Diagnostics of HNSCC Patients

Subjects: Medical Laboratory Technology

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Head and neck squamous cell carcinomas (HNSCC) are very frequent worldwide, and smoking and chronic alcohol use are recognized as the main risk factors. For oropharyngeal cancers, HPV 16 infection is known to be a risk factor as well. By employing next-generation sequencing, both HPV-positive and negative HNSCC patients were detected as positive for PI3K mutation, which was considered an optimal molecular target. The treatment of HNSCC includes surgery, chemotherapy, and radiotherapy alone or combined. In some cases, resistance to therapy with recurrences and metastasis and/or side effects appear. This underlines the need for a new direction of research for targeted cancer therapy.

Keywords: HNSCC ; HPV ; PI3K ; cell lines ; patient-derived xenograft models

1. Introduction

HNSCC represents a heterogenous group of tumors, including cancer of the oropharynx, oral cavity, pharynx, and larynx. The recognized risk factors for HNSCC are smoking, chronic alcohol use, lack of oral hygiene, and HPV 16 in oropharyngeal cancers. Recent meta-analyses have confirmed smoking as a risk factor for HNSCC: Alotaibi et al. found that smoking is a negative prognostic factor for overall survival in patients with hr-HPV$^+$ [1], and Ference et al. found that current smoking during treatment is associated with the greatest reduction in survival [2]. Interestingly, Skoulakis et al. found in their meta-analysis that smoking is less common in HPV-positive groups than in HPV-negative groups [3]. The role of HPV in HNSCC was confirmed by a meta-analysis which included 148 studies and 12,163 cases of HNSCC from 44 countries, and the authors found HPV16 was present in more than 80% of all HPV DNA-positive cases [4]. Updated information regarding incidence, prevalence and mortality are available on the Cancer Today website by the International Agency for Research on Cancer (IARC). The estimated age-standardized incidence rates, in 2020, for lip, oral cavity, oropharynx, nasopharynx, hypopharynx cancers, both sexes, all ages, were 7.4 in USA, 12.7 in France, 12.9 in Romania, 6.5 in Brazil, 4.8 in China, 9.0 in Namibia and 9.8 in Australia [5]. The estimated numbers of prevalent cases (5-year) as a proportion in 2020 for hypopharynx, lip, oral cavity, nasopharynx, and oropharynx (both sexes, all ages) were 39.2 in USA, 65.9 in France, 59.6 in Romania, 20.6 in Brazil, 20.1 in China, 12.0 in Namibia and 51.0 in Australia [6]. The estimated age-standardized mortality rates (World) in 2020 for hypopharynx, lip, oral cavity, nasopharynx, and oropharynx (both sexes) all ages were 1.4 in USA, 3.0 in France, 6.7 in Romania, 3.2 in Brazil, 2.5 in China, 5.5 in Namibia and 1.6 in Australia [7].

CANCER TOMORROW, another project of IARC, enables a quantification of the future cancer burden changes of new cases from 2020 to 2040, both sexes, all continents, age (0–85+): hypopharynx 46.9%, lip, oral cavity 41.7%, nasopharynx 37.3%, oropharynx 35.5%. For Romania, the highest changes of new cases from 2020 to 2040, both sexes, age (0–85+) are predicted to be for lip, oral cavity (6.7%) and hypopharynx (2.8%) [8].

A recent multicenter study concluded that in some populations in the United States, more than 90% of OPSCCs are produced by HPV [9]. The updated data available on the International Agency for Research on Cancer (IARC) Cancer Today website underline the importance of this health issue and raise some questions regarding the risk factors for developing different types of head and neck squamous cell carcinoma (HNSCC), depending on age and gender. HPV 16 was recognized as a risk factor for oropharyngeal cancers, besides smoking and chronic alcohol use [10]. In a recent meta-analysis, Mariz Bala et al. analyzed the data of more than 6000 patients to reveal accurate information about the global prevalence of human papillomavirus (HPV) in oropharyngeal squamous cell carcinomas (OPSCC). Compared to the overall HNSCC prevalence, which is different for male and females, the authors identified a similar 45% pooled prevalence of HPV-driven OPSCC, for both genders, and they also suggested that double p16/HPV-DNA/RNA testing is the optimal method in regard to specificity and prognostic accuracy [11].

