Review/Praca poglądowa

Molecularly targeted therapies in head and neck cancers

Terapie nowotworów głowy i szyi celowane molekularnie

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ABSTRACT

Head and neck cancers (HNC) are 6th most common malignancies according to the incidence rate. Over 85% of tumors of this region are epithelial tumors, especially squamous cell carcinomas (head and neck squamous cell carcinomas – HNSCC). Surgery, chemotherapy and radiotherapy are still the standard for the treatment of HNC. Despite the great development of the various methods of treatment, survival of patients have not improved significantly over the last 30 years, with the overall, 5-year survival not exceeding 50%. Progress in understanding the biology of cancer leads to personalization of therapy and introduction of drugs with molecular mechanism of action to everyday practice. At present, the effectiveness of monoclonal antibodies against EGFR in the treatment of HNSCC has already been proven. Cetuximab in combination with radiotherapy was found to be effective in patients with advanced and locally advanced HNSCC. There are also some promising results of phase III trials with zalutumumab and panitumumab. Initial efficacy of sorafenib (an inhibitor of the intracellular domain of VEGFR, PDGFR and c-Kit) and afatinib (an irreversible inhibitor of pan-HER tyrosine kinase) have been demonstrated. Great hopes for the future are linked with the potential use of STAT3, EGFRvIII, abnormal proteins K-ras, H-ras and PTEN as well as proteasome as a target for therapy.

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Introduction

Head and neck cancers (HNC) are 6th most common malignancies in the world according to the incidence rate and comprise around 4% of all malignancies [1, 2]. Over 85% of tumors in this region are epithelial tumors, especially squamous cell carcinomas (head and neck squamous cell carcinomas – HNSCC) and their different histological varieties, which origin from mucous membrane of upper respiratory tract and upper section of gastrointestinal tract. Only in the rare malignancies of salivary glands and ear, adencarcinomas histology are most common. Moreover thyroid tumors are histologically papillary and follicular carcinomas.

Main cause of their formation is exposure to tobacco smoke and alcohol. Laryngeal cancer is the most common malignancy of this region. Another risk factor of HNSCC is HPV (human papilloma virus) infection, especially type 16 and, less frequently, type 18. Around 25% of squamous cell head and neck cancers contain DNA of the virus. Association between HPV infection and neoplasia is strongest in tonsil cancer, and weakest in cancers of larynx and oral cavity. HPV-associated HNSCC occur more often in non-smokers, heavy drinkers and people with immunodeficiency. They are often poorly differentiated and histologically show basal-cell structure [3, 4].

Surgery, chemotherapy and radiotherapy are still the standard for the treatment of HNC. Despite the great development of the various methods of treatment, survival of patients have not improved significantly over the last 30 years, with the overall, 5-year survival not exceeding 50% [2]. Progress in understanding the biology of cancer leads to personalization of therapy and introduction of drugs targeted at blocking defective metabolic pathways of cancer cells [5]. Targeted molecular therapies rely on repression of proliferation and neoangiogenesis, blocking the formation of metastases, and induction of apoptosis in cancer cells. What is more, drugs from this group act selectively, which reduces adverse effects of the therapy.

Monoclonal antibodies against epidermal growth factor receptor in the treatment of HNSCC

EGFR (epidermal growth factor receptor) belongs to HER family and consists of extracellular part, which binds ligand, transmembrane segment and intracellular domain with tyrosine kinase activity. Under physiological conditions EGFR is activated in the process of homo- or heterodimerization with other receptor from HER family: HER 2 (ErbB2), HER 3 or HER4. Formation of homo- or heterodimeric complexes depends on attaching a specific ligand: EGF (epidermal growth factor) or TGF-β (transforming growth factor). This process activates internal cascade of reactions leading to autophosphorilation of kinase and activation of proteins of the signaling pathway. That leads to cell stimulation and division [6, 7].

In cancer cells activation of EGFR is possible through additional mechanisms, independent from ligand binding, associated among others with overexpression of receptors leading to their spontaneous dimerization and presence of mutated, permanently active forms of the receptor. Main signal pathway leads through PI3K, Akt kinases and STAT3 protein or RAS, RAF, MAPK kinase (mitogen activated protein kinase) and ERK protein, causing activation of subsequent, specific transcription agents. That conducts the signal causing proliferation and inhibiting apoptosis of cancer cells [8, 9].

