter≥7.5 cm was related worse outcome.	Gerber *et al.* [49]
HTB	HBT was defined as sum of the longest diameters (cutoff point: 101 mm) was related worse outcome	Katsurada *et al.* [57]
HTB	Disease burden subgroups (high or low) were defined using the 3rd quartile of the SLD of the target lesions or median number of met sites at BL. Per 3rd quartile SLD (108 mm) and>2 metastasis sites was considered high disease burden	Jotte *et al.* [58]

TB: Tumor burden, HTB: High tumor burden, BL: Baseline, SLD: Sum of the longest diameter, OS: Overall survival

8. Therapeutic Implications of ACT in the Selection of the First Line in NSCLC

There are very limited data about the impact of HTB on the best decision about first-line treatment in advanced previously untreated NSCLC. Available information is limited and comes from subgroup analyzes of the main pivotal studies. We currently have a wide range of first-line treatment possibilities in patients with advanced NSCLC and decision-making has become quite complex.

When we have to decide on the first-line palliative treatment for previously untreated patients with advanced non-oncogene-addicted NSCLC, we lack the factor of the speed of progression to the previous line, and those factors related to a greater aggressiveness are less defined. One possible factor could be the HTB. In a population-based study with 54,697 patients, it was observed that those patients with LM had the worst prognosis in both the univariate and multivariate analyses, even worse than those with brain metastases [59].

If we take into account the factor of the presence of LM, the IMpower150 study prospectively included, as a stratification criterion, the presence or absence of LM, and showed that the combination of atezolizumab/carboplatin/paclitaxel/bevacizumab improved OS significantly even in a subgroup of patients with worse prognosis (HR = 0.52; 95% CI: 0.33–0.82). This benefit was not observed in the arm composed of the same combination without bevacizumab (HR = 0, 87; 95% CI: 0.57–1.32) [60], reinforcing the potential important role of antiangiogenesis in this subgroup considered as HTB, with the underlying biological basis of a tumor microenvironment with greater hypoxia.

A *post hoc* study of KEYNOTE-189 in patients with LM found a greater efficacy for the combination of chemotherapy with pembrolizumab in this subgroup (HR = 0.62, 95% CI: 0.39–0.98) that was consistent results with the general population [61]. In the CheckMate 227 study, patients with PD-L1 <1% and LM had a statistically significant benefit with the combination of nivolumab and ipilimumab versus chemotherapy (11.7 mo vs. 7.8 mo), but this observed benefit was not maintained in those patients with LM and PD-L1 ≥ 1% or independent of PD-L1 expression [62].

Therefore, in the absence of a direct comparison between the different schemes, the decision must be made individually by the clinician based on the characteristics of the patient. However, if we take into account the biological rationale, in those patients with a HTB, there could be greater hypoxia that favors an increase in the expression of pro-angiogenic factors such as VEGF, which facilitates a more immunosuppressive tumor microenvironment. These cases could benefit from a treatment regimen that includes an antiangiogenic agent in addition to the combination of immunotherapy and chemotherapy [63].

On the other hand, if we conceive the presence of brain metastases as a factor with a worse prognosis and a HTB, this factor did not alter the efficacy of the combination of pembrolizumab/platinum/pemetrexed in the KEYNOTE-189 study (HR = 0.41; 95% CI: 0.24–0.67) and results were even numerically better for the group without brain metastases (HR = 0.59; 95% CI: 0.46–0.75) [61].

Therefore, HTB could be considered an important factor when selecting those patients who benefit the most from a combination treatment scheme in first-line setting.

9. Therapeutic Implications of ACT in the Selection of the Second and Subsequent Lines in NSCLC

As is logical, the second- and third-line treatment options are determined by the previously administered treatment. Four Phase III randomized trials have shown that ICIs such as nivolumab, atezolizumab, and pembrolizumab significantly improve OS when compared with docetaxel in patients who have progressed on prior treatment with a platinum double. Furthermore, the addiction of antiangiogenic drugs to docetaxel increases OS in NSCLC after failure of first-line chemotherapy.

In the second-line setting in patients who have not previously received immunotherapy, some factors are taken into account when choosing the best treatment option. These factors are time to progression to a first line of treatment and the type of response to this treatment, number and location of metastases, PDL1 expression, and performance status.

