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Health Impact Analysis of Cisplatin, Carboplatin and Oxaliplatin

Quantifying the health impact of platinum compounds

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A literature based study on the health impacts of three platinum anticancer drugs (cisplatin, carboplatin and oxaliplatin) was undertaken. The published evidence for health benefits is presented and assessed. A model was developed to quantify the health gain of adding platinum based drugs to cancer treatment at the population level for the UK and the USA. The economic value of using platinum drugs (in terms of quality-adjusted life year (QALY)) in addition to other cancer treatments can be estimated at over £556 million for the UK and over US$4.8 billion for the USA, depending on the scenario chosen.

Introduction

Cisplatin, carboplatin and oxaliplatin are platinum compounds used intravenously in the chemotherapy treatment of eight types of cancer where solid tumours are present (1).

A solid tumour is an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumours may be benign or malignant. Examples of solid tumours are sarcomas, carcinomas and lymphomas. Leukaemias (cancers of the blood) generally do not form solid tumours (2).

The use of cisplatin, carboplatin and oxaliplatin by type of cancer according to the British National Formulary (BNF) (3) is shown in **Table I**.

Even allowing for clinical decisions to use other treatments, the use of platinum compounds in the types of cancer listed in **Table I** suggests that treatment using cisplatin, carboplatin or oxaliplatin could offer significant benefit to the UK and US populations.

The aim of the present research is to quantify the health impact of key pharmaceutical compounds (cisplatin, carboplatin and oxaliplatin) on population health. The specific objectives were to undertake a targeted literature review on the health benefits of using platinum compounds in oncology treatment and to develop a *de novo* model to show the health impacts on population-level health in the UK and USA.

Method: Targeted Literature Searches

In order to capture the data necessary to populate the model a targeted literature search and literature review were carried out.

The literature search and review were targeted to capture evidence on any existing effectiveness analyses for any of the treatments (reported as progression-free survival (PFS) or overall survival (OS)); quality of life

Table I The use of Cisplatin, Carboplatin and Oxaliplatin by Type of Cancer

Type of Cancer	Cisplatin	Carboplatin	Oxaliplatin
Ovarian	✓[a]	✓	×
Lung (particularly the small cell type)	✓	✓	×
Testicular	✓	×	×
Cervical	✓	×	×
Bladder	✓	×	×
Head and neck	✓	×	×
Colorectal (metastatic)	×	×	✓
Colon (adjuvant)	×	×	✓

[a]Cisplatin can be used but carboplatin is preferred for ovarian cancer (1)

data associated with the treatments or disease area and UK and USA epidemiology data.

An initial search strategy was developed and run and this was then followed up with further targeted searches. The aim was to identify papers that used platinum compounds as an add-on treatment for each cancer type identified in **Table I** in order to calculate the additional benefit gained from platinum compound usage.

The search strategy was developed to be as sensitive as possible in order to retrieve all relevant records. Any record containing the words 'cisplatin', 'carboplatin' or 'oxaliplatin' was returned. The search was limited to records indexed as review papers, English language papers and the date was limited from 2002 until present. These limits were applied to identify the most relevant and current research and to make the amount of results retrieved manageable within the constraints of the project. This search strategy was run in Ovid MEDLINE® In-Process and Ovid MEDLINE® with over 300 records retrieved.

Next, targeted searches of PubMed®, Google™ and Google Scholar™ were carried out. Searches on each database included the type of platinum compound, the type of cancer and phrases 'plus' and 'with or without'.

These searches were carried out for each combination of platinum compound and type of cancer. The first three to five pages of search results were reviewed based on title. Any articles that appeared relevant were then reviewed based on abstract. If the abstract appeared useful or if it was not possible to tell if it would be useful, the full paper was obtained (where possible).

If no literature was identified in the above searches then further targeted searching of the specific area of interest (i.e. the cancer type and drug type) were carried out.

The Model

A model was developed in Microsoft® Excel® to calculate the health gain of adding platinum to cancer treatment. The structure of the model is outlined in **Figure 1**. The model aims to capture the health gains and the value of these health gains achieved by using platinum compounds in cancer treatment. The analysis modelled a hypothetical cohort of patients in order to show the potential health benefits that could arise from using platinum compounds. It is assumed that all patients in a cancer category are treated with platinum compounds and that all accrue the QALY gain. This is calculated for UK and USA populations in the model.

