Capecitabine in Head and Neck Cancers

Subjects: Oncology

Contributor: Camil Ciprian Mireștean , Roxana Irina Iancu , Dragoș Petru Teodor Iancu

Head and neck cancers (HNCs) are the sixth most common malignancies in the world, with more than 500,000 new cases occurring each year. Capecitabine, an oral pro-drug that is metabolized to 5-FU, the use of capecitabine has been evaluated in many trials including cases diagnosed in recurrent or metastatic settings. Induction regimens or a combination with radiation therapy were evaluated in head and neck cancers, but 5-FU still remained the fluoropyrimidine used as a part of the current therapeutic standard.

HNSCC HNC head and neck cancers capecitabine

1. Introduction

Head and neck cancers (HNCs) are the sixth most common malignancies in the world, with more than 500,000 new cases occurring each year. Some 90% of all these cancers are squamous cell carcinomas. Even though a multimodal approach with combining treatment methods (surgery, chemotherapy and radiotherapy) is considered optimal, the recurrence rate of 30–50% justifies efforts to identify new therapeutic strategies to improve the HNC prognosis. Chemotherapy brings therapeutic benefits, its role being essential, especially in the locally advanced, recurrent or metastatic disease stages. The administration of less toxic but highly effective chemotherapy regimens is a current concern, although modern therapies such as immune checkpoint inhibitors and monoclonal antibodies have entered the therapeutic arsenal of HNC [1][2].

2. Capecitabine–More Than 20 Years of Clinical Experience in Different Cancer Types

Used for several decades in therapeutic protocols for gastrointestinal cancers, breast cancer, urinary tract cancers and head and neck cancers, 5-fluoruracil has several disadvantages (reduced bioactivity time in bolus administration) and the necessity to be associated with other chemotherapy agents. This treatment also often requires frequent visits to the hospital, a continuous infusion being given for 5 days, most often through an infusion pump connected through a central venous catheter (CVC). Moreover, the protocol leads to infusion-treatment-related toxicities such as myelo-suppression, gastrointestinal toxicity, the need for dose adjustment, deterioration in quality of life and increased risk of hospital admission. In this context, an oral analogue of 5-fluorouracil is becoming a topic of interest [3][4][5].

Capecitabine is a fluoropyrimidine–carbamate, being included in the therapeutic protocol of metastatic breast cancer and colorectal cancer in combination with other agents or in concurrent treatment with radiotherapy. The

principle behind the replacement of fluorouracil with capecitabine focuses on the transformation by enzymes in tumors of this oral pro-drug in 5-FU. Thymidine phosphorylase (TP) is identified in higher amounts at the tumor level; thus the conversion of capecitabine to 5-fluorouracil occurs mainly at the tumor level, resulting in a low concentration of the agent in plasma or normal tissues. In normal and tumor cells, fluorouracil is metabolized by 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP) and 5-fluorouridine tri-phosphate (FUTP). FdUMP is involved in blocking the synthesis of a thymidine triphosphate promoter, with the final consequence of blocking the DNA site. Thus, the reduction of FdUMP levels has the inhibition of cell division as a direct consequence. FUTP can be replaced by uridine tri-phosphate (UTP) during RNA synthesis, resulting in fraudulent RNA [6][7].

3. Capecitabine in Head and Neck Cancers—A 5-FU Equivalent Substitute?

With a net benefit of 8% compared to concurrent chemotherapy, chemo–radiation has become a therapeutic standard in locally advanced HNC cases. However, for bulky disease, induction chemotherapy followed by concurrent chemo–radiation is an option often chosen by clinicians, although data on induction chemotherapy are still controversial. The Department of Veterans Affairs Laryngeal Cancer Study Group has since 1991 offered the option of induction chemotherapy followed by radiation therapy as a variant comparable to surgery in its clinical result but with the possibility of preserving the organ in advanced laryngeal cancer. A triple combination in the TPF regimen (docetaxel, cisplatin, 5-fluorouracil) is considered the standard induction regimen, demonstrating benefits over monotherapy or over platinum doublet. However, the TPF regimen is associated with high rates of toxicity, with 31% of patients having quality of life (QOL) affected but an 86% overall response rate and a 3-year survival rate of 65.1%, justifying the use of this regimen in clinical practice. The mTPF is a modified regimen with a favorable toxicity profile, being usable in patients aged >70 years but not eligible for the standard regimen. Therapeutic regimens including platinum salts, 5-fluorouracil and taxanes are among the therapeutic options in recurrent or metastatic disease. EXTREME regimen (fluorouracil/platinum/cetuximab) combines a monoclonal antibodies with chemotherapy. Until first-line immunotherapy was validated as a standard regimen, it was considered the optimal treatment for this category of patients [8][9][10][11][12].

