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Systemic therapies for recurrent or metastatic nasopharyngeal carcinoma: a systematic review

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Background: The majority of published studies in recurrent or metastatic nasopharyngeal carcinoma (RM-NPC) are single-arm trials. Reliable modelling of progression-free survival (PFS) and overall survival (OS) outcomes, therefore, is difficult. This study aim to analyse existent literature to estimate the relative efficacy of available systemic regimens in RM-NPC, as well as provide estimates of aggregate OS and PFS.

Methods: We conducted a systematic search of MEDLINE, EMBASE and the Cochrane Library to March 2015. Clinical trials (in English only) investigating cytotoxic and molecularly targeted agents in adult patients with RM-NPC were included. All relevant studies were assessed for quality using Downs and Blacks (DB) checklist (maximum quality score of 27). Aggregate data analysis and Student's *t*-test were performed for all identified studies (model A). For studies that published analysable Kaplan – Meier curves, survival data were extracted and marginal proportional hazards models were constructed (model B).

Results: A total of 56 studies were identified and included in model A, 26 of which had analysable Kaplan – Meier curves and were included in model B. The 26 studies in model B had significantly higher mean DB scores than the remaining 30 (17.3 *vs* 13.7, $P = 0.002$). For patients receiving first line chemotherapy, the estimated median OS was 15.7 months by model A (95% CI, 12.3–19.1), and 19.3 months by model B (95% CI, 17.6–21.1). For patients undergoing second line or higher therapies (2nd +), the estimated median OS was 11.5 months by model A (95% CI 10.1–12.9), and 12.5 months by model B (95% CI 11.9–13.4). PFS estimates for patients undergoing first-line chemotherapy by model A was 7.6 months (95% CI, 6.2–9.0), and 8.0 months by model B (95% CI, 7.6–8.8). For patients undergoing therapy in the 2nd + setting, the estimated PFS by model A was 5.4 months (95% CI, 3.8–7.0), and 5.2 months by model B (95% CI, 4.7–5.6).

Conclusions: We present the first aggregate estimates of OS and PFS for RM-NPC patients receiving first and second-line or higher treatment settings, which could inform the design of future clinical trials in this disease setting.

On a global scale, nasopharyngeal carcinoma (NPC) causes ~65 000 deaths annually, although its incidence varies widely by region (Ferlay *et al*, 2010). While rare in North America and Europe, the incidence of NPC exceeds 20 cases per 100 000 people in endemic regions, such as Southern China, Southeast Asia and the Middle East/North Africa (Chang and Adami, 2006). Different

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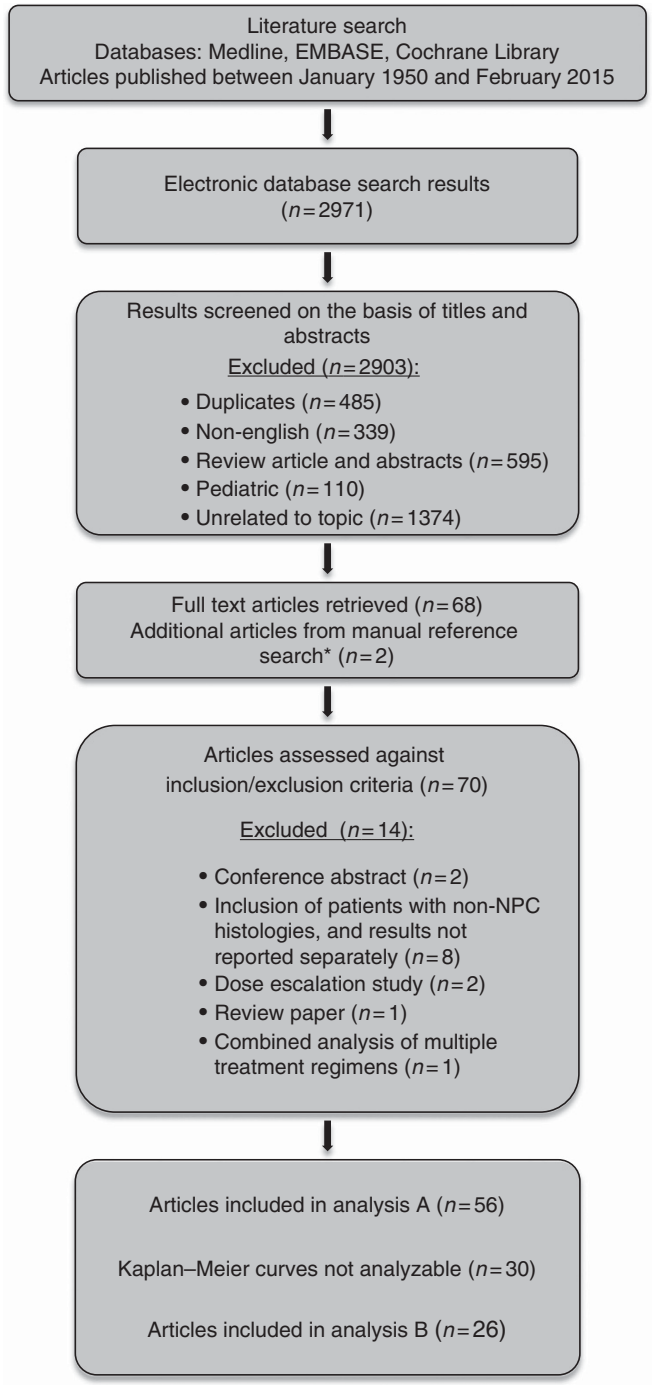