There are limited data about the role of tumor burden in this context, probably due to its complexity of definition. As we mentioned above, measurement of TB has been shown to be associated with clinical outcomes in advanced NSCLC. However, its role as a predictor of treatment response is not clear. An exploratory analysis of the LUME-Lung I study, the

DOI: http://dx.doi.org/10.18053/jctres.08.202205.008

authors showed nintedanib/docetaxel significantly decreased TB and decelerated tumor size compared with placebo/docetaxel and that the improvements in tumor burden were greatest in the adenocarcinoma PD-FLT population, comprising those patients with larger baseline tumor burden (poorest prognosis) [64]. Concerning to ICI therapy, Katsurada *et al.* retrospectively analyzed 58 patients with NSCLC who underwent ICI monotherapy. Patients were divided into two groups according to BTS (cutoff point: 101 mm) and they found that the median PFS and OS of patients with large BTS were significantly shorter than that of patients with small BTS. Nevertheless, the ORR of ICI therapy was not significantly different between the groups, but the proportion of PD of ICI therapy was significantly higher in the large BTS group [57].

Patients with NSCLC experience symptoms that commonly include dyspnea, cough, fatigue, anorexia, and pain; thus, control of symptoms is an essential part of the decision-making process regarding treatment options. In most cases, symptom burden may be related to TB; therefore, an analysis of the efficacy of treatments based on the patient's symptoms can provide indirect information on the HTB. In an exploratory analysis from the Phase III REVEL study, Pérol *et al.* demonstrated that in patients with high baseline symptom burden, the addition of ramucirumab to docetaxel significantly improved OS versus docetaxel alone (7.39 vs. 5.95 months; HR 0.749 [95% CI: 0.610–0.920]; $P = 0.0308$), and also, the ORR and DCR were significantly higher (ORR 18% vs. 11%; $P = 0.0458$; DCR 58% vs. 47%; $P = 0.0068$) [65].

For many clinicians, the presence of LM is strongly linked to a HTB. Although LM has been known to be associated with poor prognosis, only a few studies have shown an association between LM and treatment outcomes with ICI after platinum progression. A study conducted by Kitadai *et al.* [66] shown that patients with LM treated with ICI had shorter OS (HR = 2.04; 95% CI: 1.33–3.13) and PFS (HR = 1.89; 95% CI: 1.29–1.71) compared to those without the same and they had a RR of 22.5%. One previous study showed that among patients with NSCLC who received pembrolizumab, those with LM had shorter PFS (mPFS of 1.82 months) and lower RR (28.6%) compared to those without the same [67]. In addition, mPFS of 1.2 months, RR of 3.4%, and DCR of 31% among 29 nivolumab-treated patients with NSCLC harboring liver metastasis were reported [68]. However, these institution/country experiences did not compare the possible benefit of ICI with standard of care chemotherapy, docetaxel. Nevertheless, a 3-year follow-up study of CheckMate 017 and CheckMate 057 had shown the clinical advantage of nivolumab over docetaxel for NSCLC with LM. Nivolumab resulted in a greater OS benefit compared with docetaxel (HR = 0.68; 95% CI: 0.50–0.91) with an estimated 3-year OS of 8% (95% CI: 4–14%) with nivolumab versus 2% (95% CI: 0.4–7%) with docetaxel in patients with LM [69]. As with LM, brain metastases (BMs) can be considered a HTB. Patients with active, unstable, or untreated BMs were excluded from pivotal clinical trials with ICIs; and only a few retrospective analyses have investigated the efficacy of ICI therapy in this subgroup of patients [70]. In a *post hoc* analysis of the patients with asymptomatic BM treated in the OAK trial, atezolizumab showed better OS (16.0 vs. 11.9 months, HR = 0.74; CI: 0.49–1.13) and led to a prolonged time to radiologic identification of new symptomatic BM compared with docetaxel at 6 and 24 months (HR = 0.38;CI: 0.16−0.91) [71]. These results are supported by a pooled analysis of the five studies of atezolizumab in second-line NSCLC. A pooled analysis of the Checkmate 017, 057, and 063 trials of nivolumab versus docetaxel in second-line treatment of NSCLC showed a trend toward improved OS in favor of nivolumab in patients with pre-treated CNS metastases (8.4 vs. 6.2 months). Another important report on nivolumab for the treatment of CNS metastases was the Italian EAP. In the non-squamous NSCLC group, PFS was 3 months and OS 8.6 months; and achieved an ORR of 17% and a DCR of 40%. In the squamous group, PFS was 5.5 months and OS 6.5 months [72]. So far, only one prospective Phase II trial with pembrolizumab has specifically addressed the question of ICI efficacy for patients who had untreated asymptomatic BMs measuring ≤ 2 cm. The intracranial response rate among PDL1 positive patients was 29.7% (11 of 37 patients, four complete responses) [73].