The Phase III study by Custem and collaborators evaluated both the efficacy and toxicity profile of capecitabine in metastatic colorectal cancer, comparing the results with those obtained in a group of patients treated with the standard intravenous fluorouracil/leucovorin protocol (IV 5-FU/LV). Oral capecitabine has been associated with at least equivalent results. The overall toxicity profile was also favorable, with capecitabine being associated with lower grade three-fourths stomatitis and neutropenia, a reduced risk of febrile neutropenia, but an increased incidence of hand–foot syndrome compared to the standard protocol [13].

A Phase II study evaluated the efficacy and tolerability of 1,250 mg/m^2 of capecitabine twice a day as palliative monotherapy for 1–14 days every 21 days for recurrent or metastatic HNC previously treated with platinum salts. The protocol provides for the administration of at least two cycles, and the overall response rate was 24.2%. The toxicity rate was a maximum of 12.5% (asthenia), 10% for dysphagia, erythrodysesthesia mucositis and 7.5% for diarrhea. The results advocated the inclusion of capecitabine in the palliative treatment of HNC previously treated

with platinum salts. Capecitabine monotherapy has shown benefit in recurrent/metastatic nasopharyngeal carcinoma (NPC), according to a study that included 49 patients, 48 of whom were previously treated with platinum-based chemotherapy. With a median follow-up of 10 months, overall survival (OS) at one and two years was 54% and 26%, respectively, and patients who were treated for local–regional recurrences as well as those with hand–foot syndrome had better OS. Péron et al. demonstrated the benefit and feasibility of treatment with capecitabine, and in heavily pretreated frail HNC patients, fatigue, mucositis and hand–foot syndrome were the most commonly reported toxicities [14][15][16].

Won and colleagues in a Phase II study evaluated the efficacy and toxicity of chemotherapy combined with capecitabine and cisplatin (capecitabine 1250 mg/m^2 twice daily for the first 14 days of a 3-week repeat cycle and cisplatin 60 mg/m^2 IV day 1) in recurrent or metastatic cases of head and neck squamous cell carcinoma (HNSCC). With an overall survival at 1 year and a survival rate of 10.3 months, respectively, 43.3% of the reported acute grade 3 or 4 toxicities included neutropenia (14.6%), anemia (1.5%), fatigue (4.4%), anorexia (8.8%), diarrhea (4.4%), stomatitis (3.6%) and hand syndrome (1.5%). Moreover, the study did not report toxic deaths related to treatment, and the authors consider the regimen acceptable as a toxicity profile and with a satisfactory therapeutic response [17].

Patients diagnosed with metastatic oropharyngeal cancers associated with human papilloma virus (HPV-OPC) infection have a median overall survival (OS) of over 2 years, being considered eligible to receive multiple palliative therapies. The increased chemosensitivity of this particular subclass of head and neck cancers justifies the proposal by Fazer and colleagues to use capecitabine with possible benefits for heavily pretreated HPV-OPC patients. The average duration of treatment with capecitabine was 9 months in a small group of seven patients, four of them having a partial response, one case showing stationary disease and two patients being diagnosed with progressive disease. It is worth mentioning one case that continued chemotherapy with capecitabine 33 months after the initiation of treatment. The patient selection group was heterogeneous both in terms of initial treatment and metastatic sites. Among the palliative treatments, there are radiotherapy and ablation of liver metastases, but also biological therapy with cetuximab, immunotherapy with nivolumab and pembrolizumab, as well as multiple chemotherapy protocols including agents such as cisplatin, gemcitabine and pemetrexed. An average time from the diagnosis of metastatic disease to initiation of treatment with capecitabine of 21 months and a median treatment of 9 months with capecitabine-based chemotherapy discontinued for reasons of toxicity or disease progression justifies the authors' proposal of using capecitabine in heavily pretreated metastatic HPV-OPC cases [18][19].

Capecitabine in combination with lapatib has also demonstrated equivalence with the EXTREME regimen in the first line of treatment for metastatic head and neck cancer, other than nasopharyngeal carcinoma, evaluated in patients having an ECOG performance index of 0 to 2, the toxicity profile of the combination being considered favorable. A capecitabine dose of 1000 mg/m^2) twice daily and lapatinib at a dose of 1250 mg daily with an administration of capecitabine for 14 days of each 21-day protocol included four cycles of chemotherapy associating lapatinib daily until disease progression [20].

