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HER2 AND BCL-2 ALTERATIONS IN NON-SMALL CELL LUNG CANCER, BIOLOGICAL AND CLINICAL SIGNIFICANCE, THERAPEUTIC PERSPECTIVES: A LITERATURE REVIEW

A.E. AKHAYEVA[1], *M.A. AITMAGAMBETOVA*[1], *A.N. ZHEKSENOVA*[1]

[1]West Kazakhstan Marat Ospanov Medical University, Aktobe, the Republic of Kazakhstan

ABSTRACT

Relevance: *Lung cancer remains one of the leading causes of cancer mortality worldwide. Accord-ing to WHO, more than 2.2 million new cases are detected annually, and the mortality rate exceeds 1.8 million. Despite advances in diagnostics and treatment, the prognosis for non-small cell lung cancer (NSCLC), especially in the late stages, remains unfavorable. Molecular genetic biomarkers play a significant role in improving diagnostics and choosing therapy. Bcl-2 and HER2 proteins, in-volved in regulating apoptosis and proliferation, may be associated with the aggressive course of NSCLC and resistance to therapy. Their study is relevant for the development of a personalized ap-proach to the treatment of this disease.*

The study aimed to *assess the biological and clinical significance of HER2 and Bcl-2 alterations in non-small cell lung cancer and to analyze their impact on disease prognosis and the effectiveness of various therapeutic strategies.*

Methods: *The search for electronic medical sources was conducted in the PubMed, Web of Science, and Google Scholar databases using the keywords: "biomarkers," "non-small cell lung cancer," "di-agnosis," "prognosis," and "survival." The review included full-text articles in Russian and English, published over the past five years and available in open access, devoted to the role of biomarkers in lung cancer early detection and prognosis.*

Results: *The expression of Bcl-2 and HER2 plays a significant role in the pathogenesis of NSCLC. Bcl-2, a key regulator of apoptosis, is detected in 30-50% of patients and may be associated with tumor aggressiveness and improved survival, depending on histological subtype and disease stage. HER2 alterations are found in 1-30% of cases, more commonly in adenocarcinomas among non-smoking women, and are associated with poor prognosis and therapy resistance. Targeted therapies like venetoclax and HER2 inhibitors (trastuzumab deruxtecan, pyrotinib) improve progression-free survival.*

Conclusion: *Bcl-2 and HER2 are promising biomarkers and therapeutic targets in NSCLC. Their study supports personalized treatment and should be integrated into clinical practice to improve out-comes.*

Keywords: *biomarker, non-small cell lung cancer (NSCLC), diagnosis, prognosis, survival.*

Introduction: Lung cancer (LC) is the leading malignant neoplasm in terms of morbidity and mortality worldwide [1].

According to the Global Cancer Observatory (GLOBOCAN 2022), lung cancer in Kazakhstan still ranks first among malignant neoplasms in men and is among the five most common in women. The standardized incidence rate is 20.4 per 100,000 population, and the proportion of lung cancer among all cancers in the country is about 9.7%. These findings highlight the continuing high burden of the disease and the need for further improvement of early diagnostics and personalized treatment [2].

Oncological diseases remain one of the priority medical and social health problems of the Republic of Kazakhstan, having a significant impact on the overall mortality rate and life expectancy of the population. In the structure of malignant neoplasms, lung cancer is of particular epidemiological importance, which is characterized by high prevalence and marked mortality. A significant contribution of this disease to the overall cancer mortality is due mainly to the latent clinical course in the early stages, which complicates timely diagnosis, as well as an unfavorable prognosis, especially when detected at late stages [3].

Recent studies have shown that, in addition to extrinsic carcinogens, ethnicity and genetic predisposition (associated with mutations in known genes associated with a high or moderate risk of cancer) can significantly affect the risk of developing LC and its molecular profile [4].