Overexpression of EGFR is linked with more aggressive tumor phenotype, tendency to form metastases, chemoresistance and worse prognosis [9, 10]. It is present in 80–90% of HNSCC, which makes EGFR a good target for molecular therapy [11, 12].

Cetuximab is the first chimeric, mouse-human monoclonal anti-EGFR antibody registered for treatment of HNSCC. It binds with extracellular domain of EGFR, competitively inhibiting binding with EGF and its dimerization, which leads to degradation of the receptor and blocking the proliferation signal. In consequence, cell growth is brought to a halt [11]. What is more, cetuximab induces apoptosis of cancer cells in ADCC (antibody-dependent cell-mediated cytotoxicity) mechanism with the participation of NK (natural killer) cells and activation of complement proteins and causes stimulation of dendritic cells with antigens from disintegrated neoplastic cells.

In treatment of head and neck cancers, cetuximab was first used according to FDA (Food and Drug Administration) guidelines in March 2006 in combination with irradiation in patients with stage III and IV HNSCC resistant to other kinds of treatment, and in monotherapy in patients with relapse or metastases (stage IV), with disease progression despite platin-based chemotherapy [13].

Phase III clinical trial EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer), which led to cetuximab approval for the treatment of HNSCC, involved comparing the effectiveness of chemotherapy based on cisplatin and 5-fluorouracil with or without cetuximab [14–16]. It was conducted on 442 patients with recurrent or metastatic HNSCC, of which 220 received an infusion of cetuximab on top of standard chemotherapy. Patients with stable disease after a maximum of 6 cycles of chemotherapy continued to receive cetuximab until progression or severe side effects. The combination of chemotherapy and cetuximab resulted in a significant increase in overall survival, and progression-free survival. The median duration of survival and progression-free survival in patients treated with cetuximab were respectively 10.1 months and 5.6 months, and in patients receiving standard chemotherapy: 7.4 months and 3.3 months. Thanks to cetuximab, objective response rate increased from 20% to 36%. Cetuximab administration has not increased the risk of severe haematological adverse effects, but was associated with skin rashes (very severe – CTC grade 3–4 – in 9% of patients) and increased risk of sepsis.

In another phase III trial Burtness and colleagues obtained similar results. They confirmed the superiority of chemotherapy in combination with cetuximab over standard platinum based chemotherapy. The study involved 117 patients with recurrent or metastatic HNSCC. Median progression-free survival was 4.2 months for patients receiving cisplatin with cetuximab and 2.7 months in patients treated with cisplatin in monotherapy. Median overall survival was also longer in the group treated with molecularly targeted therapy (9.2 months), while in the group receiving chemotherapy alone it did not
exceeded 8 months. 77% of patients treated with cetuximab had cutaneous adverse events [17].

Cetuximab is well-tolerated by most of the patients and does not significantly increase haematological adverse effects of the treatment [16, 17]. The combination treatment with chemotherapy did not significantly deteriorate patients’ quality of life [18]. Characteristic of the drug are cutaneous adverse reactions, mainly in the form of acne-like rash, but also dry and hypersensitive skin, or changes in the nails.

In phase III trial, Bonner et al. analyzed the effectiveness of radiotherapy supplemented with cetuximab. Two hundred and eleven patients with locally advanced HNSCC were treated with radiotherapy alone, while 213 patients with the same diagnosis additionally received cetuximab administered intravenously in the course of radiotherapy. The time to progression or relapse and overall survival amounted to 24.4 months and 49 months for patients treated with radiotherapy and cetuximab, and 14.9 months and 29.3 months for patients treated with radiotherapy alone. Additionally, the occurrence of rash during cetuximab treatment was associated with significant prolongation of overall survival. In the group of patients receiving cetuximab, 45.6% were still alive 5 years after starting therapy. However, in the control group only 36.4% of patients survived that long [19].

