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REVIEW ARTICLE

A Bayesian network meta-analysis of comparison of cancer therapeutic vaccines for melanoma

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Abstract

Several approaches to active immunotherapy for melanoma, including peptide-based vaccines (PVs), autologous tumour cell vaccines (TCVs), allogeneic TCVs and autologous dendritic cell vaccines (DCVs), have been investigated in clinical trials. However, comprehensive evidence comparing these interventions remains unavailable. The objective of this study was to expand previous work to compare and rank the immunotherapeutic strategies for melanoma in terms of overall survival and toxic effects with a Bayesian network meta-analysis. Methodologically, we performed a network meta-analysis of head-to-head randomized controlled trials comparing and ranking cancer vaccine approaches for patients with melanoma. PubMed, MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov were searched up to 31 July 2020. We estimated summary hazard ratios for death and risk ratios for toxicity. The effects of the underlying prognostic variable on survival benefits were examined by meta-regression. We performed subgroup analysis for the outcomes based on metastatic categories. Overall, we identified 4776 citations, of which 15 head-to-head randomized controlled trials (3162 participants) were included in the analysis. In terms of efficacy, allogeneic tumour cell vaccines plus immunotherapy adjuvants, peptide-based vaccines plus immunotherapy adjuvants and standard therapy were more effective than peptide vaccines. The proportion of women was inversely associated with mortality risk. For safety, all treatments were inferior to allogeneic tumour cell vaccines except for allogeneic tumour cell vaccines plus chemotherapy. Peptide vaccines plus immunotherapy adjuvants led to an increased risk of adverse events compared to allogeneic tumour cell vaccines plus immunotherapy adjuvants. These results suggest that allogeneic TCV and autologous DCV are better than standard therapy. PV plus immune modulators are the most effective strategy among all comparable strategies but is associated with increased toxicity. Any combination regimens for cancer therapeutic vaccines need to be balanced between risk and benefit profiles.

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Conflict of interest

The authors declare that they have no competing interests.

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Introduction

Malignant melanoma is an aggressive malignancy with high mortality and dismal prognosis.[1–4] The incidence of melanoma has reached epidemic proportions.[5–7] Data published from the Surveillance, Epidemiology and End Results Program (SEER) database show that over the last decade, the annual cases of melanoma have increased by nearly 50% to over 287 000, which translates to more than 60 000 melanoma-related deaths per year. The latest data from the World Health Organization (WHO) predict that by 2050, the number of deaths resulting from melanoma will increase by 20%.[8]

Compared to other cancers, melanoma is characterized by higher mutation burdens, which render the tumour immunogenic. Moreover, the highly invasive nature of melanoma requires that therapies be widespread and targeted to tumour cells.[9–11] Active-specific immunotherapy in the form of cancer vaccines seems to be a promising strategy to satisfy this need. Vaccines of different types have been developed and utilized for cancer treatment and prevention throughout the past few decades. Sipuleucel-T (PROVENGE), a first-generation therapeutic cancer vaccine approved by the U.S. Food and Drug Administration (FDA) in 2010, is an autologous dendritic cell-based vaccine for the treatment of metastatic castration-resistant (hormone-refractory) prostate cancer.[12,13]

To our knowledge, antitumour responses can be induced by administering vaccines loaded with tumour-associated antigens (TAAs) or tumour-specific antigens to foster cytotoxic T-cell (CTL) activation and proliferation and thus promote cellular immune responses.[14,15] Recently, various vaccine approaches for melanoma have been explored in clinical trials. However, a majority of studies mostly focus on the efficacy and function of a subset of strategies rather than testing differences among these alternative types. The question of whether these approaches ultimately result in different curative effects is a matter of controversy.

To investigate this question, we used a Bayesian network meta-analysis approach to compare and rank nine immunotherapeutic vaccine regimens (autologous dendritic cell-based vaccine alone or in combination with chemotherapy, autologous tumour cell vaccine or autologous tumour cell vaccine plus chemotherapy, allogeneic tumour cell vaccine (TCV) or allogeneic TCV plus immune modulator or chemotherapeutic agent, and peptide protein-based vaccine alone or in combination with immune modulator) in terms of overall survival and toxic effects. A network meta-analysis is capable of expanding the scope of traditional pairwise analysis by evaluating both direct comparisons within trials and indirect comparisons across trials, thus enabling comparisons of treatments that have not been compared directly in head-to-head trials. The network meta-analysis presented here aims to provide additional evidence to guide adjuvant treatment options and inform immunization policies for patients with melanoma.