As part of a global analysis conducted by F. Islami et al., trends in lung cancer mortality by major morphological forms in 48 countries over the past decades were studied. The results of the study demonstrated significant changes in the structure of LC histological types. The authors noted that in most countries of the world, including high- and middle-income countries, there is a steady trend towards an increase in the proportion of non-small cell lung cancer (NSCLC), especially adenocarcinoma. The study highlights that adenocarcinoma has become the predominant histo-

logical type of lung cancer among both men and women, in virtually all countries involved in the analysis. In addition, F. Islami et al. focused on the fact that despite the general trend towards a decline of overall mortality from lung cancer in several countries, the proportion of lethal outcomes due to adenocarcinoma continues to be high. This is due to the difficulties of early diagnosis of this histological type, the tendency to metastasis in the early stages, and the variability of the molecular characteristics of tumors, which determines the relevance of further research in the field of molecular genetic profiling and the development of personalized approaches to NSCLC therapy [5].

According to R.L. Siegel et al., NSCLC accounts for about 81% of all lung cancer cases in the United States, remaining the most common form of the disease [1].

According to GLOBOCAN 2022, lung cancer has the highest mortality rate among all malignant tumors. Non-small cell lung cancer (NSCLC) accounts for about 82-85% of all lung cancer cases in all regions of the world, with a remaining upward trend of adenocarcinoma, especially among women and never-smokers. In the NSCLC structure, the major share is occupied by adenocarcinoma, which has been the leading subtype for more than 10 years. This is due to a change of smoking style (switching to filter cigarettes) and an elevation of the proportion of cases among non-smokers [2].

The choice of NSCLC as a study object is due to its high prevalence, prognostic and biological diversity, as well as the possibility of molecular profiling necessary for the development of personalized approaches to therapy. In the context where late diagnosis and resistance to treatment remain the key problems, the emphasis on the NSCLC study allows identifying new biomarkers and approaches to risk stratification, which is a critical task of modern oncology.

With the development of molecular medicine and the creation of drugs targeting specific molecular targets, the treatment of non-small cell lung cancer (NSCLC) has become personalized in recent years. It focuses on molecular aspects of the disease pathogenesis.

As of today, personalized targeted therapy based on molecular tumor profiling is actively used in the treatment of NSCLC, especially in patients with mutations in the epidermal growth factor (EGFR) gene and rearrangements of the anaplastic lymphoma kinase (ALK) gene. According to D.R. Camidge et al., the introduction of tyrosine kinase inhibitors EGFR and ALK significantly improved survival and disease control in these patient groups. Concurrently, despite the success of targeted therapy, the prognosis of most patients with NSCLC remains unfavorable due to the high rate of late diagnostics and a limited number of available molecular targets [6].

One of the promising prognostic and potential therapeutic biomarkers is the Bcl-2 protein, an anti-apoptotic regulator, that plays a key role in the mechanisms of cellular survival. As noted by T. Miyashita et al. [7] and J. Ni et al. [8], overexpression of Bcl-2 is associated with tumor cell resistance to apoptosis, decreased chemotherapy efficacy, and poor prognosis in patients with NSCLC. The identification of such molecular markers and their further study opens up prospects for the development of new therapeutic strategies in the treatment of that pathology.

Human Epidermal Growth Factor Receptor 2 (HER2) is a transmembrane receptor protein in the epidermal growth factor receptor family that plays an important role in carcinogenesis. It was initially investigated as a key biomarker for breast cancer, but in recent years, scientists have focused on its significance in NSCLC [9]. HER2 mutations and amplifications are detected in approximately 2-4% of patients with lung adenocarcinoma, which makes it a promising target for targeted therapy [10]. Recent clinical studies have shown the efficacy of HER2 inhibitors such as trastuzumab deruxtecan in treating patients with HER2-positive NSCLC, opening up new opportunities for personalized therapies [11].

The study of the role of Bcl-2 and HER2 as biomarkers of lung cancer is an important direction of modern oncology. This allows not only a better understanding of tumor biology, but also the development of personalized approaches to patient treatment, by improving its effectiveness. This review is devoted to the analysis of the role of Bcl-2 and HER2 in the pathogenesis, diagnosis, and prognosis of lung cancer, as well as their possible use in personalized therapy of patients.

The study aimed to assess the biological and clinical significance of HER2 and Bcl-2 alterations in non-small cell lung cancer and to analyze their impact on disease prognosis and the effectiveness of various therapeutic strategies.

