Review of doxorubicin as a medicine for treatment of rhabdomyosarcoma on the WHO Model List of Essential Medicines

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 doxorubicin for the list of WHO Essential Medicine as treatment for individuals with rhabdomyosarcoma.

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents. While global epidemiological data are limited, its prevalence is estimated in of 4.4 cases per 100,000 children/adolescents per year.

For many years, doxorubicin was been used as single agent in the treatment of rhabdomyosarcoma. This was based in a couple of small randomized trials from the nineties, that showed that monotherapy with doxorubicin, especially in high doses, was associated with some response.[1]

Over thew years, new chemotherapies drugs have been introduced to the treatment of rhabdomyosarcoma. In our review, we identified only one randomized trial, comparing the addition of doxorubicin to the combination of ifosfamide, vincristine and dactinomycin (IVA). The results suggest that although doxorubicin was associated with an increment in free-progression survival (HR 0.87, 95% CI 0.65 - 1.16; low certainty evidence), this benefit may not translate into a longer survival (HR 1.17, 95% CI 0.82 - 1.67; low certainty evidence).

Additionally, the use of doxorubicin was associated with an increment of adverse events, mainly infections (RR 1.41, 95% CI 1.24 - 1.61; low certainty evidence).

Doxorubicin has been considered an effective therapeutic option as single agent before triplets become the standard. However, now the role of doxorubicin as an appropriate first-line chemotherapy option for advanced or metastatic rhabdomyosarcoma is controversial. For this reason, we do not propose inclusion of doxorubicin on the Model List for this indication.

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
Doxorubicin	L01DB01

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

The recommended dose of doxorubicin when used as a single agent is 60 to 75 mg/m2 intravenously every 21 days. The recommended dose of doxorubicin, when administered in combination with other chemotherapy drugs, is 30 to 75 mg/m2 intravenously every 21 to 28 days.

There are no recommended dose adjustments for pediatric age. In heavily pretreated patients, elderly patients or obese patients a lower doxorubicin dose may be used. Cumulative doses above 550 mg/m2 are associated with an increased risk of cardiomyopathy.
Doxorubicin is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C or serum bilirubin >5.0 mg/dL).
Also, doxorubicin may be teratogenic when administered to pregnant women.

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

On the randomized trial identified, doxorubicin was used on the first 4 cycles of IVA (ifosfamide, vincristine and dactinomycin) in a dose of 30 mg/m2.

8. Information supporting the public health relevance.

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents. While global epidemiological data are limited, there are country-specific studies that examine the incidence and prevalence of Rhabdomyosarcoma. For instance, data from the Surveillance, Epidemiology, and End Results (SEER) Program were used to determine incidence of Rhabdomyosarcoma in the USA from 1975 to 2005. Investigators estimated an incidence of 4.4 cases per 100,000 children/adolescents per year.[2]
Rhabdomyosarcoma is divided into six histological groups with different prognosis. Pleomorphic and alveolar rhabdomyosarcoma had the worst overall survival with a 26.6% and 28.9% 5-year survival, respectively, while Embryonal rhabdomyosarcoma had the highest 5-year survival rate (73.9%).[3]

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

Methods

We searched for randomized trials up to March 2021 on MEDLINE and EMBASE, from date of inception and without language limits. Additionally, we searched for up-to-date systematic reviews in MEDLINE, EMBASE and The Cochrane Library (see appendix).

We used the following inclusion criteria:

1. Study design: Randomized trial
2. Population: Individuals with Rhabdomyosarcoma
3. Intervention: Doxorubicin
4. Comparison: No Doxorubicin

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.

Results

We identified only 1 randomized trial.[4] Investigators allocated 484 children and adolescents with non-metastatic rhabdomyosarcoma to receive either nine cycles of IVA (ifosfamide, vincristine and dactinomycin) or to four cycles of IVA with doxorubicin 30 mg/m2, followed by five cycles of IVA alone.

The trial showed that the use of doxorubicin may decrease overall survival, however the results were not statistically significant (HR 1.17, 95% CI 0.82–1.67, low certainty evidence). The trial reported a follow-up of only 3 years. In that period, neither the median of overall survival nor the median of free-progression survival was reached.