Methods

Search strategy and selection criteria

A network meta-analysis was done following the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA) guidelines. Details about methods and procedures are reported in the PRISMA NMA checklist (Appendix S12). The study is registered with PROSPERO (CRD42020196452) and includes a prespecified analytical plan.

We searched PubMed, MEDLINE, Embase, Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for clinical trials from database inception to 31 July 2020, using the following search terms: 'cancer vaccine', 'cancer therapeutic vaccine', 'vaccine therapy', 'peptide vaccine', 'PV', 'tumour cell vaccine', 'TCV', 'dendritic cell vaccine', 'DCV', 'melanoma' and 'clinical trial'. We included published and registered but unpublished trials with no language restrictions to limit publication bias. When duplicate publications were identified (e.g. trials published more than once), we included only the report with the most complete data. Two investigators (PL and MS) independently searched the databases. Details about search strategy are listed in the appendix (Appendix S1).

We identified large-scale RCTs investigating cancer therapeutic vaccines alone or in combination with single agents (e.g. immune modulator or chemotherapeutic agent) for patients who fulfilled diagnostic criteria for malignant melanoma. Studies investigating multiple malignancies including melanoma were also considered for inclusion. All potentially eligible trials were considered irrespective of outcomes. We excluded studies if they used a regimen other than the strategies as aforementioned or contained more than one standard adjuvant therapy as an intervention.

Three investigators (PL, FM and HL) independently selected the trials, reviewed study tittles and abstracts. Trials met inclusion criteria were retrieved for full-text evaluation. Any discrepancies and disagreements were resolved with the consensus of all investigators.

Data extraction and risk of bias assessment

Two reviewers (FM and HL) independently extracted information from each selected study, including first author and year of publication, study design, trial size, masking, median age, sex distribution, median follow-up and details of the intervention. For trials enrolling multiple malignancies, we only extracted data related to melanoma. We assessed methodological quality and internal validity of individual trials in accordance with the Cochrane Collaboration's Risk of Bias tool in Review Manager (RevMan) v5.3 based on the following domains: random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment,

incomplete outcome data (overall survival or toxicity), selective reporting, and major baseline imbalance. Judgments were graded as low, unclear or high risk of bias. Any disagreements were resolved by a third investigator (XC).

Outcomes

Our prespecified primary outcome was overall survival (OS) (time-to-death), defined as the time from randomization until death from any cause or censored at the time of last known alive. The secondary outcome was treatment-related toxic effects consisted of the collection of all. Since we found the inconsistencies in grading assessment criteria, and some terms were classified in different system organ categories from different versions, National Institute of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE v5.0) was applied based on extensive international participation to perform a unified statistical analysis of all-grade adverse events reported in each study.

Data analysis

We estimated hazard ratios (HRs) and associated 95% confidence intervals (CIs) or credible intervals (CrIs) for death in the overall population. When HRs were not reported, we calculated them from published time-to-event analyses based on the methods described by Tierney and colleagues.[16] For the dichotomous endpoint for overall toxic effects between studies, summary risk ratios (RRs) and 95% CIs or CrIs were analysed from the number of any-grade adverse events.

Two levels of analyses were conducted: first, we did the traditional pairwise meta-analysis with Stata MP 16.0 (StataCorp, College Station, Texas, USA). Pooled HRs for death and RRs for toxicity were calculated via the generic inverse variance and the Mantel-Haenszel (M-H) methods. Between-study heterogeneity was examined by using the Cochran Q test and I2 statistic, with the I2 index greater than 50% representing indicative of moderate-to-high heterogeneity. Second, a network meta-analysis was performed for each outcome that was computed in a Bayesian framework by WinBUGS version 1.4.3 (MRC, UK).[17–19] Both time-to-event estimates and dichotomous were calculated, respectively, by fixed-effects and random-effects models, and we used posterior mean of residual deviance (__Dres) and deviance information criteria (DIC) to access the fit of each model. Models were computed with Markov Chain Monte Carlo simulations.[20] For each outcome, three independent Markov chains with over-dispersed initial values from −2.50 to 2.50 were run with 100 000 inference iterations and a thinning interval of 10 per chain after a burn-in phase of 20 000 iterations to estimate the posterior distributions of parameters. Convergence of iterations was assessed graphically according to Gelman and Rubin.[21] Inconsistency was evaluated by comparing direct and indirect evidence on a specific node (the split node) from the entire network, and p values less than 0.1 were considered to be significant in inconsistency evaluation. The heterogeneity between trials as measured by a random-effects model was evaluated by the estimate of the corresponding SD. The surface under the cumulative ranking curve (SUCRA) and the mean ranks were estimated to express the percentage of effectiveness or safety of each intervention. A treatment with SUCRA value of 0 is the worst without uncertainty while a treatment with 1 is certain to be the best. To account for the dependency between outcomes, we further used a two-dimensional clustered ranking graph according to cluster analysis to obtain meaningful treatments.