Materials and methods: An electronic search of the medical literature using the PubMed, Web of Science, and Google Scholar databases was conducted within this study. The search was carried out by the following keywords: “biomarkers”, “lung cancer”, “lung cancer diagnosis”, “lung cancer prognosis “, “survival”. A total of 252 sources were found; the review involved 27 full-text publications in English and Russian, published over the past 5 years, available in the public domain, and devoted to the study of the role of biomarkers in the early diagnosis and prognosis of lung cancer.

Results: The HER2 and Bcl-2 alterations occur in a significant proportion of patients with NSCLC, affecting the tumor aggressiveness, its resistance to standard therapy, and disease prognosis.

The discovery of the BCL2 gene in 1984-1985 as an oncogene involved in the specific translocation t(14; 18) (q32; q21) in follicular B-cell lymphomas has become one of the key events in molecular oncology [7]. This was the first time that an oncogene was associated not with increased proliferation, but with dysregulation of apop-

tosis - a physiological process of controlled cell death [12]. Later, this discovery was confirmed by the identification of the homologous anti-apoptotic gene ced-9 in the nematode Caenorhabditis elegans, which proved the universality of apoptosis mechanisms in eukaryotes [13]. Modern studies have confirmed that the Bcl-2 protein is localized predominantly in the outer membrane of mitochondria, playing a central role in controlling the mitochondrial-dependent apoptosis pathway through the regulation of pro- and anti-apoptotic members of the Bcl-2 family [14]. This became the basis for the concept of apoptosis as the most important mechanism for maintaining tissue homeostasis and the target of antitumor therapy, which is reflected in the drug development, for example, the Bcl-2 inhibitor Venetoclax, which is actively used in the treatment of hematological and some solid tumors [15].

Bcl-2 is a key anti-apoptotic protein that regulates the survival of tumor cells. In NSCLC, Bcl-2 expression occurs in 30-50% of patients, especially in adenocarcinomas. In small cell lung cancer, Bcl-2 levels are elevated in 75-90% of cases. High expression of Bcl-2 in SCCL is associated with resistance to chemotherapy and a more aggressive course of the disease. In NSCLC, Bcl-2 may be a marker of a better prognosis because it correlates with a less aggressive phenotype [16].

The HER2 amplification is detected in 2-4% of patients with lung adenocarcinoma. HER2 mutations are more common in non-smoking patients and women, and HER2 mutations (insertions in exon 20) are detected by next-generation sequencing (NGS) [17].

HER2-positive NSCLC is characterized by a more aggressive course and rapid progression. Patients with HER2 mutations show worse survival in the absence of targeted therapy [18]. Bcl-2 inhibitors, such as Venetoclax, have shown promising results in the treatment of some forms of lung cancer. The combination of Bcl-2 inhibitors with chemotherapy may increase the sensitivity of the tumor to treatment [19]. HER2 inhibitors (Afatinib, Trastuzumab, Trastuzumab deruxthecan) significantly improve the prognosis of patients with HER2-positive lung cancer. Trastuzumab deruxtecan showed an improvement of progression-free survival for 9.3 months in HER2-positive patients [20]. Analysis of the expression of Bcl-2 and HER2 proteins in NSCLC revealed their significant role in the progression of the tumor process and response to therapy.

According to N.F. Underwood et al., HER2 changes occur in 7-27% of cases of de novo NSCLC and are a mechanism of resistance in 10% of mutated EGFR-NSCLC cases. The most common mutation is the insertion of HER2 exon 20, which leads to increased activity of the PI3K/Akt and MEK/ERK signaling pathways, which promotes oncogenesis and disease progression. The studies show that patients with HER2 amplification and overexpression demonstrate lower progression-free survival and overall survival, compared to HER2-negative patients [21].

E. Loeffler et al. note that HER2 is a receptor tyrosine kinase of the EGFR/ErbB family, and its disorders can occur in the form of gene mutation, gene amplification, protein overexpression, and hyperphosphorylation.

HER2 abnormalities contribute to abnormal proliferation, angiogenesis, mesenchymal tumor properties, and immune response evasion, making HER2 a significant target for targeted therapy. HER2 mutations occur in 1-4% of patients with NSCLC, HER2 amplification in 2-5%, and overexpression in 2-30% of patients. HER2 mutations are more common in women, non-smoking patients, and in adenocarcinoma. High HER2 expression is associated with a worse prognosis and lower efficacy of standard chemotherapy and immunotherapy [22].