As we mentioned above, the concept of HTB may be related to aggressive disease. Clinical trial results suggest that patients with aggressive NSCLC, usually defined as disease that rapidly progresses on first-line treatment or disease that is refractory to first-line chemo, may have clinical benefit from second-line treatment with an antiangiogenic therapy added to docetaxel [74].

Regarding to immunotherapy, the studies of ICI in second-line setting have not investigated the efficacy of these agents in patients with aggressive or refractory disease. Only CheckMate

Table 2. Potential biomarkers of high tumor burden.

Biomarkers	Biological sample	References
Ki-67	Tumor	Hitchcock [28] Foltyn *et al.* [29] Warth *et al.* [30] Wang *et al.* [31] Wei *et al.* [32]
VEGF overexpression	Tumor	Vaupel *et al.* [33]
Genes involved to primary chemotherapy resistance: CTR1, GSTM1	Tumor	Reck *et al.* [25]
Genes involved in platinum resistance: ERCC1, BRCA1, and RRM1	Tumor	Reck *et al.* [25]
PD-L1	Tumor	Pawelczyk *et al.* [34] Sterlacci *et al.* [35]
KRAS/LKB1 mutations	Tumor	Skoulidis *et al.*[37] Galan-Cobo *et al.* [38]
LDH	Serum	Rotenberg *et al.* [53]
PLR	Serum	Jiang *et al.* [75]
Albumin	Serum	Jiang *et al.* [75]
miR-185	Serum	Liu *et al.* [54]
Transthyretin	Serum	Shimura *et al.* [55]
Periostin	Serum	Zhang *et al.* [56]

PLR: Platelet-to-lymphocyte ratio, PD: Progression of disease, LDH: Lactate dehydrogenase, VEGF: Vascular endothelial growth factor

DOI: http://dx.doi.org/10.18053/jctres.08.202205.008

057 has a reference to patients with this poor prognosis (TSPT > 3 months) and the outcomes seem to suggest that patients with aggressive disease may have a delayed onset of effect with nivolumab treatment, relative to docetaxel.

Finally, Table 2 summarizes the potential biomarkers of HTB.

10. Conclusions

HTB is a relevant concept in LC without a clear definition in the literature. According to different authors, number of metastasis sites, metastasis location, the sum of the diameters of target lesions, high serum levels of LDH, and high expression of pathological markers such as Ki-67 could be used for HTB characterization. In our opinion, after this literature review and considering the different authors' contributions in this review, we could define HTB in those patients with following characteristics: More than 3 metastatic sites, the sum of the longest diameters larger than 100 mm, metastatic liver involvement, multiple symptomatic brain involvement, and relevant functional patient deterioration. The choice of these characteristics is based on the evidence presented above, being proven prognostic parameters (with a greater or lesser level of evidence). However, a validation prospective study of this definition should be carried on. Different studies tried to demonstrate better results in OS and PFS for patients with HTB versus no HTB in the first- and second-line setting. Nevertheless, these results are obtained from subgroup analysis and they should be confirmed in randomized studies. We are very concerned about the need to identify this subgroup of patients for defining and optimizing a more aggressive treatment strategy.

Acknowledgments

None.

Funding

No funding has been received for this work.

Conflicts of Interest

Luis Cabezón Gutiérrez declares the following conflicts of interest: Advisory role; Boehringer-Ingelheim, AstraZeneca, Roche and Brystol Myers Squibb. Speakers' bureau; Roche, AstraZeneca, Brystol Myers Squibb, Merck Serono, Ipsen Pharma, Lilly and Amgen, Angelini, Grunenthal, Kyowa Kirin, Mudipharma, Pfizer, Roche, Rovi, Leo Pharma and Boehringer Ingelheim.

Xabier Mielgo-Rubio declares the following conflicts of interest: Advisory role; Boehringer-Ingelheim, AstraZeneca, Brystol Myers Squibb. Speakers' bureau; Roche, AstraZeneca, Brystol Myers Squibb, MSD, Abbott. Research funding; Brystol Myers Squibb.

Maria Serono, Raquel Cervera-Calero, and Oliver Higuera declare no conflicts of interests.

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