As recommended by National Institute for Health and Care Excellence (NICE), a meta-regression model based on trial-level covariate and single interaction term was performed to determine whether the effects of interventions on survival were affected by different distribution of prognostic factors.[22,23] The following factors were prespecified as potential covariates, the percentage of patients with induced CTL responses, sex (e.g. female), ulcerations, prior treatments, Eastern Cooperative Oncology Group (ECOG) performance and elevated serum lactate dehydrogenase (e.g. LDH higher than upper limit of normal).

We also performed subgroup analyses based on metastases categories. Preplanned sensitivity analyses were conducted to guarantee the robustness of overall results. The first analysis restricted studies with 1:1 allocation, and the second analysis excluded multi-arm trials.

The potential publication bias (small-study effects) was estimated using visual inspection of funnel plots and corresponding Egger's regression test.[24] P values less than 0.10 correspond to statistically significant publication bias. If statistical analyses suggested a potential publication bias, non-parametric trim-and-fill computation (Duval-Tweedie) was used to adjust for the effect of publication bias.[25]

Results

We identified 4776 citations from database searches, of which 1109 were duplicates (Fig. 1). After initial screening, the full text of 58 potentially eligible studies was retrieved for detailed assessment. We included 20 studies (which described 15 randomized controlled trials) in the final network meta-analysis as they met our predefined eligibility criteria.[26,27,36–45,28–35] The characteristics of the included trials are summarized in Table 1.

Overall, 15 trials were conducted between 1976 and 2019, with a total of 3162 participants randomly assigned to receive one of the ten treatment approaches (Appendix S2). Sixty-one per cent (1937) of the 3162 patients were men. Patient age ranged from 18 years to 88 years, and follow-up ranged from 0 to 144.2 months. In one study, patients with melanoma and renal cell carcinoma (RCC) were enrolled. Seven of 15 studies were multicentre trials, two were single-centre trials, and the remaining six trials did not report the number of involved centres. Two studies were double-blind, one was triple-blind, and one was

