Carboplatin

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.1. Cytotoxic medicines

ATC codes: L01XA02

Indication	Malignant neoplasms of other or ill-defined sites in the lip, oral cavity or pharynx ICD11 code: 2B6E
INN	Carboplatin
Medicine type	Chemical agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 50 mg per 5 mL ; 150 mg per 15 mL ; 450 mg per 45 mL ; 600 mg per 60 mL
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Tags	Cancer
Wikipedia	Carboplatin
DrugBank	Carboplatin

Expert Committee recommendation

The Expert Committee noted that concomitant chemotherapy and radiotherapy using cisplatin or carboplatin is the standard of care for treating early-stage head and neck cancers and that both agents are effective radiosensitizers. The evidence presented in the application evaluated overall survival and found only a limited overall survival benefit associated with the addition of cisplatin or carboplatin to radiotherapy compared with radiotherapy alone, with no significant difference between the two agents. However, the Committee noted that the most relevant outcome measure for chemoradiation is local control of the disease, for which both cisplatin and carboplatin are associated with benefit, particularly in early-stage disease. More evidence is available for cisplatin, and it is already included on the EML for head and neck cancer as a radiosensitizer. However, cisplatin is associated with relevant acute and late toxicities and cannot be used in the considerable proportion of patients who are unfit for this chemotherapy. The Committee considered that carboplatin can be an alternative option as a radiosensitizer for patients in whom cisplatin is contraindicated or not tolerated, due to its different and better tolerated toxicity profile. The Expert Committee also acknowledged that the Cancer Working Group supported the inclusion of carboplatin on the EML as an alternative option to cisplatin for this indication. The Expert Committee therefore recommended the inclusion of carboplatin as a radiosensitizer for head and neck cancers in patients unable to tolerate cisplatin.

Background

As part of the comprehensive review of cancer medicines undertaken by the Expert Committee in 2015, cisplatin was added to the complementary list of the EML for use as a radiosensitizer in treatment protocols for head and neck cancer. Compared with postoperative radiotherapy alone, the Committee considered that the benefits associated with the addition of cisplatin, in terms of local and regional control rates, disease-free survival and progression-free survival, were of clinical relevance. The Committee also considered that the use of primary combined chemotherapy with cisplatin and radiation was associated with a clinical benefit, compared with radiation alone, in patients who have unresectable tumours (1).

Public health relevance

Head and neck cancers include many site-specific tumours, including oral cavity and oropharyngeal cancers. However, about 90% of all head and neck cancers are squamous cell carcinomas (2). This group of cancers accounts for 890 000 new cases and 450 000 deaths annually and is the sixth most common cancer worldwide (3). Although the incidence for nasopharyngeal cancers has decreased over the past 20 years, the incidence of oropharyngeal and hypopharyngeal cancers, and lip and oral cavity cancers has increased (4). The incidence of head and neck cancer varies markedly by geographical location; it is noticeably more frequent in South Asia and less frequent in western sub-Saharan Africa and Andean Latin America (4,5). The prognosis of head and neck cancers depends largely on the location of the tumour and its stage. Overall, the 5-year survival is 66.9%. However, localized stages have a 5-year survival ranging from 62% to 96% depending of the anatomic site, while metastatic disease has a 5-year survival in the range of 20–40% (6).

Benefits

The applicants conducted a literature search for randomized controlled trials and systematic reviews of platinum-based chemotherapy for head and neck cancer, and conducted a meta-analysis of the results. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool, and judgements about precision, consistency, directness and likelihood of publication bias were made following the GRADE approach. Seventeen systematic reviews (used to identify relevant studies) were identified (7–23). No new trial evidence was found since the 2015 application. Eight trials, in seven publications, provided data to estimate the effect of cisplatin or carboplatin on overall survival. Six trials assessed the effect of cisplatin (24–28), while two evaluated carboplatin (29,30). In almost all of the trials, platinum chemotherapy was used as a single chemotherapy agent; in one trial, it was used in combination with 5-fluorouracil (30). Participants in most of the trials had locally advanced disease. The meta-analysis showed that the addition of cisplatin or carboplatin to radiotherapy may increase overall survival by 2 months (hazard ratio (HR) 0.95, 95% (confidence interval (CI) 0.80 to 1.12; low-certainty evidence).

Harms

Twenty-six trials reporting data on adverse events were identified from the systematic reviews and included in the meta-analysis. The addition cisplatin or carboplatin to radiotherapy may increase the risk of adverse events (risk ratio (RR) 1.16, 95% CI 1.01 to 1.16; low-certainty evidence). In absolute terms, 52 more patients per 1000 experience adverse events. The most common adverse events were mucositis, skin toxicity, dysphagia and stomatitis.