Figure 1. PRISMA flow diagram.

factors are thought to contribute to the pathogenesis of cases in endemic and non-endemic regions. Epstein – Barr virus (EBV) infection, environmental factors and genetic predisposition are proposed to be the main contributing factors in endemic regions, while the classic risk factors for other head and neck tumors such as smoking, alcohol and human papilloma virus (HPV) infection are thought to account more for cases in non-endemic areas (Vaughan *et al*, 1996; Chua *et al*, 2016).

Approximately 5 – 11% of patients present with *de novo* metastatic disease, while a further 15 – 30% of patients who were treated for locally advanced NPC will develop local recurrence and/or distant metastatic disease (Lee *et al*, 2015). Most recurrent cases are not amenable to salvage therapy with surgery and/or radiotherapy with or without concurrent chemotherapy. Hence, treatment options for the majority of patients with recurrent or metastatic NPC (RM-NPC) are largely limited to palliative systemic therapies (Lee *et al*, 2015).

NPC is a chemosensitive disease with some studies reporting response rates of over 80% with platinum-based chemotherapy regimens in recurrent or metastatic settings (Leong *et al*, 2008; Chen *et al*, 2013). Durable responses and prolonged survival have been observed in a subset of patients (de Graeff *et al*, 1987; Siu *et al*, 1998; Taamma *et al*, 1999). Therefore, despite the lack of direct comparison to supportive care, systemic chemotherapy is presently the mainstay of treatment for patients with RM-NPC. Due to the relatively low disease incidence, clinical trials investigating systemic therapies for RM-NPC typically enroll a heterogeneous patient population in a single treatment arm, which makes modelling of historical patient outcomes difficult (Lee *et al*, 2015).

This systematic review qualitatively examined studies of systemic therapies in RM-NPC to determine the relative efficacies of available drug regimens, and provide estimates of aggregated progression-free survival (PFS) and overall survival (OS); In particular, we seek to compare platinum to non-platinum regimens and investigate aggregate survival outcomes in the second line and beyond treatment setting. Trends over time in overall response rates (ORR), PFS and OS were also investigated. The Downs and Blacks (DB) checklist was chosen to assess the methodological quality of identified clinical trials as it allows assessment of both randomised and non-randomised studies (Downs and Black, 1998). Analysis of the association between clinical trial outcomes (ORR, PFS and OS) and characteristics of the study, including region where it was conducted, number of patients involved, study DB score and the year the trial was performed.

MATERIALS AND METHODS

Search strategy. A systematic search of MEDLINE (from 1950), EMBASE (from 1980), and the Cochrane Library was conducted to March 2015. Clinical trials investigating cytotoxic and molecularly targeted agents in adult patients with RM-NPC were included. The search was limited to human trials and studies published in the English language. Dose escalation or phase I clinical trials, immune therapies, concomitant and/or sequential use of radiotherapy or surgery, curative-intent systemic therapies, trials of patients with non-NPC histology where patient outcomes were not reported separately, conference proceedings and abstracts were excluded. The same search inclusion and exclusion criteria were applied to studies in models A and B; however, only studies with analysable Kaplan – Meier curves were used in model B analysis.

All search results were initially screened for relevance on the basis of article titles and abstracts by two authors (AP and AH). Full text articles were then retrieved for shortlisted studies. Additional trials were identified through manual searches of reference lists from the included articles. Reviewers were not blinded to study authors or outcomes. The decision to include a study for review was made by consensus between two authors (AP and AH). Disagreements would be resolved by a third author, but there were no unresolved differences.

Data extraction. Data were extracted by two teams of two reviewers (AP with AH and SO with TC). The following data were extracted for each trial: (1) study characteristics including clinical phase, region conducted and number of patients involved; (2) reported outcomes including ORR, PFS and OS; (3) grade 3 and 4 toxicities affecting at least 25% of study population; (4) patient characteristics including age, gender, prior treatment in the metastatic setting; and (5) details of the systemic therapy regimen under investigation.