The model inputs were identified from the targeted literature searches. Generally, for carboplatin and cisplatin it seemed that these compounds were already established as effective and so were often used in standard care rather than as an add-on. Otherwise, articles tended to compare the two types of platinum compound and so could not be included. Various strategies to deal with 'poor' evidence were employed. For example, research on small cell lung cancer was not identified for carboplatin so this was replaced with research on non-small cell lung cancer. In many groups (for instance, ovarian and lung) data were found for one type of platinum compound but not another so this

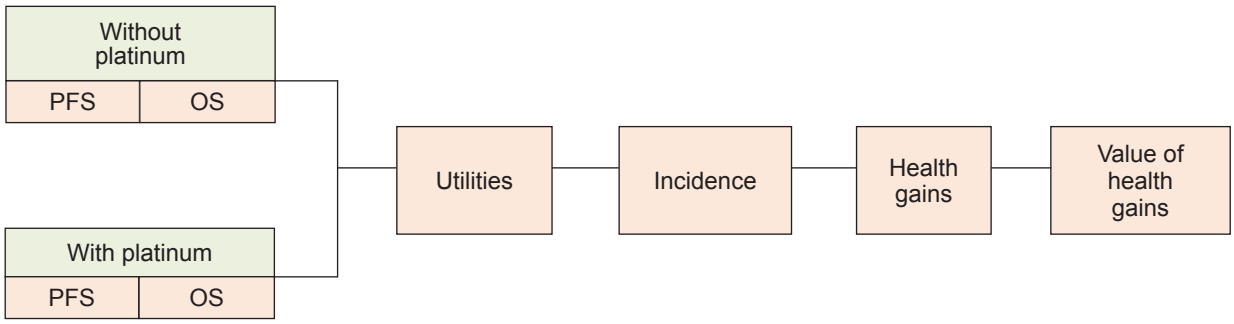

Fig. 1. Structure of the model. PFS = progression free survival, OS = overall survival

patient group was still accounted for. Testicular cancer and bladder cancer were excluded due to a lack of data.

One article that investigated cisplatin as an add-on treatment for bladder cancer was identified (4). However, this study reported a negative difference in overall survival for using platinum as an add-on treatment. The decision was made to exclude this article based on the fact that it appears that platinum compounds are well-established first line therapies for bladder cancer, suggesting that cisplatin is effective in improving cancer health outcomes. In addition, the trial failed to meet its recruitment targets and a larger study was recommended. Cisplatin is already a well-established standard therapy which may explain why no further studies were identified investigating cisplatin as an add-on treatment.

Table II shows the PFS and OS with and without platinum and the sources from which the data were extracted. Where more than one source is given, a weighted average based on sample size was calculated.

For cervical cancer the results show that there is a gain in PFS in the 'with platinum' arm while there is a reduction in OS. Two of the three studies identified showed lower PFS and lower OS in the treatment arm (9, 10) while the third study (8) showed an improvement in both PFS and OS when platinum was used (see **Appendix A**). The combination of the weighting (one study has a much larger sample size) and the relative difference in survival in each study results in this weighted average result. **Appendix B** shows the significance levels between treatment arms reported in the study.

Health-related quality of life inputs (utilities) were applied to each health state in order to generate QALYs. The utilities that were used in the model for PFS and post-progression survival (PPS) are outlined in **Table III**.

Table II Weighted Averages of PFS and OS Included in the Model

		Weighted averages (months)				
		Without platinum		With platinum		
Cancer type	Platinum compound	PFS	OS	PFS	OS	Source
Lung	Carboplatin	4.62	11.83	5.55	12.41	(5, 6)
Ovarian	Cisplatin	15.58	37.37	20.34	37.94	(7)
Cervical	Cisplatin	101.39	121.17	105.64	117.22	(8–10)
Head and neck	Cisplatin	24.24	41.84	34.62	67.81	(11)
Colorectal	Oxaliplatin	6.50	22.61	9.65	22.92	(12–18)

Table III Utilities Included in the Model

Cancer type	Utility PFS	Source	Utility PPS	Source
Lung	0.653	(19)	0.473	(19)
Ovarian	0.85	(20)	0.65	(20)
Cervical	0.72	(21)	0.29	(21)
Head and neck	0.65	(22)	0.51	(22)
Colorectal	0.8	(23)	0.46	(24)

Results for UK

In the base case model, it has been assumed that 100% of the patients from the population cancer incidence statistics are treated with platinum. The results show that using platinum compounds in cancer treatment offers potential health gains over cancer treatment not including platinum compounds. **Table IV** shows that, based on the base case inputs in the model, using platinum compounds could result in a potential gain of over 27,000 QALYs per year in the UK. In the UK a value of £20,000 per QALY is considered to be cost-effective (1). Therefore, assuming a threshold of up to £20,000 per QALY, the total QALYs gained would be valued at over £556 million.

