Update of the application about chemotherapy for the WHO Model List of Essential Medicines

As a Medicine for early- and advanced-stage head and neck cancers

Submitted by:

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Potential conflicts of interest

All the authors declare no conflict of interest

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General items

1. Summary statement of the proposal for inclusion, change or deletion.

This report updates a previous application evaluating platinum-based chemotherapy for the list of WHO Essential Medicine as treatment for early- and advanced-stage head and neck cancers.

Head and neck cancers encompasses many site-specific tumours, including oral cavity and oropharyngeal cancers. Together, they account for a significant number of new cases and deaths every year. Their incidence shows a significant geographical variation, with a higher incidence in South Asia and a lower incidence in Western Sub-Saharan Africa and Andean Latin America. Overall, the 5-year survival is around 67%. Although it largely depends on the location of the cancer and its stage.

We found no new trial since the last application assessing the effect of standard chemotherapy (without monoclonal antibodies) plus radiotherapy versus radiotherapy alone. However, we summarized the data regarding the use of platinum-based chemotherapy.

In our analysis, we found that the addition of cisplatin or carboplatin to radiotherapy may increase overall survival in 2 months (HR 0.95, 95% CI 0.80-1.12; low certainty evidence). However, use of platinum-based chemotherapy was associated with an increment in adverse events, mainly mucositis and skin toxicity (52 more patients with adverse events per 1000 treated; RR 1.16, 95% CI 1.01-1.34; low certainty evidence).

2. Relevant WHO technical department and focal point.

Department of Health Products Policy and Standards, World Health Organization, Geneva, Switzerland

3. Name of organization(s) consulted and/or supporting the application.

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

WHO Collaborating Center for Evidence Informed Policy, McMaster University, Hamilton, Ontario, Canada

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

International Nonproprietary Name (INN)	Anatomical Therapeutic Chemical (ATC) code
Cisplatin	L01XA01
Carboplatin	L01XA02

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

The current scheme listed is: Cisplatin 100 mg/m2 IV every 3 weeks x 3 cycles

Both, cisplatin and carboplatin can cause dose-related and cumulative renal toxicity. Also, can cause fetal harm when administered to a pregnant woman.

Safety and effectiveness in pediatric patients have not been established.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

As individual medicine

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details

The current scheme listed is: Cisplatin 100 mg/m2 IV every 3 weeks (on days 1, 22, 43) x 3 cycles, which is the most frequent approach. In one trial, however, cisplatin was used in a lower dose (20 mg/m2) for 5 consecutive days during weeks 1 and 5, in attempt to reduce the toxicity and increase the tolerability of concomitant chemotherapy and radiation.

8. Information supporting the public health relevance.

Head and neck cancers encompasses many site-specific tumours, including oral cavity and oropharyngeal cancers. However, about 90% of all head and neck cancers are squamous cell carcinomas.[1] This group of cancers account for 890,000 new cases and 450,000 deaths annually, being the sixth most common cancer worldwide.[2]

Although the incidence for nasopharyngeal cancers have decreased over the last twenty years, the incidence of oro/hypopharyngeal cancers and lip/oral cavity cancers have increased.[3] There is a marked geographical variation on the incidence of head and neck cancer as well, being noticeably more frequent in South Asia and less frequent in Western Sub-Saharan Africa and Andean Latin America.[3, 4]

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%.[5]

9. Review of benefits: summary of evidence of comparative effectiveness.

Methods

We searched for systematic reviews up to March 2021 on MEDLINE, EMBASE and the Cochrane Library, from date of inception and without language limits (see appendix). We used the systematic reviews as a way to identify relevant studies but conducted our own meta-analysis.

We used the following inclusion criteria:

1. Study design: Randomized trial
2. Population: Individuals with head and neck cancer
3. Intervention: Any chemotherapy (in addition to radiotherapy)
4. Comparison: Radiotherapy only

We assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool. We also made judgments about precision, consistency, directness, and likelihood of publication bias following the GRADE approach.