Table 1. Study summary

Authors year	Region study conducted	Total number of evaluable patients	Regimen(s) under investigation	Median ORR (%)	Median PFS (months)	Median OS (months)	DB Score
First-line treatment settings							
Au, 1994	Asia	24	Cisplatin 33.3 mg m^{-2} on days 1–3; 5-fluorouracil 1000 mg m^{-2} daily on days 1–5, every 3 weeks.	66	8	11	8
Au and Ang, 1998	Asia	24	Paclitaxel 175 mg m^{-2} every 3 weeks.	22	2.5	12	14
Chen *et al*, 2013	Asia	95	Paclitaxel 135 mg m^{-2} on day 1, cisplatin 25 mg m^{-2} per day on days 1–3, 5-fluorouracil continuous infusion over 120 h, 600–1000 mg m^{-2} per day, every 3 weeks. Maximum of 6 cycles.	78.9	8.6	22.7	18
Chua and Au, 2005	Asia	19	Docetaxel 75 mg m^{-2} on day 1, cisplatin 75 mg m^{-2} on day 1, every 3 weeks. Protocol was later modified to 60 mg m^{-2} for both agents.	63	5.6	12.4	23
Chua *et al*, 2012	Asia	39	Cisplatin 100 mg m^{-2} on day 1, capecitabine 1000 mg m^{-2} twice daily for 14 days, every 3 weeks. Maximum of 6–8 cycles (8 if PR or CR).	54	8.5	28	20
Ciuleanu *et al*, 2004	Europe	40	Paclitaxel 175 mg m^{-2}, carboplatin AUC 6, every 3 weeks.	28	3.5	11.5	15
de Graeff *et al*, 1987	Europe	4	Doxorubicin 50 mg m^{-2} every 3 weeks, CCNU 120 mg m^{-2} every 6 weeks.	80	Not reported	Not reported	9
Fountzillas *et al*, 1997	Europe	14	Paclitaxel 200 mg m^{-2}, carboplatin AUC 7, every 4 weeks, with G-CSF.	57	16.5	Not reached	13
Hasbini *et al*, 1999	Europe	44	5FU 800 mg mc^{-2} on days 1–4, epirubicin 70 mg m^{-2} on day 1, cisplatin 100 mg m^{-2} on day 1, every 4 weeks. Mitomycin C 10 mg m^{-2} on cycle 1 day 1, cycle 3 day 1, and cycle 5 day 1. Maximum of 6 cycles.	52	9	14	16
Hsieh *et al*, 2013	Asia	22	Cisplatin 50 mg m^{-2} on days 1 and 22, mitomycin C 6 mg m^{-2} on day 1, oral tegafur-uracil 300 mg m^{-2} day on days 1–14, oral leucovorin 60 mg per day on days 22–35, every 6 weeks.	59	10	16	13
Jelic *et al*, 1997	Europe	80	Arm A: Zorubicin 325 mg m^{-2} per 24 h on day 1; Arm B: Zorubicin 250 mg m^{-2}/24 h on day 1 and Cisplatin 30 mg m^{-2} per 24 h on days 2–5. All repeated every 4 weeks.	$A=20$; $B=67.5$	Not reported	Not reported	15
Ji *et al*, 2012	Asia	46	Docetaxel 35 mg m^{-2} on days 1 and 8, Cisplatin 70 mg m^{-2} on day 1, every 3 weeks.	70.2	9.6	28.5	25
Leong *et al*, 2005	Asia	32	Paclitaxel 70 mg m^{-2} on days 1 and 8, carboplatin AUC 5 on day 1, gemcitabine 1000 mg m^{-2} on days 1 and 8, every 3 weeks until 2 cycles beyond maximum response, maximum total of 8 cycles.	78	8.1	18.6	18
Leong *et al*, 2008	Asia	28	Gemitabine 1000 mg m^{-2}, paclitaxel 70 mg m^{-2}, carboplatin AUC 2.5, on days 1 and 8, every 3 weeks, until 2 cycles beyond maximum response, maximum total of 6 cycles. If PR or CR then continue with weekly 5FU 450 mg m^{-2} and Leucovorin 30 mg m^{-2}, until PD or maximum treatment duration of 48 weeks.	86	8	22	21
Li *et al*, 2008	Asia	48	Capecitabine 1000 mg m^{-2} on days 1–14, cisplatin 80 mg m^{-2} on day 1, every 3 weeks. Maximum of 6 cycles.	63	7.7	13.5	16
Ma *et al*, 2009	Asia	40	Gemcitabine 1000 mg m^{-2} on day 1, oxaliplatin 100 mg m^{-2} on day 2, every 2 weeks. Maximum of 12 cycles.	56	9	19.6	18
McCarthy *et al*, 2002	North America	9	Docetaxel 75 mg m^{-2} on day 1, cisplatin 75 mg m^{-2} on day 1, every 3 weeks.	22	8.4	1-year survival rate 76%	19

Table 1. (Continued)

