

HPV infections in head and neck cancers (HNSCC) – clinical course and efficiency of therapy

Zakażenie HPV a przebieg kliniczny i skuteczność terapii w nowotworach głowy i szyi (HNSCC)

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ABSTRACT

Head and neck cancers represent a heterogeneous group of neoplasms. Among them, the most frequently occurring is squamous cell carcinoma. Risk factors that can contribute to the development of head and neck cancers are smoking, high proof alcohol abuse and human papilloma virus (HPV) infection. Head and neck cancers may be divided into HPV positive and HPV negative. This division shows the different landscape of carcinogenesis, median age of onset, etiopathogenesis, clinical course and treatment efficiency. Head and neck squamous cell carcinoma (HNSCC), especially HPV positive, belongs to highly immunogenic cancers. Its development relates to HPV infection and host immune response, especially with T regulatory lymphocytes response. Programmed cell death protein-1 (PD-1), which shows immunosuppressive effect on host's immune system, takes part

in cancerogenesis. That favours carcinogenesis. The development of immuno-oncology and better understanding of HNSCC pathogenesis has contributed to developments in immunotherapy, a method of care which is used preferably in the treatment of advanced, refractory or relapsed cancers that did not respond to standard-of care cancer treatments – in the case of HNSCC it is surgical resection with possible radiochemotherapy or chemotherapy. The idea of immunotherapy is to remove tumor immunosuppressive effect and to boost host immune response to eliminate neoplasm.

This article shows a review of current knowledge and new methods of therapy concerned with HNSCC treatment, especially HPV positive HNSCC.

Keywords: head and neck cancer; human papilloma virus; immunotherapy; T lymphocytes; immunity.

ABSTRAKT

Nowotwory głowy i szyi stanowią heterogenną grupę chorób rozrostowych, spośród których najczęściej występuje rak płaskonabłonkowy. Czynniki mogące predysponować do rozwoju nowotworów głowy i szyi są: palenie papierosów, spożywanie alkoholu wysokoprocentowego, a także zakażenie ludzkim wirusem brodawczaka (*human papilloma virus* – HPV). Z tego powodu nowotwory głowy i szyi często dzieli się na HPV pozytywne i HPV negatywne. W zależności od statusu HPV obserwuje się różnice w medianie wieku zachorowania oraz w samym przebiegu klinicznym choroby i w odpowiedzi na stosowane leczenie. Rak płaskonabłonkowy głowy i szyi (*head and neck squamous cell carcinoma* – HNSCC), szczególnie HPV dodatni, należy do nowotworów, które są ściśle związane z układem immunologicznym. Jego rozwój związany jest z reakcjami pomiędzy wirusem HPV a limfocytami T regulatorowymi gospodarza. W karcynogenezie główną rolę odgrywa m.in. receptor programowanej śmierci-1

(*programmed cell death protein-1* – PD-1), którego pobudzenie wykazuje immunosupresyjne działanie na układ immunologiczny gospodarza, co sprzyja rozwojowi nowotworu. Rozwój immunoonkologii oraz poznanie i zrozumienie patogenezy nowotworów głowy i szyi przyczyniły się do opracowania metod terapii wykorzystujących składowe układu immunologicznego. Leczenie to stosowane jest głównie w zaawansowanych i nawrotowych nowotworach, które nie odpowiadają na standardowe procedury lecznicze. Immunoterapia ma na celu zniesienie immunosupresyjnego działania guza i zwiększenie aktywności limfocytów T gospodarza do zwalczania nowotworu.

W pracy przedstawiono przegląd obecnej wiedzy dotyczącej przebiegu klinicznego i odpowiedzi na leczenie w nowotworach głowy i szyi, które związane są z zakażeniem wirusem HPV.

Słowa kluczowe: nowotwory głowy i szyi; ludzki wirus brodawczaka; immunoterapia; limfocyty T; odporność.