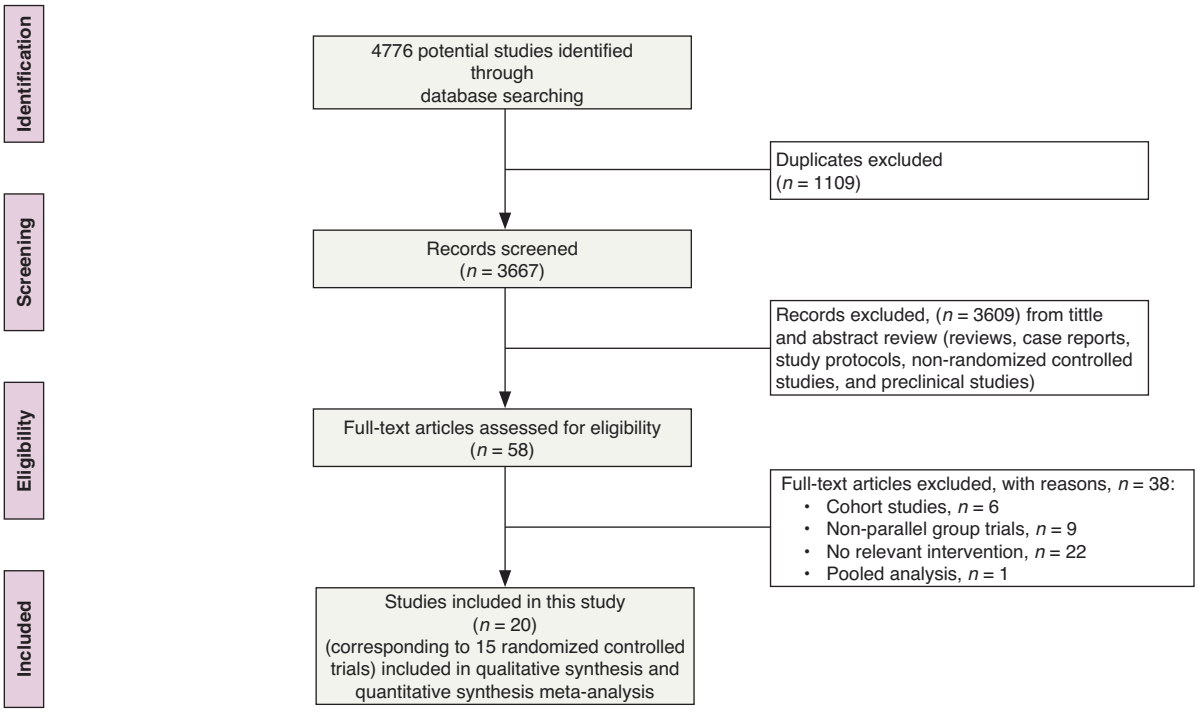

Figure 1 PRISMA flow diagram

single-blind. Eight studies were open-label, and the other three were not explicit about methods of masking.

Among the 15 selected trials, all were included in a network to analyse HRs for death, which were explicitly reported in 2 studies and could be estimated in the other 13 trials, and all trials were included in a network to analyse RRs for the proportion of adverse events. Figure 2 summarizes the detailed results of the risk of bias evaluation.

Direct meta-analysis for overall survival and toxicity profile shows that peptide vaccine plus immunotherapy was significantly more efficacious than peptide vaccine alone (HR 0.72, 95% CI 0.59–0.88, $P = 0.002$), and peptide vaccine was significantly less effective for promoting overall survival (HR 1.45, 95% CI 1.16–1.81, $P = 0.001$) than immunotherapy (Appendix S3). Allogeneic TCV plus adjuvant immunotherapy led to a significant reduction of 18% in any-grade adverse events compared with immunotherapy (RR 0.82, 95% CI 0.69–0.97, $P = 0.02$). Publication bias of traditional meta-analysis for outcomes by visual inspection of funnel plots and Egger's test did not suggest any small-study effect (Appendix S10).

The overall results of the network for efficacy and safety outcomes are summarized in Figure 3. The efficacy results of efficacy were obtained using the consistency fixed-effects model since the fit of the fixed-effects model was better than that of the random-effects model. Allogeneic tumour cell vaccine plus adjuvant immunotherapy provided an overall survival benefit over the peptide vaccine (HR 0.67, 95% CrI 0.50–0.91). Furthermore, the peptide vaccine was associated with poorer overall survival than the peptide vaccine plus immunotherapy (HR 1.69, 1.23–2.32) or standard treatment (HR 1.38, 1.16–1.64). Tests for inconsistency by the node-splitting method did not suggest significant differences (Appendix S5). A meta-regression model with covariate centring suggested strong interaction effects between overall survival benefits and sex. The proportion of female patients who received vaccination was positively related to survival benefits. The mortality risk for vaccination decreased by 2.74% per 1.00% increase in the number of females (95%CrI −5.23 to −0.38).

For the secondary endpoint of the safety profile in the consistency random-effects model, we found that allogeneic TCV plus adjuvant immunotherapy demonstrated a higher risk of adverse events than peptide vaccine plus adjuvant immunotherapy (RR 1.44, 1.02–2.06). Allogeneic TCV resulted in a decreased risk of adverse events compared to that of autologous DCV (RR 0.17,