M. Miladinović et al. found that HER2 was overexpressed in 7.4% of patients with lung adenocarcinoma when using HercepTest, and in 2.7% of patients when testing with the 4B5 antibody. In 90.9% of cases, a correlation was found between high HER2 expression and amplification of the HER2 gene, which confirms its importance as a molecular target [23].

In a study of W. Chen et al., HER2 mutations were more common in younger patients and non-smokers. Such tumors tend to show slower growth, compared to wild-type HER2 [24].

Discussion: The data obtained confirm the importance of HER2 and Bcl-2 molecular alterations in the pathogenesis and clinical course of non-small cell lung cancer (NSCLC). Both targets are involved in the regulation of key processes of tumor growth and apoptosis, determining the aggressiveness of the tumor, its sensitivity to treatment, and the disease prognosis.

The Bcl-2, being an important anti-apoptotic protein, affects the survival of tumor cells by suppressing the mitochondrial-mediated pathway of apoptosis. Bcl-2 overexpression is most frequent in small cell lung cancer, where it reaches 75-90%, while in NSCLC, it occurs in 30-50% of cases. However, the role of Bcl-2 in NSCLC remains controversial: on the one hand, high protein expression is associated with resistance to chemotherapy, on the other hand, it can serve as a marker of a less aggressive tumor phenotype. This highlights the need for further research to clarify the prognostic and predictive value of Bcl-2 in different histological subtypes of NSCLC, as well as to optimize the use of Bcl-2 inhibitors as part of combination regimens of therapy.

HER2, in turn, is a receptor tyrosine kinase of the EGFR/ErbB family, the alterations of which include mutations, amplification, and overexpression. HER2 mutations occur in 1% to 4% of patients with NSCLC, mainly in women, non-smokers, and patients with adenocarcinoma. The most common option is insertion in exon 20, resulting in activation of the PI3K/Akt and MEK/ERK signaling path-

ways and promoting tumor progression. HER2 amplification and overexpression also demonstrate an association with poor prognosis and reduced efficacy of standard chemotherapy and immunotherapy. At the same time, the presence of HER2 alterations predetermines the possibility of prescribing targeted drugs such as Afatinib, Trastuzumab, and Trastuzumab deruxtecan, the use of which has already demonstrated improvement in progression-free survival and overall survival of patients with HER2-positive NSCLC.

Of particular interest are the data on the relationship between HER2 amplification and overexpression of its protein, which emphasizes the need for a comprehensive assessment of these parameters to optimize the choice of therapy. In addition, HER2 alterations play the role not only in primary oncogenesis, but also as a mechanism of acquired resistance in patients with EGFR-mutated NSCLC, which is important for the subsequent selection of therapy after disease progression.

Accordingly, HER2 and Bcl-2 are topical biomarkers and therapeutic targets in the treatment of NSCLC. Their study allows not only to enhance the understanding of the molecular basis of the tumor process, but also to justify the feasibility of personalized treatment selection, including targeted therapy and combined regimens. Further multicenter studies with enrollment of large patient cohorts and standardized diagnostic methods are needed to refine the prognostic value of these biomarkers and optimize the treatment approaches.

Conclusion: The findings highlight the important role of HER2 and Bcl-2 molecular alterations in the pathogenesis, prognosis, and individualization of therapy for non-small cell lung cancer. These biomarkers have a significant impact on tumor biological behavior, sensitivity to therapy, and patient survival. Expression of Bcl-2 shows a dual role: in NSCLC, it may be associated with a less aggressive course, while in small cell lung cancer, it correlates with resistance to chemotherapy. Taking into account the above, the inclusion of HER2 and Bcl-2 assays in the algorithm of molecular tumor profiling seems appropriate and can contribute to more accurate stratification of patients, optimization of treatment tactics, and increased effectiveness of personalized treatment in NSCLC. Further studies are needed to validate these markers in routine clinical practice and develop the combined therapeutic strategies.