Additional evidence

A meta-analysis of 93 randomized trials (17 346 participants) provides a comprehensive evaluation of the effect of chemotherapies in locally advanced head and neck cancer (31). The meta-analysis showed that chemotherapy, when compared with radiotherapy alone, was associated with a relevant benefit in overall survival, with about 4.5% more patients being alive at 5 years (absolute improvement). This benefit was larger for concomitant chemotherapy, whereas the observed benefit for induction and adjuvant chemotherapies was uncertain. Among chemotherapies, concurrent high-dose cisplatin (100 mg/m2 on days 1, 22 and 43 during radiotherapy) was the most effective regimen compared with 5-fluorouracil and carboplatin. Based on these results, concurrent chemoradiotherapy with cisplatin became the preferred choice for the treatment of patients with locoregionally

advanced squamous cell carcinoma of the head and neck in the clinical practice guidelines of the European Head and Neck Society, the European Society of Medical Oncology and European Society for Radiotherapy and Oncology, and the National Comprehensive Cancer Network (32,33). However, platinum-based concomitant chemoradiotherapy has acute and late toxic effects. Adding cisplatin to radiotherapy is associated with acute gastrointestinal, haematological, neurological and renal adverse effects. This toxicity adds to the toxicity caused by radiotherapy. In randomized controlled trials, the addition of high-dose cisplatin doubled the number of cases of severe acute mucositis (34). More than one third of patients developed severe acute dysphagia (35). Severe adverse effects are also associated with decreased compliance, with a relevant proportion of patients (up to a third) unable to receive all planned cycles of chemotherapy (34,36). Late toxicity is also extremely problematic when cisplatin-based induction chemotherapy is followed by cisplatin-based concomitant chemoradiotherapy, as it decreases the quality of life of patients for the rest of their lives. For these reasons carboplatin is frequently used in routine clinical practice when cisplatin is not tolerated or contraindicated. Based on the above-mentioned meta-analysis, carboplatin and 5-fluorouracil are considered acceptable alternatives as they are associated with gains in survival (31). Carboplatin has a similar mode of action to cisplatin, but it is associated with less acute and late toxicities (e.g. ototoxicity, nephrotoxicity, neurotoxicity and emesis) (37,38). Carboplatin can be used in patients with impaired kidney function and can be easily dosed based on glomerular filtration rate (39).

Cost / cost effectiveness

No economic evaluation studies were identified.

WHO guidelines

WHO guidelines for the treatment of head and neck cancers are not available.

Availability

Carboplatin has marketing approval from many national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and the United States Food and Drug Administration. It is currently included on the Model List for other indications and is available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group noted that concomitant chemotherapy and radiotherapy using cisplatin or carboplatin is the standard of care for the treatment of head and neck cancers. Both agents are effective radiosensitizers, cisplatin is more active, but also more toxic than carboplatin. The available evidence suggests that there are no significant differences between agents in terms of survival. The Working Group therefore advised that it supported the inclusion of carboplatin on the Model List as an alternative treatment option to cisplatin for concomitant chemoradiation therapy of head and neck cancers in patients unable to tolerate cisplatin. Comments were received from the WHO Department of Noncommunicable Diseases. The technical department concurred with the conclusion that carboplatin provides similar clinical benefit to cisplatin, with a different safety profile and less toxicity. The technical department agreed that the addition of carboplatin to the EML for use in the treatment of head and neck cancer as a radiosensitizer primarily relates to patients unable to tolerate cisplatin.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 994; https://apps.who.int/iris/handle/10665/189763, accessed 16 May 2021).
2. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
4. Aupérin A. Epidemiology of head and neck cancers: an update. Curr Opin Oncol. 2020;32(3):178–86.
5. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abd el-Rahman O, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the Global Bur