Authors year	Region study conducted	Total number of evaluable patients	Regimen(s) under investigation	Median ORR (%)	Median PFS (months)	Median OS (months)	DB Score
Siu *et al*, 1998	North America	90	Schedule 1 A: Cyclophosphamide 250 mg m^{-2}, doxorubicin 25 mg m^{-2}, cisplatin 50 mg m^{-2}, methotrexate 50 mg m^{-2}, bleomycin 15 mg m^{-2}, every 4 weeks. Schedule 1B: Cyclophosphamide 200 mg m^{-2}, doxorubicin 20 mg m^{-2}, cisplatin 50 mg m^{-2}, methotrexate 50 mg m^{-2}, bleomycin 10 mg m^{-2}, folinic Acid 10 mg every 6 h for 4 doses, every 4 weeks. Schedule 2 A: Cyclophosphamide 350 mg m^{-2}, doxorubicin 35 mg m^{-2}, cisplatin 70 g m^{-2}, methotrexate 50 mg m^{-2}, bleomycin 15 mg m^{-2}, every 4 weeks. Schedule 2B: Cyclophosphamide 350 mg m^{-2}, doxorubicin 35 mg m^{-2}, cisplatin 70 mg m^{-2}, methotrexate 50 mg m^{-2}, bleomycin 10 mg m^{-2}, folinic Acid 10 mg every 6 h for 4 doses, every 3 weeks.	All patients 73; VALD 86; MLD 41; MMD 80.	Not reported	All patients 16; VALD 47; MLD 16; MMD 14.	9
Stein *et al*, 1996	Africa	18	Cisplatin 50 mg m^{-2} and ifosfamide 3 g m^{-2} on days 1–2, every 3–4 weeks.	59	6.5	13.6	10
Tan *et al*, 1999	Asia	32	Paclitaxel 175 mg m^{-2} and carboplatin AUC 6, every 3 weeks.	75	7	1-year survival rate 52%	13
Villalon and Go Machica, 1990	Asia	24	Mitoxantrone 12–4 mg m^{-2}, every 3 weeks.	38	4.4	5.3	10
Xue *et al*, 2013	Asia	54	Sorafenib 400 mg twice daily, cisplatin 80 mg m^{-2} on day 1, 5-fluorouracil 1000 mg m^{-2} per day continuous infusion for 4 days, every 3 weeks to a maximum of 6 cycles, then followed by maintenance sorafenib.	78	7.2	11.8	20
You *et al*, 2012	North America	19	Gemcitabine 1000 mg m^{-2} on days 1 and 8, cisplatin 70 mg m^{-2} or Carboplatin AUC 5 on day 1, every 3 weeks. Then switch to Erlotinib 150 mg daily Q28D after 6 cycles, or prior if PD.	Chemotherapy = 37; Erlotinib = 0	6.3	Not reached (1-year survival rate 80%)	20
2nd + treatment settings							
Airoldi *et al*, 2002	Europe	12	Carboplatin AUC 5.5, paclitaxel 175 mg m^{-2}, every 3 weeks.	25	10	9.5	10
Altundag *et al*, 2004	Asia	21	Ifosfamide 2500 mg m^{-2} on days 1–3, mesna 2500 mg m^{-2} on days 1–3, doxorubicin 60 mg m^{-2} on day 1, every 3 weeks.	33.5	7	Not reported	9
Chan *et al*, 2005	Mixed	60	Cetuximab 400 mg m^{-2} then 250 mg m^{-2} weekly, carboplatin AUC 5, every 3 weeks to a maximum of 8 cycles.	11.7	2.7	7.7	16
Chen *et al*, 2012	Asia	56	Vinorelbine 25 mg m^{-2} and gemcitabine 1000 mg m^{-2} on days 1 and 8, every 3 weeks.	37.7	5.2	14.1	23
Chua and Au, 2003	Asia	17	Capecitabine 1.25 g m^{-2} twice daily for 2-weeks, every 3 weeks.	23.5	4.9	7.6	18
Chua *et al*, 2008	Asia	49	Capecitabine 1–1 · 25 g m^{-2} twice daily for 2-weeks, every 3 weeks.	37	5	14	12
Ciuleanu *et al*, 2008	Europe	23	Capecitabine 2500 mg m^{-2} per day for 14 days, every 3 weeks, to a maximum of 6 cycles.	48	14	Not reached at 18 months	15
Fandi *et al*, 1997	Europe	20	5-fluorouracil continuous infusion 300 mg m^{-2} per day until PD.	25	4	10	10
Lim *et al*, 2011	Asia	33	Pazopanib 800 mg daily.	6.1	4.4	10.8	23
Ma *et al*, 2008	Asia	15	Gefitinib 500 mg per day every 4 weeks. Maximum treatment duration of 8 months.	0	2.7	12	18
Peng *et al*, 2013	Asia	45	Capecitabine 1000 mg m^{-2} on days 1–14, Nedaplatin IV 8-mg m^{-2} on day 1, every 3 weeks.	41.7	5.8	12.4	16

Table 1. (Continued)