We meta-analysed the data using the Mantel–Haenszel method, random effect model. We assessed heterogeneity with the Chi-square test and with the I2 statistic. Meta-analyses were conducted using RevMan (Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) or STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

Results

We identified 17 systematic reviews.[6-22] We found no new trial since the last application. However, we summarized the data regarding the use of platinum-based chemotherapy.

Eight trials, in seven publications, provided data to estimate the effect of cisplatin or carboplatin in overall survival. Six trials assessed the effect of cisplatin,[23-27] while two evaluated carboplatin.[28, 29] In almost all of the trials, platinum was used as single chemotherapy agent; only in one trial, it as used associated with another drug (fluorouracil).[29] Most of the trials were conducted in individuals with locally advanced disease.

Our analysis showed that the addition of cisplatin or carboplatin to radiotherapy may increase overall survival in 2 months (HR 0.95, 95% CI 0.80-1.12; low certainty evidence).

Summary of Potential Benefits

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Chemotherapy	WITHOUT Chemotherapy	Difference (CI 95%)	
Overall survival 8 RCTs (n=2,235)	**HR 0.95** (0.80 - 1.12)	**34** months	**32** months[a]	**2** months more (From 4 less to 8 more)	⨁⨁◯◯ [b,c] **LOW**

Abbreviations: HR: Hazard ratio; CI: Confidence interval

a. The anticipated absolute effect was estimated from the median survival observed in controls groups and the hazard ratio.
b. We rated down the certainty of the evidence due to risk of bias. Most of the studies were unblinded. Additionally, two studies report incomplete data.
c. We rated down the certainty of the evidence due to imprecision. The confidence interval around the absolute effect probably crosses decision thresholds.

10. Review of harms and toxicity: summary of evidence of safety.

From the systematic reviews identified (see previous section), we found 26 trials that reported data on adverse effects. We observed that the addition cisplatin or carboplatin to radiotherapy may result in 52 more patients with adverse events per 1000 treated (RR 1.16, 95% CI 1.01-1.34; low certainty evidence). The most common adverse events were mucositis, skin toxicity, dysphagia and stomatitis.

Summary of Potential Harms

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Doxorubicin	WITHOUT Doxorubicin	Difference (CI 95%)	
Adverse events grade 3 or more 26 RCTs (n=5,086)	**RR 1.16** (1.01 - 1.34)	**376** per 1000	**324** per 1000	**52 more** (3 to 110 more)	⨁⨁◯◯[a,b] **LOW**

Abbreviations: RR: Risk ratio; CI: Confidence interval

a. We rated down the certainty of the evidence due to risk of bias. Most of the studies were unblinded. Additionally, two studies report incomplete data.
b. We rated down the certainty of the evidence due to inconsistency. We observed a substantial heterogeneity on the meta-analysis (I^2=79%)

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Methods

We searched for economic evaluations up to March 2021 on MEDLINE, EMBASE and the Cochrane library (see appendix). Additionally, we hand-searched the websites of the following agencies and organizations: The National Institute of Health Research, The Center of Review and Dissemination, The Canadian Agency for Drugs and Technologies in Health (CADTH), The National Institute for Health and Care Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC) and The International Network of Agencies for Health Technology Assessment (INHATA).

Inclusion/exclusion

Inclusion

We included full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population.

Exclusion

We excluded studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects. Also, we excluded abstracts, posters, reviews, letters/editorials, and unpublished studies

Results

We identified no new economic evaluation addressing the use of standard chemotherapy regimens in addition to radiotherapy in individuals with head or neck cancers.