Table 1 Characteristics of included trials

Study	Masking	Phase	Treatment, *n*	*N*	Number of men(%)	Stage	Median follow-up, months (range)	Median age, years (range)
Steve *et al*. (2019)	Open-label	II	Autologous DCV (10*106 cells, ic and 20*108 cells, iv) plus cisplatin (50 mg/m^2·100 mg/dose, iv), *n* = 27;	54	36 (66.7)	III–IV	63	54.5 (25–69)
			Autologous DCV (10*106 cells, ic and 20*108 cells, iv), *n* = 27					
Robert *et al*. (2018)	Open-label	II	Autologous DCV loaded with autologous TAA(sc), *n* = 18;	42	27 (84.3)	III–IV	24 (8–47)	58(NA)
			Autologous TCV (sc), *n* = 24.					
Mark *et al*. {2017)	Double-blind	III	CanvaxinTh1 plus BCG (1.5*106·3*106 cfu/dose, lc), *n* = 248;				19.7	55.5 (21–79)
			Placebo plus BCG (1.5*108-3*106 cfu/dose, ic), *n* = 250.					
David *et al*. (2015)	Double-blind	III	GM·CSF (250 ug/day) plus multiepitope vaccine (Montanide ISA-51,sc), *n* = 109‡;	435	259 (59.5}	III–IV	82.1 (0–144.2)	58.5 (22–87)
			GM-CSF placebo plus multiepitope vaccine (Montanide ISA-51, sc),*n* = 111;					
			GM-CSF (250 ug/day) plus peptide placebo (sc), *n* = 109;					
			GM·CSF placebo plus peptide placebo (sc), *n* = 107					
Gautam *et al*. (2014)	Open-label	II	Allogeneic L.MI 0.2 mL (1*107,5 um silica spheres,ic) plus IL·2 (2*1061Uid, sc), *n* = 11;	21	10 (47.6)	IV	16	NA
			IL-2 (2*106 IU/day, sc), *n* = 10.					
McDermott *et al*. (2013)	Triple-blind	III	Gp100 vaccine (2 mL/dose, sc) plus ipilimumab (3 mg/kg, iv), *n* = 403;	878	401 {59.3)	III–IV	69 (49–78)	56 (19–88)
			Placebo plus lpIIImumab (3 mglkg, lv), *n* = 137;					
			Gp100 vaccine (2 mL/dose, sc) plus placebo, *n* = 138.					
Douglas *et al*. (2011)	Single-blind (Investigator)	III	Gp100 vaccine (Montanide ISA-51,sc) plus Aldesleukin (720 000 IU/kg,iv), *n* = 91;	185	120 (64.9)	III–IV	41.5	48.5 (18–85)
			Aldesleukin (720000 IU/kg,iv), *n* = 94.					
Mark *et al*. (2009)	Open-label	II	CanvaxinTh1 (25*106 calls/dose) plus GM-CSF (200 ug/m2/day, ic), *n* = 46;	94	60 (63.8)	II–IV	31	NA
			CanvaxinTh1 (25*108 cells/dose, ic), *n* = 48.					
Alessandro *et al*. (2008)	Open-label	III	Vitespen (sc), *n* = 215;	322	190 (59.0)	IV	NA	55 (19–87)
			IL-2 (60 million U/m^2) and/or OTIC (1000 mg/m^2)/temozolomide (600 mg/m^2) and/or tumour resection, *n* = 107					
Arkadiusz *et al*. (2008)	Unclear	II	Autologous LMI (1*107,5 um silica spheres, ic), *n* = 10;	20	14 (70.0)	IV	20.4 (1.8–71.4)	58 (36–82)
			Autologous LMI (1*107,5 um silica spheres, ic) plus Cyclophosphamide (300 mg/m^2,iv), *n* = 10.					
Malcolm *et al*. (2007)	Open-label	III	Melacine (2 mL/dosa, sc) plus IFN-a·2b (5 MU/m2,sc), *n* = 299;	600	395 (85.8)	III	32	48.5
			IFN-a-2b (10.20 MU/m2, iv/sc), *n* = 301§.					

Table 1 *Continued*

Study	Masking	Phase	Treatment, *n*	*N*	Number of men(%)	Stage	Median follow-up, months (range)	Median age, years (range)
Esteban *et al.* (2007)	Unclear	II	MPS180 vaccine (Montanide ISA-51,sc), *n* = 10;	28	18 (57.1)	IV	12	58 (33–74)
			MPS180 vaccine (Montanide ISA-51, sc) plus GM·CSF (75 ug), *n* = 9;					
			MPS180 vaccine (Montanide ISA-51,sc) plus GM·CSF (100 ug), *n* = 9.					
Schadendor f *et al.* (2006)	Open-label	III	Autologous peptide loaded ocv (4*106 cells/ dose, sc.), *n* = 53;	108	68 (63.0)	IV	22.2	58 (19–80)
			OTIC 850 (mg/m2, iv), *n* = 55.					
Svetomir *et al.* (2006)	Unclear	II	Multiepitode vaccine (Montanide ISA-51, sc), *n* = 8‡	25	14 (56.0)	IV	12	64 (29–87)
			Multiepitode vaccine (Montanide ISA-51,sc) plus GM-CSF (10 ug), *n* = 9;					
			Multiepitode vaccine (Montanide ISA-51,sc) plus GM•CSF (50 ug), *n* = 8.					
Newlands *et al.* (1976)	Open-label	II	Allogeneic melanoma cells (2*107) mixed with BCG (50 ug,ic) plus OTIC (1OO mg/ m^2, IV) and ICRF·159 (125 mg,iv), *n* = 27;	56	24 (42.9)	IIB-III	11	NA
			DTIC (100 mg/m^2,iv) and ICRF-159 (125 mg), *n* = 29					