INTRODUCTION

Head and neck cancers are a heterogeneous group of tumors with an origin in the oral cavity, nasal cavity, paranasal sinuses, pharynx and larynx. Squamous cell carcinoma is a histological type appearing most frequently but other cancer variants as

well as sarcomas and lymphomas can be present in this region. Head and neck squamous cell carcinoma (HNSCC) is characterized with a poor prognosis. Recurrent and metastatic disease is usually incurable, so newer more effective methods of treatment are being sought [1]. These diseases belong to neoplasms highly associated with the immune system. Patients suffering

from HNSCC have lower lymphocyte numbers in peripheral blood than healthy people, spontaneous apoptosis of cytotoxic T lymphocytes can be observed, and natural killer (NK) cells show limited activity in presenting antigen processes [2, 3, 4]. Tumor immunosuppressive effect and the amount of tumor infiltrating lymphocytes became a base for introducing immunotherapy for this malignancy [5]. This type of treatment is more effective in some groups of patients – greater complete response rate (CRR) and overall survival (OS) can be observed with less intensified adverse events in comparison with standard therapy [6, 7]. It is crucial for patients who have developed HNSCC with pathogenesis associated with human papilloma virus (HPV) infection – immunotherapy has the best efficacy in this group of patients.

EPIDEMIOLOGY

Head and neck squamous cell carcinoma is the sixth most frequently diagnosed malignancy in the world and over half a million of new cases are diagnosed every year [8]. Most tumors are localized in the oral cavity, nasopharynx, oropharynx and hypopharynx. Considering all the places of origin and clinical advancement stages, HNSCC is characterized with a 65.9% 5-year OS and 2.5 year median survival when treated [9]. Recently, a trend in reducing HNSCC connected with smoking and alcohol and increasing population with HNSCC connected with HPV infection is observed [10]. Human papilloma virus positive HNSCC in the global population is noted in 25–80% of cases [11]. These patients are younger; a typical HPV positive HNSCC patient is a 40–59 year old male of Caucasian origin, not smoking, with high socioeconomic status, having many sexual partners [12, 13]. Patients with this type of cancer do not abuse alcohol. Most frequently anatomical localization of HPV positive HNSCC is oropharynx, where 90% of cases are infected with HPV-16 [11, 13]. The International Agency for Research on Cancer classified HPV-16 as a Group 1 carcinogen (proven cancerogenic effect) of the oropharynx and oral cavity [14]. Beside HPV-16, HPV-18, 33 and 52 types are strongly associated with HNSCC, especially in the hypopharynx [15]. Human papilloma virus positive oral HNSCC patients show greater disease-free survival (DFS) and OS rate in comparison with HPV negative oral HNSCC (75% vs. 14% and 79 vs. 19% respectively) [16]. A difference in response to chemotherapy and chemoradiotherapy is observed depending on the HPV status in HNSCC of oropharynx. Chemotherapy response rates (RR) are higher in HPV positive patients – 82% vs. 55% in HPV negative patients. A similar phenomenon is observed when receiving chemoradiotherapy – 84% vs. 57% respectively [17].

ETIOPATHOGENESIS

Human papilloma virus is a DNA-virus belonging to the *Papillomaviridae* family and showing squamous epithelium tropism. By 2015, 202 of HPV types had been isolated [18]. They can be

distinguished into 2 groups depending on malignancy potential. High-risk group are: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. Low-risk group are: HPV-26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85 [11]. Low-risk types contribute to benign condylomata acuminata lesion development. High-risk types favour intraepithelial neoplasia which can develop into cancer. Among all cancers, 5% are tumors with high-risk type HPV infection.

In chronic HPV infection, E2 viral protein controls expression of 2 viral oncoproteins – E6 and E7. They are inhibitors of cancerogenesis suppressors – pRb and p53. In precancer lesions and cancers, the function of E2 is impaired which results in a greater E6 and E7 expression. Inhibiting pRb and p53 expression leads to destabilization of the cell cycle where proliferation, apoptosis and genetic stability is controlled, so epithelial lesions can occur [18].