Radiotherapy in combination with cetuximab is an alternative to chemotherapy and should be particularly taken into account in patients who cannot tolerate cytotoxic therapy [20].

Sok et al. [21] used immunohistochemistry (IHC) and RT-PCR (reverse transcription polymerase chain reaction) to find different forms of EGFR – EGFRVIII – in the cells of head and neck tumors, which have a mutation (large deletion) in the gene for the extracellular domain of EGFR. This abnormality occurs also in other tumors, such as gliomas, ependymomas, non-small cell lung cancer, breast cancer and ovarian cancer [22–25]. EGFRVIII expression is specific to cancer cells, and is not present in normal human tissue. Presence of this form of the receptor is associated with high chemotherapic and radiotherapy resistance of tumors, and the lack of response to cetuximab therapy. EGFRVIII is suggested to be next target in the search for future molecular anticancer therapies [21].

However, currently the subject of intensive clinical trials is to evaluate the efficacy of different EGFR inhibitors. Zalutumumab is a human monoclonal anti-EGFR antibody. The results of the first randomized phase III trial in patients with advanced HNSCC after failure of chemotherapy are very encouraging. The median overall survival and median progression-free survival in patients treated with molecularly targeted monotherapy were respectively: 6.7 months and 9.9 weeks, whereas in the control group receiving methotrexate: 5.2 months and 8.4 weeks. Zalutumumab therapy was closely correlated with the appearance of cutaneous adverse effects, but has not intensified severe hematological adverse effects [26].

The Danish Head and Neck Cancer Group of researchers is currently preparing a phase III clinical trial, which will recruit approximately 600 patients with HNSCC that were not subjected to prior treatment. Aim of this study is to compare the effectiveness of treatment in patients receiving radiotherapy alone, and radiotherapy in combination with zalutumumab [27].

Panitumumab – another human monoclonal anti-EGFR antibody, is currently in phase II studies evaluating the effectiveness of: radiation therapy alone, radiation therapy in combination with cisplatin and radiotherapy in combination with panitumumab. Other phase III study compares the effectiveness of radiotherapy combined with cisplatin and radiotherapy combined with panitumumab in patients with locally advanced HNSCC [28].

### Small molecule EGFR tyrosine kinase inhibitors in the treatment of HNSCC

Reversible, small molecule tyrosine kinase inhibitors EGFR (TKI-EGFR), such as gefitinib or erlotinib, have limited efficacy in the treatment of HNSCC. Effects of treatment with gefitinib and methotrexate in patients with recurrent or metastatic HNSCC are comparable [29]. Response to gefitinib therapy occurs only in 1–11% of patients. The reason for this situation is an extremely rare occurrence of activating mutations in exons 18–21 of the EGFR gene in tumors of squamous histology, which warrant the constitutive efficiency of TKI-EGFR. Probably for the same reason lapatinib – a dual inhibitor of EGFR and ErbB2 tyrosine kinases – does not show efficacy in the treatment of head and neck cancer [30].

Eastern Cooperative Oncology Group is currently studying (E1302 trial) the efficacy of docetaxel in monotherapy and in combination with gefitinib in the first and second-line treatment of patients with recurrent and metastatic HNSCC [20].

Effectiveness of afatinib, which is an irreversible inhibitor of the tyrosine kinase of EGFR, HER2 and HER4, and is active in spite of the EGFRVIII mutation [31, 32], was compared to the efficacy of cetuximab monotherapy in 124 patients after failure of chemotherapy with platinum compounds [33]. Partial response to afatinib treatment occurred in 22% of patients, compared to 13% patient in cetuximab-treated group, while the average progression-free survival was respectively 16 and 10 weeks. This study demonstrated similar or even higher efficiency of afatinib compared to cetuximab in patients with HNSCC. There are two phase III trials currently in preparation – one of them is supposed to compare afatinib and methotrexate efficacy in patients resistant to cisplatin. Another study aims to examine the efficacy of the drug in the adjuvant therapy of HNSCC [34].