Authors year	Region study conducted	Total number of evaluable patients	Regimen(s) under investigation	Median ORR (%)	Median PFS (months)	Median OS (months)	DB Score
Poon *et al*, 2005	Asia	28	Irinotecan 100 mg m^{-2}, weekly for 3 weeks, every 4 weeks.	14	3.9	11.4	23
Wang *et al*, 2006	Asia	35	Vinorelbine 20 mg m^{-2}, gemcitabine 1000 mg m^{-2}, on days 1 and 8, every 3 weeks.	36	5.6	11.9	21
Zhang *et al*, 2008	Asia	30	Gemcitabine 1000 mg m^{-2} on days 1, 8 and 15, every 3 weeks.	43.8	5.1	16	15
Zhang *et al*, 2012	Asia	35	Pemetrexed 500 mg m^{-2} every 3 weeks.	2.9	1.5	13.3	14
Mixed first-line and 2nd+ treatment settings							
Azli *et al*, 1995	Europe	44	Cisplatin 100 mg m^{-2} on day 1, epirubicin 80 mg m^{-2} on day 1, bleomycin 15 mg m^{-2} bolus on day 1, bleomycin continuous infusion 16 mg m^{-2} per day on days 1–5, every 3 weeks for 3 cycles; Followed by 3 further cycles without bleomycin, total maximum of 6 cycles.	20	Not reported	Not reported	10
Boussen *et al*, 1991	Europe	49	Cisplatin 100 mg m^{-2} on day 1, bleomycin 15 mg on day 1 and 16 mg m^{-2} per day continuous infusion on days 1–5, 5-fluorouracil 650 mg m^{-2} per day on days 1–5, every 4 weeks, to a maximum of 3 cycles.	79	Not reported	Not reported	11
Chan *et al*, 1998	Asia	14	Temozolomide 150 mg m^{-2} daily for 5 days, every 4 weeks. If previous chemotherapy, 150 mg m^{-2}; if treatment naive 200 mg m^{-2}.	0	Not reported	Not reported	17
Chua *et al*, 2000	Asia	18	Ifosfamide 1.2 g m^{-2}, leucovorin 20 mg m^{-2}, 5-fluorouracil 375 mg m^{-2}, all on days 1–5 with mesna, every 3 weeks.	56	6.5	1-year survival probability 51%	12
Chua *et al*, 2008	Asia	19	Gefitinib 250 mg daily, continuous.	0	4	16	21
Dugan *et al*, 1993	Asia	99	Mitoxantrone 12 mg m^{-2} every 3 weeks.	25	4.6	13	11
Foo *et al*, 2002	Asia	Chemotherapy-naive = 25; previously treated = 27	Gemcitabine 1250 mg m^{-2} on days 1 and 8, every 3 weeks. Maximum of 6 cycles.	Chemotherapy-naive = 28; previously treated = 48.1	Chemotherapy-naive = 3.6; previously treated = 5.1	Chemotherapy-naive = 7.2; previously treated = 10.5	17
Foo *et al*, 2002	Asia	44	Gemcitabine 1000 mg m^{-2} on days 1 and 8, cisplatin 50 mg m^{-2} no days 1 and 8, every 4 weeks.	73	10·6	15	15
Lin and Hsu, 1998	Asia	44	Cisplatin 25 mg m^{-2}, 5-fluorouracil 1250 mg m^{-2} by continuous infusion over 24 h, weekly to a maximum of 24 cycles. Dose escalated after 19 patients to: Cisplatin 33.3 mg m^{-2} and 5-fluorouracil 1667 mg m^{-2}.	52.7	CR 6.5; PR 5.5	9	14
Ma *et al*, 2002	North America	32	Gemcitabine 1000 mg m^{-2} on days 1, 8 and 15, with or without cisplatin 70 mg m^{-2} on day 2, every 28 days.	G = 34; GC = 64	G = 4.6; GC = 9	G = 48; GC = 69; Median OS not reached	18
Ngeow *et al*, 2011	Asia	30	Docetaxel 30 mg m^{-2} on days 1, 8 and 15, every 4 weeks.	37	5.3	12.8	17
Su *et al*, 1993	Asia	25	Cisplatin 20 mg m^{-2} per day on days 1–5, 5-fluorouracil 1000 mg m^{-2} per day on days 1–5, bleomycin 15 mg m^{-2} on day 1, every 3–4 weeks.	40	Not reported	Not reported	8
Wang *et al*, 2008	Asia	75	Gemcitabine 1000 mg m^{-2} on days 1 and 8, cisplatin 25 mg m^{-2} on days 1–3, every 3 weeks.	42.7	5.6	9	14
Yau *et al*, 2012	Asia	15	Pemetrexed 500 mg m^{-2}, cisplatin 75 mg m^{-2}, every 3 weeks.	20	6.9	Not reported	11
Yeo *et al*, 1996	Asia	42	Carboplatin 300 mg m^{-2} on day 1, 5 F-fluorouracil 1 g m^{-2} per day on days 1–3, every 3 weeks to a maximum of 8 cycles.	38	Not reported	12.1	16
Yeo *et al*, 1998	Asia	27	Carboplatin AUC 6, paclitaxel 135 mg m^{-2}, every 3 weeks to a maximum of 6 cycles.	59	6	13.9	15

Table 1. (Continued)