IMMUNOTHERAPY

In recent years a lot of clinical studies focussed on monoclonal antibody therapy, so called immune checkpoint inhibitors. These antibodies are anti-programmed cell death protein-1 (PD-1) and anti-cytotoxic T-cell antigen 4 (CTLA-4). The first drug which showed an immune checkpoint inhibitor effect was registered by the Food and Drug Administration (FDA) as cetuximab. It is a monoclonal antibody which binds to the extracellular domain of epithelial growth factor receptor (EGFR) and disables its activation. Head and neck squamous cell carcinoma is characterized with EGFR overexpression and its cancerogenesis is stimulated by amphiregulin and tumor necrosis factor α which stimulate EGFR [5]. Despite EGFR overexpression being rather typical in HPV negative HNSCC, in HPV positive HNSCC EGFR pathologic signalling is observed due to viral oncoproteins effect [19]. Cetuximab treatment is indicated in metastatic/recurrent HNSCC when failure after platinum-based therapy is observed [20]. Currently, RTOG 1016 study is performed where authors are comparing cetuximab vs. cisplatin + radiotherapy in HPV-related HNSCC – results are in progress [21].

Pembrolizumab is an anti-PD-1 agent which binds to PD-1 and reduces its activity. Programmed cell death protein-1 is a protein which takes part in reducing T lymphocyte activity and this mechanism is secure from immune system auto-aggression. In cancerogenesis PD-1 action leads to a repeal of immunological surveillance. Head and neck squamous cell carcinoma cells can use PD-1 and CTLA-4 to progress. The KEYNOTE-012 study considered HNSCC patients HPV status. This study explored pembrolizumab safety and efficacy in metastatic/recurrent disease. The 28 HPV positive and 104 HPV negative patients were recruited. Overall response rate (ORR) was 32% in HPV positive patients and 14% in HPV negative patients. The 6-month progression free survival (PFS) was 37% in HPV positive group and 20% in HPV negative group, 6-month OS noted as 70% in patients infected with HPV and 56% in patients whose cancer was not connected with HPV infection [22].

Nivolumab is an anti-PD-1 antibody. Based on the results of the CheckMate 141 study, in which HNSCC treatment with

nivolumab was compared with cetuximab/methotrexate/docetaxel chemotherapy, the FDA approved nivolumab in recurrent/metastatic HNSCC disease in the group of patients who had previously received platinum-based chemotherapy. The study results suggest that patients treated with nivolumab have better median OS outcome (7.5 months) than patients treated with cetuximab/methotrexate/docetaxel (5.1 months). Nevertheless, the authors did not consider patient HPV status and its influence on the studied results [23]. In another study, 29 patients not-pretreated with HNSCC of the oropharynx, hypopharynx or larynx received 240 mg of nivolumab twice before surgical resection. The study population included 12 HPV positive and 17 HPV negative patients. Two HPV positive patients experienced treatment related adverse events graded 3–4: higher lipase concentration and glossodynia. Adverse effect was observed also in 2 HPV negative patients: higher lipase concentration. The treatment related adverse effects did not delay surgery. After the operation, tumor reduction was assessed in 11/23 patients: 5/10 patients from the HPV positive group and 6/13 from the HPV negative group [24]. Currently, the CheckMate 358 (NCT02488759) study is in progress – it will evaluate nivolumab (and nivolumab + ipilimumab + daratumumab + BMS-986016) safety and efficacy in the treatment of HPV positive and negative HNSCC.

Currently, the KESTREL (NCT02551159) study results are being developed. The study focused on treatment with durvalumab (anti-PD-1 agent) + tremelimumab (anti-CTLA-4) vs. EXTREME chemotherapy (carboplatinum or cisplatinum + 5-fluorouracil + cetuximab).

VACCINES

Human papilloma virus viruses, mainly HPV-16 and HPV-18, are responsible for about 70% of cervical cancer diagnoses, one of most frequently occurring female cancers [25, 26]. In 2006, the first vaccinations against HPV-16 and HPV-18 appeared. Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and Gardasil® (Merck & Co., Whitehouse Station, NJ USA) were used. They contain virus-like particles L1 [27]. Gardasil® is a tetravalent vaccine against HPV-6, -11, -16 and 18, while Cervarix® is a bivalent vaccine against HPV-16 and 18 infections. The PATRICIA study showed a 93.2% efficacy of the bivalent vaccine in the prevention of intraepithelial cervical neoplasia grade III (CIN III) and almost a 100% efficacy in the prevention of occurring *carcinoma in situ* [27]. In the FUTURE II study 95% efficacy of tetravalent vaccine in the prevention of CIN II, CIN III and *carcinoma in situ* was revealed [28]. Since 2014, the World Health Organisation began to recommend the vaccination of young women before first sexual intercourse, in 2 dose schemes [29]. Results of a recent performer randomized trial seem to support this recommendation [30]. The authors of the trial mention that in every group of vaccinated patients, post-vaccination anti-HPV-16 and anti-HPV-18 titre were higher than titre in women infected with HPV.