Histone deacetylase-inhibitor vorinostat was tested in combination with capecitabine in head and neck cancers, considering the in vivo and in vitro data supporting the activity of vorinostat in combination with deoxy-5-fluorouridine (5′-DFUR) and the potential of vorinostat to upregulate TP. The synergistic antiproliferative result of capecitabine and vorinostat justifies the proposal of Di Gennaro and collaborators to implement clinical trials to support this treatment, the hypothesis formulated more than 10 years ago. Wisniewska-Jarosinska et al. mentioned both an effect of free radicals and an increase in the G0/G1 cell population and reduction of the populations in the S phase as factors that support the cyto- and genotoxic effects in head and neck cancer cells and the protection of healthy cells associated with chemotherapy based on capecitabine [21][22].

Evaluated in a Phase I trial, vorinostat in a maximum tolerated dose (MTD) of 300 mg was administered in cases of Stage III, IVa, IVb HNSCC cancers, including larynx, hypopharynx, nasopharynx, and oropharynx, both HPV positive and negative cases, concurrent with standard chemoradiotherapy. The complete response rate of 96.2% and the favorable toxicity profile, including especially cases of hematological toxicity, justify the testing of vorinostat in Phase II and III trials [23].

References

1. Starzyńska, A.; Sobocki, B.K.; Alterio, D. Current Challenges in Head and Neck Cancer Management. Cancers 2022, 14, 358.
2. Marur, S.; Forastiere, A.A. Head and Neck Cancer: Changing Epidemiology, Diagnosis, and Treatment. Mayo Clin. Proc. 2008, 83, 489–501.
3. Lokich, J.J.; Ahlgren, J.D.; Gullo, J.J.; Philips, J.A.; Fryer, J.G. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: A Mid-Atlantic Oncology Program Study. J. Clin. Oncol. 1989, 7, 425–432.
4. Iqbal, H.; Pan, Q. Capecitabine for treating head and neck cancer. Expert Opin. Investig. Drugs 2016, 25, 851–859.
5. Heggie, G.D.; Sommadossi, J.P.; Cross, D.S.; Huster, W.J.; Diasio, R.B. Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine, and bile. Cancer Res. 1987, 47, 2203–2206.
6. Thomas, D.; Zalcberg, J.R. 5-Fluorouracil: A Pharmacological Paradigm in the Use of Cytotoxics. Clin. Exp. Pharmacol. Physiol. 1998, 25, 887–895.
7. Walko, C.M.; Lindley, C. Capecitabine: A review. Clin. Ther. 2005, 27, 23–44.
8. Department of Veterans Affairs Laryngeal Cancer Study Group; Wolf, G.T.; Fisher, S.G.; Hong, W.K.; Hillman, R.; Spaulding, M.; Laramore, G.E.; Endicott, J.W.; McClatchey, K.; Henderson, W.G. Induction Chemotherapy plus Radiation Compared with Surgery plus Radiation in Patients with Advanced Laryngeal Cancer. N. Engl. J. Med. 1991, 324, 1685–1690.