12. Summary of regulatory status and market availability of the medicine.

US Food and Drug Administration: Approved

European Medicines Agency: Approved

Australian Government: Approved

Japanese Pharmaceuticals and Medical Devices Agency: Approved

Health Canada: Approved

13. Availability of pharmacopoeial standards

Cisplatin and carboplatin

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

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Appendix

Appendix 1: Search strategies

Search strategy for systematic reviews in MEDLINE and EMBASE (via OVID)

DATE: March 2021

1. (head and neck squamous cell carcinoma).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
2. (head and neck neoplasm).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
3. (head and neck cancer).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
4. 1 or 2 or 3
5. chemotherapy.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
6. cisplatin.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
7. 5 or 6
8. systematic review/
9. meta-analysis/
10. (meta analy* or metanaly* or metaanaly*).ti,ab.
11. ((systematic or evidence) adj2 (review* or overview*)).ti,ab.
12. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
13. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
14. cochrane.jw.
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 7 and 15

Search strategy for economic evaluations in MEDLINE (via OVID)

DATE: March 2021

((adjuvant chemotherapy[MeSH Terms]) OR ("chemotherapy, adjuvant/pharmacology"[MeSH Terms]) OR (chemotherapy OR chemothera*)) AND (("squamous cell carcinoma of head and neck"[MeSH Terms] OR squamous cell carcinoma)) AND (Economics[Mesh:NoExp] OR "Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab] OR “Single Technology Appraisal”OR “HTA” OR “Technology Appraisal”)

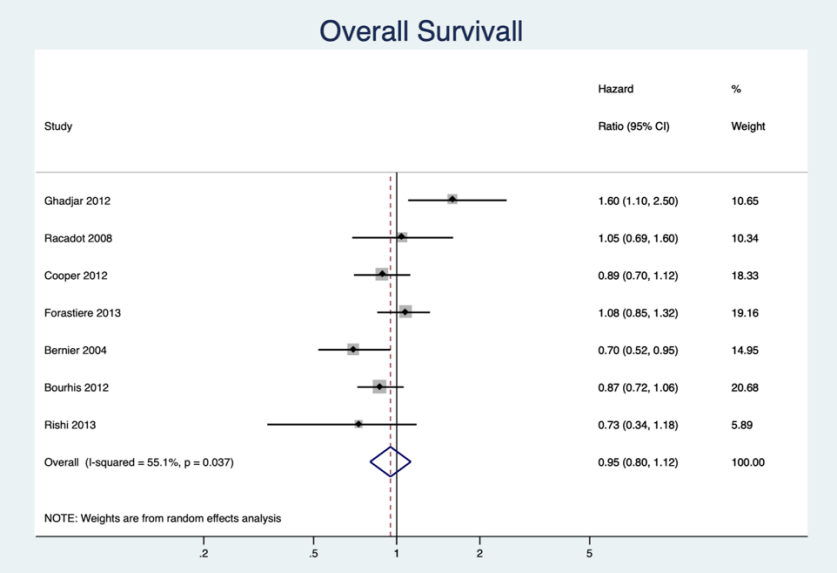
Search strategy for economic evaluations in EMBASE (via OVID)

DATE: March 2021

(induction chemotherapy.tw OR induc$ chemotherapy.tw OR neoadjuvant chemotherapy.tw OR preoperative chemotherapy.tw OR sequential chemotherapy.tw OR adjuvant chemotherapy.tw OR primary chemotherapy.tw OR initial chemotherapy.tw) AND (squamous cell carcinoma/ OR Squamous cell can*.tw) AND (Cost-effectiveness.mp. or "cost utility analysis"/ or "cost benefit analysis"/ or "cost minimization analysis"/ or "cost"/ or "cost effectiveness analysis"/ or QALY.mp. or quality adjusted life year/ or health technology assessment.mp. or biomedical technology assessment/ or economics/ or willingness to pay.mp. or "health care cost"/ or life years gained.mp. or disability-adjusted life years.mp. or disability-adjusted life year/ or Statistical Model/ or economic model*.ab,ti. or Probability/ or markov.ti,ab,kw. or monte carlo method/ or monte carlo.ti,ab. or Decision Theory/ or Decision Tree/ or health technology assessment.mp.)

Appendix 2: Forest plots

Chemotherapy in addition to radiotherapy in individuals with head and neck cancers - Overall survival.



Chemotherapy in addition to radiotherapy in individuals with head and neck cancers – Adverse events