The treatment of HNSCC includes surgery, chemotherapy, and radiotherapy alone or combined. In some cases, resistance to therapy with recurrences and metastasis and/or side effects appear. This underlines the need for a new direction of research for targeted cancer therapy. Phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway components are key therapeutic targets in cancer, immunity, and thrombosis. In normal cells, the PI3K/mTOR pathway has regulatory roles in cell survival, proliferation, and differentiation. However, aberrant variants of activation of this pathway frequently occur in human cancers [12]. PI3K is believed to be one of the key therapeutic targets for cancer treatment, based on the observation that hyperactivity of PI3K signaling is significantly correlated with human tumoral progression, an increase in tumor micro vessel density and enhanced chemotaxis and invasive potential of cancer cells. Enormous efforts have been dedicated to the development of drugs targeting PI3K signaling, many of which are currently employed in clinical trials evaluation. PI3K inhibitors are subdivided into dual PI3K/mTOR inhibitors, pan-PI3K inhibitors and isoform-specific inhibitors [13].

The most used inhibitors in the treatment of solid tumors are the pan-PI3Kis (Buparlisib—BKM120; Pictilisib—GDC-0941 and Copanlisib—BAY 80-6946), which target each of the four catalytic isoforms of class I PI3K; therefore, they have the potential for broad activity in several tumors types, with a range of different molecular alterations. However, such broad inhibition of this molecular pathway may lead to a potentially higher risk of adverse events, which could limit the use of such agents in therapeutic doses. BEZ235 is a potent, oral, ATP-competitive dual inhibitor of the four class I PI3K isoforms and the downstream effectors mTORC1/2. Alpelisib—BYL719 isoform-specific PI3Kis have the narrowest profile and may require careful patients' selection based on potential biomarkers of sensitivity and resistance [12].

The novelty of these targeted therapies meant that besides having the promise of potentially serving as new treatment strategies, several lessons had to be learned from early studies. The findings to date suggest that PIK3CA and PTEN alterations are relatively weak biomarkers of clinical activity. However, PIK3CA mutations appear to be more promising as predictive factors for p110a catalytic isoform-specific inhibitors, with PTEN alterations possibly associated with resistance. Secondly, it is increasingly evident that single-agent targeting of the PI3K pathway has limited activity. Therefore, the identification of appropriate biomarkers of efficacy and the development of optimal combination therapies and dosing schedules for PI3Kis are likely to be required for the broad acceptance of this class of compounds in clinical practice [13].

The acquired amplification and mutation of PIK3CA and PIK3CB, which resulted in a marked upregulation of the PI3K signaling itself, has been shown to cause resistance to selective PI3K inhibitors [12].

Overall, PI3K inhibition is being investigated as a potential strategy to develop novel therapeutics for cancer management. Although different researchers are moving forward with the clinical development of PI3K inhibitors, maximizing the utility of these agents in the treatment of cancer patients remains challenging. Certainly, understanding the precise mechanisms of PI3K signaling and PI3K inhibition will be critical. Optimization of the patient selection strategies and combination approaches will help increase the practical efficacy of these agents. Continued work to clarify the resistance mechanisms and the novel strategies to overcome resistance will also be important [12].

2. HNSCC Patients PI3K Inhibitors Clinical Trials

Over the last 5 years, five clinical trials were published (three from the USA, one from Canada and one from France), which evaluated the PI3K targeted therapy in recurrent or metastatic HNSCC patients, heavily pre-treated HNSCC patients, or locoregionally advanced SCCHN (LA-SCCHN) patients.

Chronologically, the clinical trials analyzed the synergistic effects of the combination of temsirolimus with low-dose weekly carboplatin and paclitaxel [14]; assessed the maximum tolerated dose (MTD) of the PI3K inhibitor buparlisib given concurrently with cetuximab [15]; evaluated the addition of BYL719 to cetuximab and radiation [16]; and assessed the effects of alpelisib, a class I α-specific PI3K inhibitor in combination with concurrent cisplatin-based chemoradiation [17] and a combination of copanlisib, an intravenous, pan-class I PI3K inhibitor, with the anti-EGFR monoclonal antibody cetuximab [18]. Tumor regressions and benefit from the given PI3K therapy was reported for combining mTORC1 inhibitors with carboplatin and paclitaxel chemotherapy, buparlisib at 100 mg daily plus cetuximab, BYL719 associated with cetuximab and radiation, Alpelisib in combination with cisplatin-based CRT (where the three-year overall survival was 77.8%), and Axitinib, a potent inhibitor of vascular endothelial growth factor receptor [14][15][16][17][19]. The most recent trial [18] studied the novel drug copanlisib combined with cetuximab and demonstrated unfavorable toxicity and limited efficacy, and the trial was stopped earlier than initially planned.