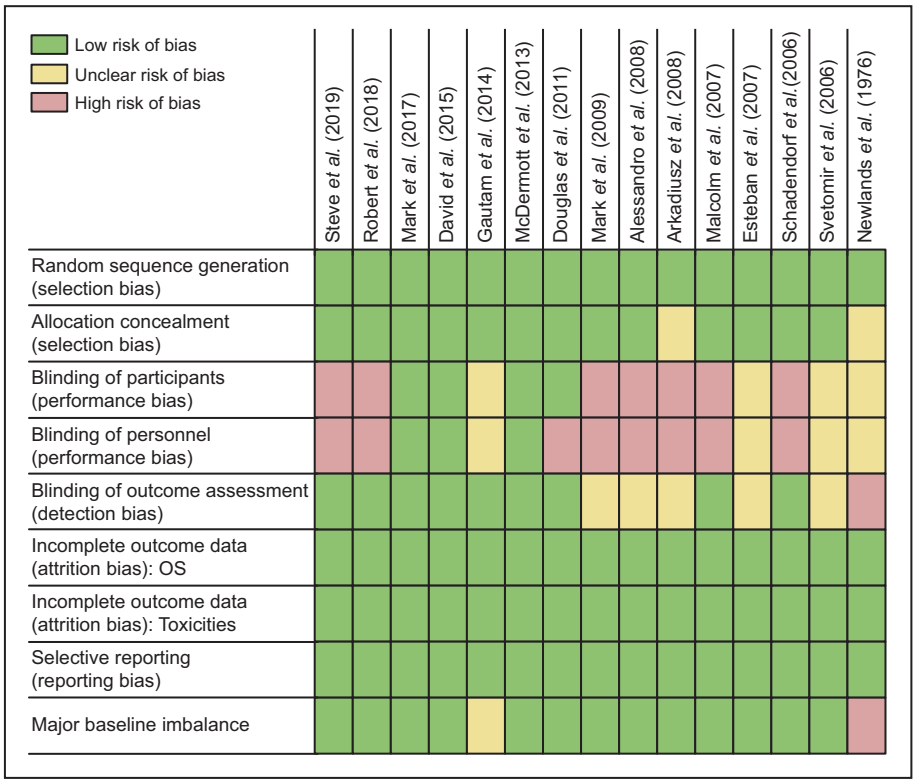

Figure 2 Quality assessment of included trials in the meta-analysis. Summary of risk of bias assessment (a) and graph of risk of bias assessment (b)

Efficacy (overall survival, HR [95% CrI]) Treatment Toxicity (any-grade adverse events, RR [95% CrI])

AUD	1.31 (0.78-2.23)	1.21 (0.70-2.11)	1.58 (0.32-6.66)	0.17 (0.04-0.67)	1.02 (0.32-3.04)	1.32 (0.11-8.41)	1.37 (0.44-3.98)	1.50 (0.49-4.29)	1.24 (0.41-3.53)
0.55 (0.21-1.44)	**AUDC**	0.94 (0.46-1.69)	1.18 (0.24-3.24)	0.15 (0.03-0.62)	0.80 (0.24-2.06)	1.01 (0.09-3.66)	1.04 (0.33-2.47)	1.12 (0.36-2.61)	0.95 (0.30-2.29)
0.76 (0.25-2.34)	1.40 (0.32-6.08)	**AUT**	1.34 (0.29-5.00)	0.14 (0.03-0.64)	0.86 (0.22-2.90)	1.16 (0.09-7.12)	1.17 (0.31-3.72)	1.29 (0.35-4.02)	1.05 (0.29-3.34)
0.23 (0.04-1.51)	0.42 (0.05-3.50)	0.30 (0.07-1.36)	**AUTC**	0.10 (0.01-0.81)	0.63 (0.08-3.75)	0.86 (0.04-7.75)	0.88 (0.11-4.77)	0.98 (0.12-5.12)	0.78 (0.10-4.33)
1.17 (0.33-4.07)	2.13 (0.44-10.30)	1.53 (0.29-8.24)	5.14 (0.53-48.56)	**ALT**	2.38 (1.56-3.90)	2.37 (0.88-5.15)	2.57 (1.60-4.55)	2.63 (1.62-4.73)	2.51 (1.59-4.32)
0.97 (0.60-1.54)	1.77 (0.60-5.12)	1.27 (0.38-4.27)	4.25 (0.63-29.26)	0.83 (0.26-2.64)	**ALTI**	1.29 (0.17-6.24)	1.32 (0.93-1.90)	1.44 (1.02-2.06)	1.20 (0.92-1.56)
0.97 (0.41-2.34)	1.78 (0.49-6.53)	1.28 (0.31-5.34)	4.30 (0.54-33.82)	0.84 (0.21-3.39)	1.01 (0.46-2.22)	**ALTC**	0.90 (0.10-5.39)	1.00 (0.11-5.85)	0.80 (0.09-4.80)
0.65 (0.40-1.06)	1.19 (0.40-3.48)	0.86 (0.25-2.90)	2.86 (0.42-19.84)	0.56 (0.17-1.84)	0.67 (0.50-0.91)	0.67 (0.30-1.49)	**PV**	1.12 (0.83-1.51)	0.91 (0.69-1.21)
1.10 (0.69-1.75)	2.01 (0.69-5.81)	1.45 (0.43-4.85)	4.84 (0.71-33.26)	0.95 (0.29-3.08)	1.14 (0.89-1.47)	1.13 (0.52-2.48)	1.69 (1.23-2.32)	**PVI**	0.83 (0.65-1.04)
0.98 (0.64-1.50)	1.79 (0.63-5.09)	1.29 (0.39-4.22)	4.31 (0.64-29.09)	0.85 (0.26-2.72)	1.02 (0.84-1.22)	1.01 (0.47-2.17)	1.38 (1.16-1.64)	0.85 (0.71-1.02)	**STT**