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АҢДАТПА

HER2 ЖӘНЕ BCL-2 АЛЬТЕРАЦИЯЛАРЫНЫҢ ҰСАҚЕМЕСЖАСУШАЛЫ ӨКПЕ ОБЫРЫНДАҒЫ БИОЛОГИЯЛЫҚ ЖӘНЕ КЛИНИКАЛЫҚ МАҢЫЗЫ, СОНДАЙ-АҚ ТЕРАПИЯЛЫҚ ӘДІСТЕРДІҢ ПЕРСПЕКТИВАЛАРЫ: ӘДЕБИЕТКЕ ШОЛУ

А.Е. Ахаева[1], М.А. Айтмагамбетова[1], А.Н. Жексенова[1]

[1]«Марат Оспанов атындағы Батыс Қазақстан медицина университеті» КеАҚ, Ақтөбе, Казақстан Республикасы

Өзектілігі: *Өкпенің қатерлі ісігі бүкіл әлемде қатерлі ісік өлімінің жетекші себептерінің бірі болып қала береді. Дүниежүзілік денсаулық сақтау ұйымының мәліметі бойынша, жыл сайын бұл аурудан 2,2 миллионнан астам жаңа жағдай және 1,8 миллион адам қайтыс болады. Диагностика мен емдеудегі жетістіктерге қарамастан, ұсақемесжасушалы өкпе обырының (ҰЕЖӨО) болжамы, әсіресе соңғы кезеңдерінде, қолайсыз болып қала береді. Молекулярлық және генетикалық биомаркерлер диагностиканы жақсартуда және терапияны таңдауда маңызды рөл атқарады. Апоптозды және пролиферацияны реттеуге қатысатын Bcl-2 және HER2 ақуыздары ҰЕЖӨОагрессивті ағымымен және терапияға төзімділікпен байланысты болуы мүмкін. Олардың зерттеуі осы ауруды емдеудің жеке көзқарасын дамыту үшін өзекті болып табылады.*

Зерттеу мақсаты *– ұсақемесжасушалы өкпе обыры кезінде HER2 және Bcl-2 өзгерістерінің биологиялық және клиникалық маңыздылығын бағалау, сондай-ақ олардың аурудың болжамына және әртүрлі терапевтік стратегиялардың тиімділігіне әсерін талдау.*

Әдістері: *Бұл шолуда PubMed, Web of Science және Google Scholar дерекқорларында «биомаркерлер», «ұсақемесжасушалы өкпе обыры», «диагностика», «болжам», «тірі қалу қабілеттілігі» кілт сөздері бойынша медициналық әдебиеттерге электрондық іздеу жүргізілді. Шолуда соңғы бес жылда жарияланған, өкпе обырының ерте диагностикасы мен болжамындағы биомаркерлердің рөліне арналған орыс және ағылшын тілдеріндегі толық мәтінді мақалалар қамтылды.*

Нәтижелері: *Bcl-2 және HER2 экспрессиясы ҰЕЖӨО патогенезінде маңызды рөл атқарады. Апоптоздың реттеушісі Bcl-2 30-50% науқастарда анықталады және бұл ісіктің түрі мен сатысына байланысты өршумен де, өмір сүрудің жақсаруымен де байланысты болуы мүмкін. HER2-дегі өзгерістер науқастардың 1-30%-ында кездеседі, көбінесе темекі шекпейтін әйелдердегі аденокарциномаларда байқалады және қолайсыз болжаммен әрі терапияға төзімділікпен байланысты. Қазіргі нысаналы препараттар, соның ішінде венетоклакс және HER2-ингибиторлары (трастузумаб дерукстекан, пиротиниб) тиімділігін көрсетіп, рецидивсіз өмір сүру ұзақтығын арттырады.*

Қорытынды: *Bcl-2 және HER2 зерттеу ҰЕЖӨО-ның молекулярлық механизмдерін түсінуге және емдеуге жекелендірілген тәсілді дамытуға мүмкіндік туғызады. Бұл ақуыздар перспективті биомаркерлер және емдеу үшін нысаналар болып табылады, сонымен қатар оларды кешенді бағалау емдеудің тиімділігін жоғарылату және болжамды жақсарту үшін клиникалық практикаға енгізілуі керек.*

Түйінді сөздер: *биомаркер, ұсақемесжасушалы өкпе обыры (ҰЕЖӨО), диагностика, болжам, тірі қалу қабілеттілігі.*