It is more than obvious that nowadays, there is a growing amount of important research and discoveries in the field of developing specific inhibitors and in the field of technology for assessing the efficiency of these cell lines treatment with

specific inhibitors. At the same time, medical specialties develop practices separately from other specialties, sometimes without taking into consideration the discoveries of other medical fields. The results obtained from laboratory should be transmitted and applied in clinical practice for the optimization of the cancer patients' follow-up. For example, it would be necessary to know the cytotoxic effect needed for each patient. With selected antibiotics, it is possible to determine the lowest dose of antibiotic needed to kill a bacterium. Researchers might try to come up with a similar approach for tumor target therapy, as for the moment, it is not sure if oncologists measure the levels of anti-tumoral drugs, while the oncologic patients continue therapy despite moderate side effects. For example, patients could have to tolerate pneumonitis and leg edema from high doses of everolimus. One needs uninterrupted, high levels of a certain drug when using prolonged therapy (antibiotic or likely anticancer); resistance develops with stops/starts or lower doses. Another important aspect to be taken into consideration is if the absorption of oral drugs may be affected by food intake. To delay or avoid resistance, researchers might have to use a combination of multiple drugs that attack the same target in a similar matter to how researchers avoid resistance when administering antibiotics, by combining two drugs that act on the same target, e.g., the cell wall. By looking at how other medical specialties deal with similar negative outcomes, such as resistance and establishing minimum effective doses, researchers may develop better strategies for the treatment of cancer patients [20].

References

1. Alotaibi, M.; Valova, V.; Hänsel, T.; Stromberger, C.; Kofla, G.; Olze, H.; Piwonski, I.; Albers, A.; Ochsenreither, S.; Coordes, A. Impact of Smoking on the Survival of Patients with High-Risk HPV-Positive HNSCC: A Meta-Analysis. In Vivo 2021, 35, 1017–1026.
2. Ference, R.; Liao, D.; Gao, Q.; Mehta, V. Impact of Smoking on Survival Outcomes in HPV-Related Oropharyngeal Carcinoma: A Meta-Analysis. Otolaryngol. Head Neck Surg. 2020, 163, 1114–1122.
3. Skoulakis, A.; Tsea, M.; Koltsidopoulos, P.; Lachanas, V.; Hajiioannou, J.; Petinaki, E.; Bizakis, J.; Skoulakis, C. Do Smoking and Human Papilloma Virus Have a Synergistic Role in the Development of Head and Neck Cancer? A Systematic Review and Meta-Analysis. J. BUON 2020, 25, 1107–1115.
4. Ndiaye, C.; Mena, M.; Alemany, L.; Arbyn, M.; Castellsagué, X.; Laporte, L.; Bosch, F.X.; de Sanjosé, S.; Trottier, H. HPV DNA, E6/E7 MRNA, and P16INK4a Detection in Head and Neck Cancers: A Systematic Review and Meta-Analysis. Lancet Oncol. 2014, 15, 1319–1331.
5. Ferlay, J.; Ervik, M.; Lam, F.; Colombet, M.; Mery, L.; Piñeros, M.; Znaor, A.; Soerjomataram, I.; Bray, F. Global Cancer Observatory: Cancer Today. Available online: http://gco.iarc.fr/today/home (accessed on 20 March 2022).
6. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin. 2021, 71, 209–249.
7. Ferlay, J.; Colombet, M.; Soerjomataram, I.; Parkin, D.M.; Piñeros, M.; Znaor, A.; Bray, F. Cancer Statistics for the Year 2020: An Overview. Int. J. Cancer 2021, 149, 778–789.
8. Ferlay, J.; Laversanne, M.; Ervik, M.; Lam, F.; Colombet, M.; Mery, L.; Piñeros, M.; Znaor, A.; Soerjomataram, I.; Bray, F. Global Cancer Observatory: Cancer Tomorrow. Available online: https://gco.iarc.fr/tomorrow/en (accessed on 15 April 2022).
9. Scott-Wittenborn, N.; D'Souza, G.; Tewari, S.; Rooper, L.; Troy, T.; Drake, V.; Bigelow, E.O.; Windon, M.J.; Ryan, W.R.; Ha, P.K.; et al. Prevalence of Human Papillomavirus in Head and Neck Cancers at Tertiary Care Centers in the United States over Time. Cancer 2022, 128, 1767–1774.
10. IARC monograph on the evaluation of carcinogenetic risks to humans; v. 100B. In A Review of Human Carcinogens: Biological Agents; International Agency for Research on Cancer (Ed.) IARC Monographs of the Evaluation of Carcinogenic Risks to Humans; IARC: Lyon, France, 2012; ISBN 978-92-832-1319-2.
11. Mariz, B.A.L.A.; Kowalski, L.P.; William, W.N.; de Castro, G.; Chaves, A.L.F.; Santos, M.; de Oliveira, T.B.; Araújo, A.L.D.; Normando, A.G.C.; Ribeiro, A.C.P.; et al. Global Prevalence of Human Papillomavirus-Driven Oropharyngeal Squamous Cell Carcinoma Following the ASCO Guidelines: A Systematic Review and Meta-Analysis. Crit. Rev. Oncol. Hematol. 2020, 156, 103116.
12. Janku, F. Phosphoinositide 3-Kinase (PI3K) Pathway Inhibitors in Solid Tumors: From Laboratory to Patients. Cancer Treat. Rev. 2017, 59, 93–101.
13. Yang, J.; Nie, J.; Ma, X.; Wei, Y.; Peng, Y.; Wei, X. Targeting PI3K in Cancer: Mechanisms and Advances in Clinical Trials. Mol. Cancer 2019, 18, 26.