Figure 3 Head-to-head comparisons for overall survival and toxic effects in network meta-analysis. The column-defining treatment is compared to row-defining treatment. For efficacy in the left lower half, the first line in black is crude HR for death, and the second line in red is HR adjusted for the proportion of patients received prior treatments. HRs lower than 1 favour the column-defining treatment. For toxicity in the right upper half, RRs lower than 1 favour the column-defining treatment. Cells in bold print indicate significant results. AUD, autologous DCV; AUDC, autologous DCV plus chemotherapy; AUT, autologous TCV; ALT, allogeneic TCV; ALTI, allogeneic TCV plus immunotherapy; ALTC, allogeneic TCV plus chemotherapy; PV, peptide vaccine; PVI, peptide vaccine plus immunotherapy; IMM, immunotherapy; CHE, chemotherapy; HR, hazard ratio; RR, risk ratio

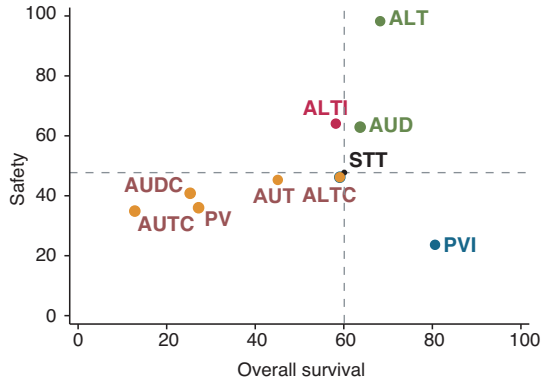

Figure 4 Two-dimensional ranking plot of treatments for overall survival benefit and safety. Treatments lying in the upper right corner are more effective and less toxic

95% CrI 0.04–0.67), autologous DCV plus chemotherapy (RR 0.15, 0.03–0.62), autologous TCV (RR 0.14, 0.03–0.64) or autologous TCV plus chemotherapy (RR 0.10, 0.01–0.81). Moreover, allogeneic TCV plus adjuvant immunotherapy (RR 2.38, 1.56–3.90), peptide vaccine (RR 2.57, 1.60–4.55), peptide vaccine plus adjuvant immunotherapy (RR 2.63, 1.62–4.73) or standard treatment (RR 2.51, 1.59–4.32) were significantly associated with a higher risk for any-grade adverse events than allogeneic TCV. For the analysis of RR, the average SD was 0.16 (95% CrI 0.02–0.46), and we noted no evidence of statistical inconsistency between direct and indirect estimates (Appendix S5). The comparison-adjusted funnel plots of the network meta-analysis for both endpoints did not show any publication bias (Appendix S11).

Regarding the outcomes in patients with metastatic melanoma, direct pairwise and network meta-analyses for efficacy and toxicity profiles subdivided according to metastasis categories were conducted, and nine treatment strategies were

available for comparison (Appendix S7). In terms of overall survival, the significant differences between autologous DCV, peptide vaccine (HR 0.57, 95% CrI 0.36–0.92) and autologous TCV plus chemotherapy (HR 0.21, 95% CrI 0.04–0.97) supported autologous DCV as an option for patients with advanced melanoma. For toxicity, allogeneic TCV remained superior among the comparable treatments in the metastasis subgroup.