Authors year	Region study conducted	Total number of evaluable patients	Regimen(s) under investigation	Median ORR (%)	Median PFS (months)	Median OS (months)	DB Score
Number of prior treatment lines not described							
Dede *et al*, 2012	Asia	30	Ifosfamide 2500 mg m^{-2} on days 1–3, mesna 2500 mg m^{-2} on days 1–3, doxorubicin 60 mg m^{-2} on day 1, every 3 weeks to a maximum of 6 cycles.	30	4	Not reported	9
Taamma *et al*, 1999	Europe	26. · 23 evaluable for response	5FU 700 mg m^{-2} per day on days 1–4, epirubicin 70 mg m^{-2} on day 1, bleomycin 10 mg on day 1 and bleomycin 12 mg m^{-2} on days 1–4 by continuous infusion, every 3 weeks. Bleomycin omitted after 3 cycles. Maximum total of 6 cycles.	69	9	15	15

Abbreviations: CMF = cyclophosphamide, methotrexate and 5FU; CR = complete response; DB = Downs and Blacks; G = gemcitabine; GC = gemcitabine and cisplatin; G-CSF = granulocyte colony-stimulating factor; MLD = measurable locoregional disease; MMD = measurable metastatic disease; NA = not available; PD = progressive disease; PR = partial response; VALD = very advanced local disease.

Table 2a. Survival analyses for use of combination *vs* single agent regimens in the first-line settings

		Model A/months (95% confidence interval)	*P*-value	Model B/HR (95% confidence interval)	*P*-value
First-line combination	mPFS	8.4 (6.9–9.8)	0 · 007	0.48 (0.41–0.56)	<0.0001
First-line single agent		3.5 (1.1–5.9)			
First-line combination	mOS	17.8 (14.2–21.4)	0 · 020	1.16 (0.98–1.38)	0.084
First-line single agent		8.2 (0.0–16.7)			

Abbreviations: HR = hazard ratio; mOS = median overall survival; mPFS = median progression-free survival.

Table 2b. Response rate analyses for use of combination *vs* single agent regimens in the first-line settings

	Model A mean ORR (95% confidence interval)	*P*-value	Model A weighted ORR	Model B (95% confidence interval)	*P*-value
First-line combination	61.8 (53.5–70.1)	<0.001	63.5	61.8 (54.6–69.1)	<0.001
First-line single agent	26.8 (14.2–39.4)		24.3	26.8 (22.2–61.4)	

Abbreviation: ORR = overall response rate.

Table 3a. Survival analyses for use of platinum-based *vs* non-platinum based regimens in the first line settings

		Model A/months (95% confidence interval)	*P*-value	Model B/HR (95% confidence interval)	*P*-value
First-line platinum	mPFS (months)	8.3 (7.0–9.6)	0.007	0.48 (0.41–0.56)	<0.0001
First-line non-platinum		3.5 (1.1–5.9)			
First-line platinum	mOS (months)	17.4 (13.9–20.8)	0.023	1.16 (0.98–1.38)	0.080
First-line non-platinum		8.2 (0.0–16.7)			

Abbreviations: HR = hazard ratio; mOS = median overall survival; mPFS = median progression-free survival.

Data analysis. All relevant studies were assessed for quality using the DB checklist (Downs and Black, 1998), which provided an overall score indicating reporting quality, internal validity (bias and confounding), power and external validity (Downs and Black, 1998). Aggregated data analysis and Student's *t*-tests were performed for all identified studies (model A). Two-sided *P*-values were calculated with a cutoff of 0 · 05 for significance. For studies that published Kaplan – Meier (KM) curves with sufficient resolution and details regarding censoring, survival data were extracted from the KM curves using electronic software, DigitizeIt, Germany, and individual patient-level data were recreated (Guyot *et al*, 2012). Survival analysis with marginal proportional hazard model methods was used to account for the clustering of patients within trials (model B) (Lin, 1994).

Response rate analyses were performed for all identified studies in model A. To account for clustering of data within studies, a

Table 3b. Response rate analyses for use of platinum-based *vs* non-platinum based regimens in the first line settings

	Model A Mean ORR (95% confidence interval)	*P*-value	Model A Weighted ORR	Model B (95% confidence interval)	*P*-value
First-line platinum	59.5 (50.5–68.6)	0.122	59.5	59.5 (50.5–68.5)	0.354
First-line non-platinum	41.8 (0.0–83.6)		31.7	41.8 (22.2–61.4)	

Abbreviation: ORR = overall response rate.

Table 4. Spearman correlation coefficients

Outcome under analysis	Year of publication	Number of patients enrolled	DB score
ORR	−0.05	0.18	−0.04
PFS	0.04	−0.08	0.03
OS	0.43	0.19	0.29

Abreviations: DB = Downs and Blacks; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

random intercept model was used in model B (Raudenbush and Bryk, 2002).

Fisher's Exact test was used to examine the difference in rates of occurrence of grades 3 and 4 haematological toxicities of the treatment regimens. Spearman correlation was used to analyse the relationship between study outcomes (ORR, PFS and OS) and the region where it was conducted, number of patients involved, study DB score and the year the trial was conducted.

All analyses were conducted in SAS (version 9·4, Cary, NC, USA). *P*-values of $<0·05$ were considered statistically significant.

Role of the funding source. There is no specific funding source for this study.

RESULTS

Systematic search. Systematic search results are summarised in Figure 1. A total of 56 articles were included in the final analysis of this review (summarised in Table 1).