14. Dunn, L.A.; Fury, M.G.; Xiao, H.; Baxi, S.S.; Sherman, E.J.; Korte, S.; Pfister, C.; Haque, S.; Katabi, N.; Ho, A.L.; et al. A Phase II Study of Temsirolimus Added to Low-Dose Weekly Carboplatin and Paclitaxel for Patients with Recurrent and/or Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC). Ann. Oncol. 2017, 28, 2533–2538.
15. Brisson, R.J.; Kochanny, S.; Arshad, S.; Dekker, A.; DeSouza, J.A.; Saloura, V.; Vokes, E.E.; Seiwert, T.Y. A Pilot Study of the Pan-Class I PI3K Inhibitor Buparlisib in Combination with Cetuximab in Patients with Recurrent or Metastatic Head and Neck Cancer. Head Neck 2019, 41, 3842–3849.
16. Dunn, L.A.; Riaz, N.; Fury, M.G.; McBride, S.M.; Michel, L.; Lee, N.Y.; Sherman, E.J.; Baxi, S.S.; Haque, S.S.; Katabi, N.; et al. A Phase 1b Study of Cetuximab and BYL719 (Alpelisib) Concurrent with Intensity Modulated Radiation Therapy in Stage III-IVB Head and Neck Squamous Cell Carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 2020, 106, 564–570.
17. Day, D.; Prawira, A.; Spreafico, A.; Waldron, J.; Karithanam, R.; Giuliani, M.; Weinreb, I.; Kim, J.; Cho, J.; Hope, A.; et al. Phase I Trial of Alpelisib in Combination with Concurrent Cisplatin-Based Chemoradiotherapy in Patients with Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck. Oral Oncol. 2020, 108, 104753.
18. Marret, G.; Isambert, N.; Rezai, K.; Gal, J.; Saada-Bouzid, E.; Rolland, F.; Chausson, M.; Borcoman, E.; Alt, M.; Klijanienko, J.; et al. Phase I Trial of Copanlisib, a Selective PI3K Inhibitor, in Combination with Cetuximab in Patients with Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma. Investig. New Drugs 2021, 39, 1641–1648.
19. Swiecicki, P.L.; Bellile, E.L.; Brummel, C.V.; Brenner, J.C.; Worden, F.P. Efficacy of Axitinib in Metastatic Head and Neck Cancer with Novel Radiographic Response Criteria. Cancer 2021, 127, 219–228.
20. Schmid, G. An Infectious Diseases Specialist NET Patient Looks at Management of NETs. In Proceedings of the 17th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease, Barcelona, Spain, 11–13 March 2020.