### Neangiogenesis inhibitors, multi-kinase inhibitors and proteasome inhibitors in the treatment of HNSCC

The process of angiogenesis is closely associated with tumor growth and metastases. The main role in its regulation is played by vascular endothelial growth factor (VEGF) and its receptor – VEGFR [35]. On the surface of pericytes and vascular smooth muscle cells there are additional receptors for platelet-derived growth factor (PDGFR) and fibroblast growth factor (FGFR). VEGF is the most important cytokine existing in five different isoforms A–E, which stimulate the migration and proliferation of endothelial cells, contributing to the formation
of new blood vessels [36]. It is providing a biomarker for tumor progression and formation of metastases to lymph nodes [20, 35].

There is no convincing evidence for the efficacy of bevacizumab, a monoclonal humanized antibody directed against VEGF, in the treatment of HNSCC. Despite an increase in response rates of up to 45% in patients with recurrent or metastatic disease treated with chemotherapy based on cisplatin, docetaxel, or 5-fluorouracil in combination with bevacizumab, this kind of therapy is burdened with significant additional adverse effects, especially bleeding and hemorrhage, hypertension, increased risk of thromboembolism and fluid retention [36].

The combination of bevacizumab and erlotinib in the case of HNSCC recurrence after first line chemotherapy results in objective response only in 14.6% of patients and prolongation of median survival to 7.1 months [37]. This therapy was well tolerated by patients, and the adverse effects were rash, diarrhea and weakness.

Sorafenib is an inhibitor of the intracellular domain of VEGFR, PDGFR and c-Kit, and blocks the signal transmission pathway for the proliferation of endothelial cells. Early results of sorafenib use are promising. In a small 26-person group of patients with metastatic HNSCC who were resistant to other kinds of therapy, 10 patients were able to achieve over 8-months of survival [38]. Another study using sorafenib is in progress. Other patients tested in monotherapy and in combination with chemotherapy in patients with advanced HNSCC include intedanib (PDGFR, VEGFR and FGFR kinase inhibitor), wandetanib (an inhibitor of EGFR and VEGFR kinase) and sunitinib (VEGFR, PDGFR, c-Kit, and Ret kinase inhibitor).

Another potential target for therapy in HNSCC is the Src kinase responsible for the phenomenon of cell proliferation and apoptosis, cell migration and angiogenesis. Src kinase activation may contribute to disease progression in the mechanism similar to activation of the pathway starting from the EGFR, by stimulating PI3K kinase and STAT transcription factor [39]. Excessive Src kinase activity was found in patients with resistance to cetuximab therapy. Blocking Src kinase may be crucial in restoring tumor cell sensitivity to the cetuximab [40].

Phase I clinical trials in patients with solid tumors including HNSCC involve dasatinib, which is an antagonist of kinases JAK2, STAT3, Src and also c-Kit, Bcr-Abl and PDGFR [41].

Second phase of clinical trials with bortezomib, a proteasome inhibitor, in patients with HNSCC was completed. The main role of proteasome in oncogenesis is associated with proteases, which are part of its structure. They play a key role in the degradation of proteins responsible for apoptosis. In patients with recurrent and metastatic HNSCC, bortezomib has obtained disease control in 50% of patients, which enabled to commence phase III trials [42].

Summary

The development of molecularly targeted therapy in squamous cell head and neck tumors is expressed through the exploration of ways to individualize cancer therapy. Great hopes for the future involve blocking proteasome function and the use of STAT3 transcription factor, abnormal proteins EGFRvIII, K-ras, H-ras and PTEN as a target for molecular therapy [21, 25, 43].

At the moment, the effectiveness of molecularly targeted therapy using monoclonal antibodies against EGFR have already been proved. Cetuximab was approved in patients with advanced and locally advanced HNSCC in combination with chemotherapy and radiotherapy, and there are promising results of phase III trials with zalutumumab and panitumumab. Although the reversible EGFR tyrosine kinase inhibitors do not show significant efficacy in the treatment of HNSCC, irreversible pan-HER tyrosine kinase inhibitors such as afatinib may soon find application in the treatment of this malignancy. Other molecularly targeted therapies, despite the initial demonstration of efficacy in patients with HNSCC, require further clinical trials.

Authors’ contributions/Wkład autorów

Conflict of interest/Konflikt interesu
None declared.

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