Assessment of study quality. All 56 studies were included in model A analysis and 26 trials had analysable KM curves for inclusion in model B. The mean DB score for all studies was 15.3 (range 8–25). The 26 studies included in model B analysis had significantly higher mean DB scores than the other 30 studies (17.3 (95% CI 15.5–19.0) *vs* 13.7 (95% CI 12.2–15.1), $P=0.002$).

Survival analyses. For RM-NPC patients undergoing systemic therapy (chemotherapy and molecularly targeted agents) in the first-line setting, the estimated median OS by model A was 15.7 months (95% CI, 12.3–19.1), while model B estimated this at 19.3 months (95% CI, 17.6–21.1). For patients undergoing second line or higher therapies (2nd+), the estimated median OS by model A was 11.5 months (95% CI 10.1–12.9), while model B estimated this at 12.5 months (95% CI 11.9–13.4). Aggregate KM curves for OS from model B analysis are presented in the Supplementary Appendix Figures S1 and S2. PFS estimates for patients undergoing first-line chemotherapy by model A was 7.6 months (95% CI, 6.2–9.0), while model B estimated this at 8.0 months (95% CI, 7.6–8.8). For patients undergoing therapy in the 2nd+ setting, the estimated PFS by model A was 5.4 months (95% CI, 3.8–7.0), which was closely approximated by the model B analysis at 5.2 months (95% CI, 4.7–5.6). Aggregate KM curves for PFS from model B analysis are presented in the Supplementary Appendix Figures S3 and S4.

Combination chemotherapy regimens. The use of combination therapy in the first-line setting produced a statistically significant PFS improvement over single agent using both statistical models. Estimated PFS by model A was 8.4 months (95% CI, 6.9–9.8) for patients treated with combination therapy regimens in the first line setting, in comparison to 3.5 months (95% CI, 1.1–5.9, $P=0.007$) for monotherapy. Hazard ratio is estimated at 0.48 (95% CI 0.41–0.56, $P=<0.0001$) using model B analysis, in favor of combination therapy regimens. The OS outcomes were different between the two models as outlined in Table 2a and 2b. Model A showed a statistically significant improvement with use of combination therapy, but this was not corroborated in model B analysis.

Studies using combination chemotherapy regimens were more likely to report the occurrence of grades 3 and 4 haematological toxicities affecting at least 25% of all the patients enrolled in the study (56.7 *vs* 9.1%, $P=0.011$). Fifteen studies were excluded from this analysis due to missing toxicity reporting.

Platinum-containing regimens. Model A analysis supported the use of combination platinum-containing regimens in the first line setting with an estimated PFS of 8.3 months (95% CI, 7.0–9.6), in comparison to 3.5 months for non-platinum-containing therapies (95% CI, 1.1–5·9, $P=0.007$). Hazard ratio for the two treatment strategies was estimated at 0.48 by model B analysis (95% CI, 0.41–0.56, $P=<0.0001$), in favor of the platinum-containing regimens. The two statistical models again differed in their OS analyses, where model A showed statistically significant improvement with the use of first-line platinum-containing chemotherapy over non-platinum regimens, while the difference was not significant for model B. Statistical results and study distributions are summarised in Table 3a and b.

Studies using platinum-containing regimens are more likely to report the occurrence of grades 3 and 4 haematological toxicities affecting at least 25% of all the patients enrolled in the study (55.2 *vs* 12.5%, $P=0.010$). Eleven studies were excluded from this analysis due to missing toxicity reporting.

Response rate analysis. Model A analysis of mean and weighted ORR supports the use of combination chemotherapy in the first-line setting. The improvement in ORR with the use of platinum-based regimens for treatment-naive patients; however, was not found to be statistically significant when comparing to non-platinum based regimens (Tables 2a, b and 3a, b). ORR estimations by model B further supported the results from model A.

Use of targeted agents. Four clinical trials investigating three molecularly targeted agents (MTAs) were identified in this systematic review. MTAs investigated include pazopanib, gefitinib and cetuximab (Chan *et al*, 2005; Chua *et al*, 2008; Ma *et al*, 2008; Lim *et al*, 2011). One of the studies investigated cetuximab in

combination with carboplatin (Chan *et al*, 2005), while the other studies investigated the pazopanib and gefitinib in three separate studies as monotherapy (Chua *et al*, 2008; Ma *et al*, 2008; Lim *et al*, 2011). In three of the studies that investigated MTAs in the 2nd+ settings, the median PFS was lower than that estimated from all studies using both models A and B analyses. With the exception of one study investigating gefitinib, the median OS for MTAs in the 2nd+ setting was also lower than that estimated from all studies using both models A and B analyses (Chua *et al*, 2008; Ma *et al*, 2008; Lim *et al*, 2011). Currently, no MTA has been approved for treatment of RM-NPC (Lee *et al*, 2015).

Analysis of outcome generalisability. Wilcoxon signed-rank test of PFS comparing studies conducted in Asian *vs* non-Asian populations showed statistically significant differences in PFS, with higher values in non-Asian populations ($P = 0.02$). However, there was no statistically significant difference in ORR or OS outcomes ($P = 0.54$ and $P = 0.53$, respectively).