den of Disease Study. JAMA Oncol. 2019;5(12):1749–68.
6. Surveillance, Epidemiology, and End Results [internet]. Bethesda, MD: National Cancer Institute; National Institutes of Health; 2020 (https://seer.cancer.gov/, accessed 16 May 2021).
7. Dauzier E, Lacas B, Blanchard P, Le Q-T, Simon C, Wolf G, et al. Role of chemotherapy in 5000 patients with head and neck cancer treated by curative surgery: a subgroup analysis of the meta-analysis of chemotherapy in head and neck cancer. Oral Oncol. 2019;95:106–14.
8. Suton P, Skelin M, Rakusic Z, Dokuzovic S, Luksic I. Cisplatin-based chemoradiotherapy vs. cetuximab-based bioradiotherapy for p16-positive oropharyngeal cancer: an updated meta-analysis including trials RTOG 1016 and De-ESCALaTE. Eur Arch Otorhinolaryngol. 2019;276(5):1275–81.
9. Haussmann J, Tamaskovics B, Bölke E, Djiepmo-Njanang FJ, Kammers K, Corradini S, et al. Addition of chemotherapy to hyperfractionated radiotherapy in advanced head and neck cancer—a meta-analysis. Strahlenther Onkol. 2019;195(12):1041–9.
10. Xu B, Zeng M, Zeng J, Feng J, Yu L. Meta-analysis of clinical trials comparing the efficacy and safety of liposomal cisplatin versus conventional nonliposomal cisplatin in nonsmall cell lung cancer (NSCLC) and squamous cell carcinoma of the head and neck (SCCHN). Medicine. 2018;97(46):e13169.
11. Gao P, Gong L, Wang X. Induction chemotherapy in patients with resectable laryngeal cancer: a meta-analysis. Mol Clin Oncol. 2018;9(2):155–62.
12. Winquist E, Agbassi C, Meyers BM, Yoo J, Chan KKW; Head and Neck Disease Site Group. Systemic therapy in the curative treatment of head and neck squamous cell cancer: a systematic review. J Otolaryngol Head Neck Surg. 2017;46(1):29.
13. Jerzak KJ, Delos Santos K, Saluja R, Lien K, Lee J, Chan KKW. A network meta-analysis of the sequencing and types of systemic therapies with definitive radiotherapy in locally advanced squamous cell carcinoma of the head and neck (LASCCHN). Oral Oncol. 2017;71:1–10.
14. Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. Lancet Oncol. 2017;18(9):1221–37.
15. Vidal L, Ben Aharon I, Limon D, Cohen E, Popovtzer A. Role of Induction chemotherapy prior to chemoradiation in head and neck squamous cell cancer—systematic review and meta-analysis. Cancer. 2017;23(2):79–83.
16. Aguiar PN Jr, Tadokoro H, da Silva GF, Landgraf MM, Noia Barreto CM, Filardi BA, et al. Definitive chemoradiotherapy for squamous head and neck cancer: cisplatin versus carboplatin? A meta-analysis. Future Oncol. 2016;12(23):2755–64.
17. Guan J, Zhang Y, Li Q, Zhang Y, Li L, Chen M, et al. A meta-analysis of weekly cisplatin versus three weekly cisplatin chemotherapy plus concurrent radiotherapy (CRT) for advanced head and neck cancer (HNC). Oncotarget. 2016;7(43):70185–93.
18. Gupta T, Kannan S, Ghosh-Laskar S, Agarwal JP. Systematic review and meta-analysis of conventionally fractionated concurrent chemoradiotherapy versus altered fractionation radiotherapy alone in the definitive management of locoregionally advanced head and neck squamous cell carcinoma. Clin Oncol (R Coll Radiol). 2016;28(1):50–61.
19. Budach W, Bölke E, Kammers K, Gerber PA, Orth K, Gripp S, et al. Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): a meta-analysis of randomized trials. Radiother Oncol. 2016;118(2):238–43.
20. Strojan P, Vermorken JB, Beitler JJ, Saba NF, Haigentz Jr M, Bossi P, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: a systematic review. Head Neck. 2016;38(S1):E2151–E8.
21. Kim R, Hahn S, Shin J, Ock C-Y, Kim M, Keam B, et al. The effect of induction chemotherapy using docetaxel, cisplatin, and fluorouracil on survival in locally advanced head and neck squamous cell carcinoma: a meta-analysis. Cancer Res Treat. 2016;48(3):907–16.
22. Gupta T, Kannan S, Ghosh–Laskar S, Agarwal JP. Concomitant chemoradiotherapy versus altered fractionation radiotherapy in the radiotherapeutic management of locoregionally advanced head and neck squamous cell carcinoma: an adjusted indirect comparison meta-analysis. Head Neck. 2015;37(5):670–6.
23. Qian X, Ma C, Hoffmann TK, Kaufmann AM, Albers AE. Taxane-cisplatin-fluorouracil as induction chemotherapy for advanced head and neck cancer: a meta-analysis of the 5-year efficacy and safety. Springerplus. 2015;4(1):208.
24. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27(10):843–50.
25. Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2012;84(5):1198–205.
26. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol. 2013;31(7):845–52.
27. Rishi A, Ghoshal S, Verma R, Oinam AS, Patil VM, Mohinder R, et al. Comparison of concomitant boost radiotherapy against concurrent chemoradiation in locally advanced oropharyngeal cancers: a phase III randomised trial. Radiother Oncol. 2013;107(3):317–24.
28. Ghadjar P, Simcock M, Studer G, Allal AS, Ozsahin M, Bernier J, et al. Concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer: 10-year follow-up of a randomized phase III trial (SAKK 10/94). Int J Radiat Oncol Biol Phys. 2012;82(2):524–31.
29. Racadot S, Mercier M, Dussart S, Dessard-Diana B, Bensadoun RJ, Martin M, et al. Randomized clinical trial of post-operative radiotherapy versus concomitant carboplatin and radiotherapy for head and neck cancers with lymph node involvement. Radiother Oncol. 2008;87(2):164–72.
30. Bourhis J, Sire C, Graff P, Grégoire V, Maingon P, Calais G, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol. 2012;13(2):145–53.