Summary of Potential Benefits

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Doxorubicin	WITHOUT Doxorubicin	Difference (CI 95%)	
Overall survival 1 RCT (n=484)	**HR 1.17** (0.82 - 1.67)	Not reached	Not reached	Not estimable	⨁⨁◯◯ [a,b] **LOW**
Progression free survival 1 RCT (n=484)	**HR 0.87** (0.65 - 1.16)	Not reached	Not reached	Not estimable	⨁⨁◯◯ [a,b] **LOW**

Abbreviations: RR: Risk ratio; HR: Hazard ratio; CI: Confidence interval

a. We rated down the certainty of the evidence due to risk of bias. The trial was open label.
b. We rated down the certainty of the evidence due to imprecision. The number of participants analyzed was relatively small and the confidence interval probably crosses decision thresholds.

Doxorubicin has been considered an effective therapeutic option as single agent before triplets become the standard. With the addition of more medicines, e.g. ifosfamide, in combinations, the role of doxorubicin and its contribution in terms of overall survival has become less certain.[5-6] This has led to discontinuation of doxorubicin by some authoritative therapeutic protocol.[7]

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

On the trial identified, the use of doxorubicin was associated with an increment of adverse events, mainly infections (RR 1.41, 95% CI 1.24–1.61, low certainty evidence).

Summary of Potential Harms

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Doxorubicin	WITHOUT Doxorubicin	Difference (CI 95%)	

Hematological adverse events (neutropenia) 1 RCT (n=484)	**RR 1.03** (0.98 - 1.09)	**944** per 1000	**916** per 1000	**28 more** (18 fewer to 82 more)	⨁⨁◯◯[a,b] **LOW**
Non-Hematological adverse events (infections) 1 RCT (n=484)	**RR 1.41** (1.24 - 1.61)	**795** per 1000	**564** per 1000	**231 more** (135 to 344 more)	⨁⨁◯◯[a,b] **LOW**

Abbreviations: RR: Risk ratio; HR: Hazard ratio; CI: Confidence interval

a. We rated down the certainty of the evidence due to risk of bias. The trial was open label.
b. We rated down the certainty of the evidence due to imprecision. The number of participants analyzed was relatively small and the confidence intervals probably crosses decision thresholds.

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 economic evaluation addressing the addition of doxorubicin in individuals with rhabdomyosarcoma.

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

Doxorubicin

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

References

1. Patel SR, Vadhan-Raj S, Burgess MA, et al. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. *Am J Clin Oncol*. Jun 1998;21(3):317-21. doi:10.1097/00000421-199806000-00025
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5. Pervaiz, N., Colterjohn, N., Farrokhyar, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer.* Aug 2008;113(3):573-81. doi:https://doi.org/10.1002/cncr.23592
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Appendix

Appendix 1: Search strategies

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

DATE: March 2021

1. exp Rhabdomyosarcoma/
2. rhabdomyosarcoma.mp.
3. 1 or 2
4. exp Doxorubicin/
5. Doxorubicin.mp.
6. 4 or 5
7. randomized controlled trial.pt.
8. random allocation/
9. double-blind method/
10. single-blind method/
11. randomi?ed controlled trial$.mp.
12. Randomi?ed clinical trial$.mp.
13. controlled clinical trial.pt.
14. ((singl$ or double$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
15. random$.mp.
16. placebo$.mp.
17. cross-over studies.sh.
18. latin square.tw.
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. animals/ not humans/
21. 19 not 20
22. systematic review/
23. meta-analysis/
24. (meta analy* or metanaly* or metaanaly*).ti,ab.
25. ((systematic or evidence) adj2 (review* or overview*)).ti,ab.
26. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
27. (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.
28. cochrane.jw.
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 3 and 6 and 21
31. 3 and 6 and 29

Search strategy for economic evaluations in MEDLINE (via OVID)

DATE: March 2021

((((baxter brand of doxorubicin hydrochloride[MeSH Terms]) OR (bedford brand of doxorubicin hydrochloride[MeSH Terms])) OR (bristol myers squibb brand of doxorubicin hydrochloride[MeSH Terms])) OR ("doxorubicin"[MeSH Terms])) AND ("rhabdomyosarcoma"[MeSH Terms] OR "rhabdomyosarco*" OR Rabdomiosarcoma) 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

Doxorubicin/

Rhabdomyosarcoma/

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.)