Results for USA

Based on the base case inputs in the model, platinum compounds in cancer treatment could result in potential health gains of over 97,000 QALYs in the US population. Although there is no official published estimate of the value of QALYs in the USA, if it is assumed that the USA values QALYs at US$50,000 this would result in potential health gains valued at over US$4.8 billion.

Analysis of Uncertainty for UK

Bladder cancer and testicular cancer were excluded because the data were not available in the literature to populate the model. A sensitivity analysis including these sub-groups was run. This is based on the assumptions that 100% of patients in this disease sub-group are treated with platinum compounds, and that the per patient QALY gain is based on an average of the QALY gain in the other disease areas included in the model. The results showed that this may add over 3800 additional QALYs with a value of over £77 million.

If treatment uptake in the base case results was reduced to 50% the health gain from the use of platinum compounds would be valued at over £278 million. If head and neck cancer uptake of platinum treatment was lowered to just 10% (note: this is the third highest incidence and has by far the highest QALY gain per

Table IV Summary of QALY Gain for the UK

Cancer type	Platinum compound	QALY gain per patient if using drug	Incidence UK	Potential QALYs gained
Lung	Carboplatin	0.03	42,026	1547
Ovarian	Cisplatin	0.08	7,011	776
Cervical	Cisplatin	0.04	2,851	166
Head and neck	Cisplatin	0.85	17,353	21,255
Colorectal	Oxaliplatin	0.07	40,695	4102
			Total QALYs gained	**27,845**
			UK total value of QALYs gained	£556,900,453

patient), the total value of the QALYs gained would be around £174 million. Finally, in a more pessimistic scenario, in which all uptake is lowered to 50% and 10% in head and neck cancer, the value of QALYs gained would be over £108 million.

Discussion

The results of the analysis depend on the inputs and assumptions that the model user has selected. However, the model demonstrates that using platinum compounds in the five cancer types included in the model results in QALY gains from which a monetary value of health gain is calculated.

A key strength of the modelling approach is that it allows the decision maker to combine evidence from a variety of sources in order to derive a single assessment of the intervention's impact upon quality of life and survival. In addition, sensitivity analyses were carried out on uncertain input parameters which showed that even in the most pessimistic scenarios; platinum compounds were associated with quantitative health benefits.

A key limitation of this analysis is the lack of robust data with which to populate the model. The literature investigating platinum compounds as an add-on to standard treatment is sparse. This is likely because platinum is already accepted as a standard treatment and is usually included in both arms of the trial or study in combination with other chemotherapy drugs. This would result in the current analysis underestimating the health value of platinum compounds. However, it should be noted that in all cancer types and platinum compound sub-groups (with the exception of one underpowered study (4)) the weighted average survival gain extracted from the literature showed that platinum as an add-on offered health benefits.

Finally, this research focuses on the health outcomes only and does not consider the costs associated with the use of cisplatin, carboplatin or oxaliplatin. Further research could extend the current work to include these costs to determine if the added health benefits outweigh the costs associated with platinum compound use in oncology treatment.

Conclusion

The study showed that platinum compounds are associated with population health gains when used in oncology treatment. This health benefit has been quantified using the value associated with a QALY. The results showed that, even in the most pessimistic scenarios, cisplatin, carboplatin and oxaliplatin were associated with a positive monetary value of health gain when used to treat a number of different solid tumours.

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Appendix A
All Studies Included in Weighted Average Calculations

Carboplatin - Non small cell lung cancer

	Without platinum median (mean)		With platinum median (mean)		Sample size
Author, year (Ref.)	**PFS**	**OS**	**PFS**	**OS**	
Smit, 2008 (5)	2.8 (4.04)	7.6 (10.96)	4.2 (6.06)	8 (11.54)	240
Ardizzoni, 2012 (6)	3.6 (5.19)	8.8 (12.70)	3.5 (5.05)	9.2 (13.27)	240
Weighted average	**3.20 (4.62)**	**8.20 (11.83)**	**3.85 (5.55)**	**8.60 (12.41)**	–

Cisplatin - Ovarian

	Without platinum median (mean)		With platinum median (mean)		Sample size
Author, year (Ref.)	**PFS**	**OS**	**PFS**	**OS**	
Muggia, 2000 (7)	10.8 (15.58)	25.9 (37.37)	14.1 (20.34)	26.3 (37.94)	414