Spearman correlation analyses did not demonstrate any significant relationship between ORR or PFS and the year the study was published, number of patients enrolled, or DB score. However, there is moderate correlation between OS and the year of publication (Spearman correlation coefficient = 0·43). See Table 4 for Spearman correlation coefficients.

DISCUSSION

The first randomised phase III clinical trial in RM-NPC compared two platinum-based combination chemotherapy regimens in the first-line setting (Zhang *et al*, 2016). The reported PFS with gemcitabine and cisplatin (GP) was seven months compared with 5.6 months for 5-fluorouracil and cisplatin (FP). PFS outcome from the superior GP regimen is comparable to the aggregate PFS presented in our systematic review (7.6 months by model A, and 8 months by model B analyses). Compared to the aggregate OS however (15.7 months by model A, and 19.3 months by model B analyses), the reported median OS from the phase III clinical trial is higher at 29.1 months and 20.9 months for the GP and FP patient cohort, respectively (Zhang *et al*, 2016). Factors that may account for this difference in OS outcomes include differences in the characteristics of the patient population under study, better supportive or palliative care, improved management of chemotherapy-related side effects, as well as opportunities for patients to receive subsequent treatment on clinical trials. In addition, the earlier identification of progression with improved medical imaging techniques may further introduce lead time bias for OS.

However, this phase III trial does not address whether combination treatment is more effective than single agent therapy, or if platinum-containing regimens are superior to non-platinum-containing schedules. Our systematic review addressed this gap in knowledge. Our analyses support the use of platinum combination regimens in the first line setting with demonstrated superior PFS and OS outcomes of combination regimens over monotherapy; and platinum treatments over non-platinum regimens. First line platinum combinations for treatment of patients with RM-NPC is also recommended by expert consensus opinions such as the National Comprehensive Cancer Network (NCCN) guideline (Network, NCC, 2016).

Beyond the first line setting there is no standard of care regimen; however, if patients are suitable for further treatment they either receive another chemotherapy option such as docetaxel or participate in a clinical trial (Network, NCC, 2016). This review now provides important benchmarks (OS 11.5 – 12.5 months; PFS 5.2 – 5.4 months) for patients receiving second line treatment, which can inform future clinical trials of systemic therapies in RM-NPC. This information will be especially useful for studies adopting a single-arm design because there is now a robust historical control for comparison.

To our knowledge this is the first review of its kind in RM-NPC. Furthermore, the results can be interpreted as reliable given that the two different models typically produced similar estimates. The reason for the discrepancy between the two models for OS estimates for both platinum *vs* non-platinum regimens and combination *vs* monotherapy treatments, is probably attributable to the fewer studies included in model B because there are less publications reporting Kaplan – Meier survival curves in an extractable form and the low number of trials investigating non-platinum-containing chemotherapy regimens and single-agent chemotherapy in the treatment-naive patient population. In addition, the significantly higher PFS rates in studies conducted in non-Asian populations compared with Asian based studies is likely due to non-Asian studies typically investigating combination treatments. Notwithstanding, the broad range of included studies would permit the application of this information to most, if not all, populations of RM-NPC patients.

Our study has several limitations. The literature review was conducted to March 2015, hence results from the phase III study comparing two platinum-based combination chemotherapy regimens in the first-line setting (Zhang *et al*, 2016) was not included in the analysis. Original or reconstructed individual patient data from all trials was not used to calculate the OS and PFS estimates. Thus the analysis is impacted by the quality of reporting of the trial information. Trials that did not have KM curves of sufficient image quality could not be used, and thus reduced the number of studies included which as result increased the variance around the estimates. The heterogeneity of included patients in the reconstruction of survival data using model B analysis may limit the robustness of the results. Differences in DB scores further highlight the heterogeneity of clinical trials design and reporting. Furthermore, given that NPC is endemic in Asia, the exclusion of studies not published in the English language may be another limitation. Hence the results of this review must be interpreted within that context. It is important to note that the analyses performed in this systematic review were not designed to identify the optimal chemotherapy regimen, which remains to be defined. We have been particularly careful not to report the superiority of one specific regimen.

Interestingly our analysis demonstrated no significant changes in ORR or PFS over time, although there is moderate correlation between OS and the year of study publication. However, this result needs to be interpreted with caution due to the potential for biases given the majority of studies are single-armed with low patient numbers, and supportive care practices may have changed over time.

Ongoing challenges facing the interpretation of clinical trials investigating systemic therapies in RM-NPC include diversity in the patient demographics enrolled in the trials, lack of standardised treatment regimens, and relatively small patient populations studied (Zhang *et al*, 2016). A number of randomised clinical trials are presently ongoing (Butte *et al*, 2007; Lutzky *et al*, 2014; Ng *et al*, 2016), the results of which are eagerly awaited to resolve treatment dilemmas with generalisable result to various patient populations. It is hoped that novel agents such as immunotherapies may provide meaningful PFS and OS improvements in future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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