АННОТАЦИЯ

АЛЬТЕРАЦИИ HER2 И BCL-2 ПРИ НЕМЕЛКОКЛЕТОЧНОМ РАКЕ ЛЕГКИХ: БИОЛОГИЧЕСКОЕ И КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ, ПЕРСПЕКТИВЫ ТЕРАПЕВТИЧЕСКИХ МЕТОДОВ: ОБЗОР ЛИТЕРАТУРЫ

А.Е. Ахаева[1], М.А. Айтмагамбетова[1], А.Н. Жексенова[1]

[1]НАО «Западно-Казахстанский медицинский университет им. Марата Оспанова», Актобе, Республика Казахстан

Актуальность: *Рак легкого остается одной из ведущих причин онкологической смертности в мире. По данным ВОЗ, ежегодно выявляется более 2,2 млн новых случаев, а смертность превышает 1,8 млн. Несмотря на достижения в диагностике и лечении, прогноз при немелкоклеточном раке легкого (НМРЛ), особенно на поздних стадиях, остаётся неблагоприятным. Существенную роль в улучшении диагностики и выборе терапии играют молекулярно-генетические биомаркеры. Белки Bcl-2 и HER2, участвующие в регуляции апоптоза и пролиферации, могут быть связаны с агрессивным течением НМРЛ и устойчивостью к терапии. Их изучение актуально для развития персонализированного подхода в лечении данного заболевания.*

Цель исследования *– оценить биологическое и клиническое значение изменений HER2 и Bcl-2 при немелкоклеточном раке легких, а также проанализировать их влияние на прогноз заболевания и эффективность различных терапевтических стратегий.*

Методы: *В обзоре проведён электронный поиск медицинской литературы в базах PubMed, Web of Science и Google Scholar по ключевым словам: «биомаркеры», «рак легкого», «диагностика», «прогноз», «выживаемость». Включены полнотекстовые статьи на русском и английском языках, опубликованные за последние пять лет и доступные в открытом доступе, посвящённые роли биомаркеров в ранней диагностике и прогнозировании рака легкого.*

Результаты: *Экспрессия Bcl-2 и HER2 играет важную роль в патогенезе НМРЛ. Регулятор апоптоза Bcl-2 выявляется у 30-50% пациентов и может ассоциироваться как с агрессивностью опухоли, так и с улучшенной выживаемостью в зависимости от подтипа и стадии. Альтерации HER2 обнаруживаются у 1-30% больных, чаще при аденокарциномах у некурящих женщин, и связаны с неблагоприятным прогнозом и резистентностью к терапии. Современные таргетные препараты, включая венетоклакс и HER2-ингибиторы (трастузумаб дерукстекан, пиротиниб), демонстрируют эффективность, повышая безрецидивную выживаемость.*

Заключение: *Изучение Bcl-2 и HER2 способствует пониманию молекулярных механизмов НМРЛ и развитию персонализированных подходов к терапии. Эти белки являются перспективными биомаркерами и мишенями для лечения, а их комплексная оценка должна быть внедрена в клиническую практику для повышения эффективности лечения и улучшения прогноза.*

Ключевые слова: *биомаркер, немелкоклеточный рак легкого (НМРЛ), диагностика, прогноз, выживаемость.*

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Information about the Authors:
A.E. Akhayeva (corresponding author) – PhD student, Master of Medicine, Senior Lecturer, Department of Histology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan, tel. +77779750487, email: gistolog89@mail.ru, ORCID: 0009-0002-8641-5727;
M.A. Aitmagambetova – PhD, Assistant Professor, Department of Histology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan, email: inzhumarzhan90@mail.ru, tel. +77026780057, ORCID: 000 0-0002-0346- 5829;
A.N. Zheksenova – Candidate of Medicine, Associated Professor, Head of the Department of Pathological Physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan, email: azhar.nikolaevna@mail.ru, tel. +77013183729, ORCID: 0000-0003-3697-2445.

Address for Correspondence: A.E. Akhayeva, West Kazakhstan Marat Ospanov Medical University, Maresyev St. 68, Aktobe 030019, the Republic of Kazakhstan.