Cisplatin - Cervical

	Without platinum median (mean)		With platinum median (mean)		Sample size
Author, year (Ref.)	**PFS**	**OS**	**PFS**	**OS**	
Pearcey, 2002 (8)	74 (106.76)	76 (109.64)	86 (124.07)	87 (125.51)	253
Garipağaoğlu, 2004 (9)	40 (57.71)	64 (92.33)	33 (47.61)	55.1 (79.49)	44
Chiara, 1994 (10)	77 (111.09)	134 (193.32)	48 (69.25)	76 (109.64)	58
Weighted average	**70.28 (101.39)**	**83.99 (121.17)**	**73.22 (105.64)**	**81.25 (117.22)**	–

Cisplatin - Head and neck

	Without platinum median (mean)		With platinum median (mean)		Sample size
Author, year (Ref.)	**PFS**	**OS**	**PFS**	**OS**	
Ghadjar, 2012 (11)	16.8 (24.24)	29 (41.84)	24 (34.62)	47 (67.81)	224

Oxaliplatin - Colorectal

	Without platinum median (mean)		With platinum median (mean)		Sample size
Author, year (Ref.)	**PFS**	**OS**	**PFS**	**OS**	
Ibrahim, 2004 (12)	2.7 (3.90)	NR	4.6 (6.64)	NR	303
de Gramont, 2000 (13)	6.2 (8.94)	14.7 (21.21)	9 (12.98)	16.2 (23.37)	420
Giacchetti, 2000 (14)	6.1 (8.80)	19.9 (28.71)	8.7 (12.55)	19.4 (27.99)	200
Hospers, 2006 (15)	5.6 (8.08)	13.3 (19.19)	6.7 (9.67)	13.8 (19.91)	302
Kemeny, 2004 (16)	2.4 (3.46)	11.4 (16.45)	4.8 (6.92)	9.9 (14.28)	214
Grothy, 2002 in Damjanovic, 2004 (17)	5.3 (7.65)	16.1 (23.23)	7.9 (11.40)	20.4 (29.43)	238
Rothenberg, 2003 (18)	2.7 (3.90)	NR	4.6 (6.64)	NR	303
Weighted average	**4.51 (6.50)**	**15.67 (22.61)**	**6.69 (9.65)**	**15.88 (22.92)**	–

Appendix B

Carboplatin - Non small cell lung cancer

	Significance levels pre-post	
Author, year (Ref.)	**PFS**	**OS**
Smit, 2008 (15)	HR 0.67; 95% CI 0.51 to 0.89, p = 0.005	HR, 0.85; 95% CI 0.63 to 1.2; p not significant
Ardizzoni, 2012 (6)	HR 1.05; 95% CI 0.81 to 1.36; p = 0.706	HR, 0.97; 95% CI, 0.73 to 1.30; p = 0.834

Cisplatin - Ovarian

	Significance levels pre-post	
Author, year (Ref.)	**PFS**	**OS**
Muggia, 2000 (7)	Statistics are not reported for paclitaxel *vs.* cis + pac	Statistics are not reported for paclitaxel *vs.* cis + pac

Cisplatin - Cervical

	Significance levels pre-post	
Author, year (Ref.)	**PFS**	**OS**
Pearcey, 2002 (8)	No significant difference was found in progression-free survival (p = 0.33)	No significant difference in survival. The HR for survival (arm 2 to arm 1) was 1.10 (95% confidence interval, 0.75 to 1.62)
Garipağaoğlu, 2004 (9)	p = 0.3	p = 0.7
Chiara, 1994 (10)	No significant difference was observed	No significant difference was observed

Cisplatin - Head and neck

	Significance levels pre-post	
Author, year (Ref.)	**PFS**	**OS**
Ghadjar, 2012 (11)	HR, 1.6; 95% CI, 1.1–2.5; p = 0.02	HR, 1.3; 95% CI, 0.9–1.8; p = 0.11

Oxaliplatin - Colorectal

	Significance levels pre-post	
Author, year (Ref.)	**PFS**	**OS**
Ibrahim, 2004 (12)	p < 0.0001	NR
de Gramont, 2000 (13)	p = 0.0003	p = 0.12
Giacchetti, 2000 (14)	p = 0.048	No significant difference was observed
Hospers, 2006 (15)	p = 0.016	p = 0.619
Kemeny, 2004 (16)	p = 0.0001	p = 0.20
Grothy, 2002 in Damjanovic, 2004 (17)	p ≤ 0.0001	No significant difference was observed
Rothenberg, 2003 (18)	p < 0.0001	NR