9. Haddad, R.; O'Neill, A.; Rabinowits, G.; Tishler, R.; Khuri, F.R.; Adkins, D.; Clark, J.; Sarlis, N.; Lorch, J.; Beitler, J.J.; et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): A randomised phase 3 trial. Lancet Oncol. 2013, 14, 257–264.
10. Albers, A.E.; Grabow, R.; Qian, X.; Jumah, M.D.; Hofmann, V.M.; Krannich, A.; Pecher, G. Efficacy and toxicity of docetaxel combination chemotherapy for advanced squamous cell cancer of the head and neck. Mol. Clin. Oncol. 2017, 7, 151–157.
11. Fayette, J.; Fontaine-Delaruelle, C.; Ambrun, A.; Daveau, C.; Poupart, M.; Ramade, A.; Zrounba, P.; Neidhardt, E.-M.; Péron, J.; Diallo, A.; et al. Neoadjuvant modified TPF (docetaxel, cisplatin, fluorouracil) for patients unfit to standard TPF in locally advanced head and neck squamous cell carcinoma: A study of 48 patients. Oncotarget 2016, 7, 37297–37304.
12. Guigay, J.; Aupérin, A.; Fayette, J.; Saada-Bouzid, E.; Lafond, C.; Taberna, M.; Geoffrois, L.; Martin, L.; Capitain, O.; Cupissol, D.; et al. Cetuximab, docetaxel, and cisplatin versus platinum, fluorouracil, and cetuximab as first-line treatment in patients with recurrent or metastatic head and neck squamous-cell carcinoma (GORTEC 2014-01 TPExtreme): A multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 2021, 22, 463–475.
13. Van Cutsem, E.; Twelves, C.; Cassidy, J.; Allman, D.; Bajetta, E.; Boyer, M.; Bugat, R.; Findlay, M.; Frings, S.; Jahn, M.; et al. Oral Capecitabine Compared with Intravenous Fluorouracil Plus Leucovorin in Patients with Metastatic Colorectal Cancer: Results of a Large Phase III Study. J. Clin. Oncol. 2001, 19, 4097–4106.
14. Martinez-Trufero, J.; Isla, D.; Adansa, J.C.; Irigoyen, A.; Hitt, R.; Gil-Arnaiz, I.; Lambea, J.; Lecumberri, M.J.; Cruz, J.J.; on behalf of the Spanish Head and Neck Cancer Treatment Group (TTCC). Phase II study of capecitabine as palliative treatment for patients with recurrent and metastatic squamous head and neck cancer after previous platinum-based treatment. Br. J. Cancer 2010, 102, 1687–1691.
15. Chua, D.; Wei, W.I.; Sham, J.S.; Au, G.K. Capecitabine Monotherapy for Recurrent and Metastatic Nasopharyngeal Cancer. Jpn. J. Clin. Oncol. 2008, 38, 244–249.
16. Péron, J.; Poupart, M.; Ceruse, P.; Ramade, A.; Girodet, D.; Zrounba, P.; Fayette, J. Efficacy and safety of capecitabine in heavily pretreated recurrent/metastatic head and neck squamous cell carcinoma. Anti-Cancer Drugs 2012, 23, 1107–1111.
17. Won, Y.-W.; Park, Y.H.; Ahn, M.J.; Do, I.-G.; Ko, Y.H.; Park, K. A phase II study of combination chemotherapy with capecitabine and cisplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck. Ann. Oncol. 2011, 22, 417–423.
18. Fakhry, C.; Zhang, Q.; Nguyen-Tan, P.F.; Rosenthal, D.; El-Naggar, A.; Garden, A.; Soulieres, D.; Trotti, A.; Avizonis, V.; Ridge, J.A.; et al. Human Papillomavirus and Overall Survival After

Progression of Oropharyngeal Squamous Cell Carcinoma. J. Clin. Oncol. 2014, 32, 3365–3373.

19. Fazer, C.; Chintakuntlawar, A.; Price, K. Capecitabine for Salvage Treatment of Patients with Heavily Pre-treated Human Papillomavirus-Associated Oropharynx Cancer (HPV-OPC) with Distant Metastases. Int. J. Radiat. Oncol. Biol. Phys. 2020, 106, 1183.
20. Weiss, J.M.; Bagley, S.; Hwang, W.-T.; Bauml, J.; Olson, J.G.; Cohen, R.B.; Hayes, D.N.; Langer, C. Capecitabine and lapatinib for the first-line treatment of metastatic/recurrent head and neck squamous cell carcinoma. Cancer 2016, 122, 2350–2355.
21. Di Gennaro, E.; Piro, G.; Chianese, M.I.; Franco, R.; Di Cintio, A.; Moccia, T.; Luciano, A.; De Ruggiero, I.; Bruzzese, F.; Avallone, A.; et al. Vorinostat synergises with capecitabine through upregulation of thymidine phosphorylase. Br. J. Cancer 2010, 103, 1680–1691.
22. Wisniewska-Jarosinska, M.; Sliwinski, T.; Kasznicki, J.; Kaczmarczyk, D.; Krupa, R.; Bloch, K.; Drzewoski, J.; Chojnacki, J.; Blasiak, J.; Morawiec-Sztandera, A. Cytotoxicity and genotoxicity of capecitabine in head and neck cancer and normal cells. Mol. Biol. Rep. 2011, 38, 3679–3688.
23. Teknos, T.N.; Grecula, J.; Agrawal, A.; Old, M.O.; Ozer, E.; Carrau, R.; Kang, S.; Rocco, J.; Blakaj, D.; Diavolitsis, V.; et al. A phase 1 trial of Vorinostat in combination with concurrent chemoradiation therapy in the treatment of advanced staged head and neck squamous cell carcinoma. Investig. New Drugs 2019, 37, 702–710.