Currently, there is no data to assess the efficiency of HNSCC prevention through performing vaccinations against HPV. It should be emphasized that such a prevention would be reasonable in a group of people who had never been exposed to HPV, mainly through sexual intercourse. Nevertheless, some data suggest that Gardasil® effectiveness is about 67% in 24–45 year old women with anti-HPV antibodies present, but no virus genetic material in blood samples [31]. The need to create such studies is expressed in 95% of HPV positive tonsil cancers and oropharynx cancers where HPV-16 and HPV-18 is detected [32].

Currently, the role of therapeutic cancer vaccines, a method of immunotherapy, is being investigated [5, 33, 34]. We are still waiting for the results from a study assessing therapeutic cancer vaccines in the treatment of HPV associated HNSCC (NCT00019110).

RADIOIMMUNOTHERAPY

The HPV-16 is detected in 90% of HPV positive HNSCC. Recently, a new therapeutic approach has been proposed. With radioactive marked monoclonal antibodies, viral antigens on cancer cells can be localized, providing a specific treatment. Such an approach in HPV positive HNSCC therapy has been widened and has resulted in the development of radioimmunotherapy targeted against E6 and E7 oncogenes. Radioactive marked antibodies bind to extracellular E6 and E7 resulting in providing radiation into the cancer cells region. Live cancer cells, cells which show little expression of E6 and E7 and healthy cells are induced into apoptosis as a result of such a cross-reaction.

CHEMOTHERAPY

One of the most frequently used cytostatics in HNSCC therapy is cisplatinum [35]. Studies results show that patients with HPV positive HNSCC show a greater treatment response than HPV negative HNSCC patients when treated with chemotherapy based on cisplatinum. However, such a therapy is related to many adverse events, including renal failure, dysphagia and polyneuropathy [36]. Other commonly used chemotherapeutics are 5-fluorouracil and docetaxel. In the EORTC 24971 study, docetaxel + cisplatinum + 5-fluorouracil (TPF) vs. cisplatinum/5-fluorouracil (PF) chemotherapies were compared in the treatment of locally advanced, nonresectable, HPV positive and negative HNSCC. Progression free survival and OS were measured. Non statistically significant differences were observed between HPV positive and HPV negative HNSCC patients. They also did not gain benefits when docetaxel was added into the PF chemotherapy regimen [37].

DISCUSSION

Young, sexually active patients are predisposed to HPV infection. With the increasing rates of risky sexual intercourses,

exposure and infection probability are getting higher and then cancer development as well. Human papilloma virus shows tropism to cervical and head and neck epithelium. The prevention method is vaccination – it reduces the high risk of cervical cancer. Because of a lack of data to assess vaccinations against HPV in the prevention of HNSCC, its role is still unsure – both in females and males. Human papilloma virus exerts an immunosuppressive effect on the immune system which favours cancerogenesis, and is simultaneously a target for immunotherapy which is highly effective in HPV positive HNSCC patients – better survival and response rates with a minimum of adverse effects is achieved. Still, new methods and targets for therapy are being sought to improve the clinical course of the disease. On the grounds of prognostic and predictive HPV infection in HNSCC, viral biomarkers in histopathological material are proposed to be detected. It seems that the coincidence of HPV infection and HNSCC is an interesting subject that demands additional studies. From a clinical point of view, knowledge of HPV status in HNSCC patient can result in better benefits because better treatment can be provided. It is highly recommended in patients with advanced disease when surgical treatment cannot be proposed and in the group of patients with recurrent and progressive disease.

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