The clustered ranking of ten competing treatments in the network based on SUCRA values for efficacy and toxicity is presented in Figure 4. Detailed results are listed in the Appendix S6. In terms of overall survival, PV plus adjuvant immunotherapy (80.6%), allogeneic TCV (68.2%) and autologous DCV (63.7%) were most likely to be ranked as the best, the second-best, and the third-best, respectively. The least effective strategy was autologous TCV plus chemotherapy (12.8%). When metastasis categories were considered, the top three interventions in terms of overall survival were PV plus adjuvant immunotherapy (86.5%), autologous DCV (75.7%) and allogeneic TCV (68.5%).

In terms of safety, the top three ranked interventions were allogeneic TCV (98.2%), allogeneic TCV plus adjuvant immunotherapy (64.1%) and autologous DCV (62.9%), while peptide vaccine plus immune modulator ranked as the worst (23.6%); further subgroup analysis did not show the difference in ranking. In other words, allogeneic TCV had a similar ranking and was more beneficial in accordance with the balance between the two outcomes.

According to two prespecified sensitivity analyses, the results of the network meta-analysis and probability of ranking the treatments did not show relevant deviations compared with the original analyses (Appendix S8 and S9).

Discussion

In this network meta-analysis, we comprehensively summarized and compared all available cancer therapeutic vaccines for melanoma using data from head-to-head trials.

Our results suggested that allogeneic TCV or allogeneic TCV plus immune modulators were consistent in providing an overall survival advantage and good safety profiles. Peptide vaccines plus adjuvant immunotherapy further improved the survival benefit but increased toxicities. Autologous dendritic cell vaccination was correlated with prolonged survival and was well tolerated by patients with advanced melanoma. Combination strategies involving cancer therapeutic vaccines plus immune-modulating agents or chemotherapies were more likely to result in adverse events in general. Allogeneic whole-cell vaccines showed a tendency toward better clinical results than autologous tumour cell vaccines in terms of efficacy and safety due to their major advantage of presenting a broader spectrum of TAAs, thus increasing the antitumour response.

Several studies point towards an association between immune-related adverse events and better outcomes among patients with melanoma who receive immune checkpoint inhibitors; the onset of immune-related adverse events (irAEs) may be considered a predictive biomarker for the response to ICIs.[46–51] This provides interesting insights into the potential mechanisms of complications that arise in patients with melanoma treated with active immunotherapy. However, because the mechanism of the specific immunotherapy-induced antitumour response is distinctly different from that of ICIs, we infer that the pathogenesis of complications is likely related to the mechanism of the whole tumour cell vaccine, in all its complexity. It seems more likely that autologous TCV mediated more complications than allogeneic TCV due to the molecular mimicry hypothesis of epitope spreading and cross-reactivity of TAAs. Self-derived TAAs may be more highly expressed in normal tissue, leading to robust activated T-cell-mediated toxicity. Moreover, previous studies demonstrated a directed interaction between memory T cells and antigen-presenting cells and tumour-specific memory T cells have the necessary specificity to distinguish tumour cells from normal cells in patients with cancer.[52–54] Allogeneic TCV with a broad spectrum of TAAs originating from the extrinsic pathway may induce a high frequency of tumour-reactive memory T cells, and these cells can be restimulated upon a second encounter with the same antigen and differentiate into effector T cells.[55]

In recent years, many researchers have focused on the issue of combination immunotherapies since many studies have revealed a synergistic effect with combinations, along with incremental toxicity.[56] In agreement with these reports, our results suggest that immunotherapeutic combinations, including cancer vaccines, increase the occurrence of toxic effects, which highlights the importance of rigorously investigating the pharmaceutical window.

The manufacture of dendritic cell-based vaccine appears promising as a strategy to induce an immune response. To our knowledge, dendritic cells (DCs) are the most potent professional antigen-presenting cells (APCs). High expression of major histocompatibility complex class I or II (MHC-I/II) on DCs ensures their robust antigen presentation capability, and costimulatory molecules on the surface of DCs can sensitize T lymphocytes and enhance T-cell activation. Furthermore, the release of cytokines by mature DCs (mDCs) can positively regulate the differentiation of circulating natural killer cells (NKs).[57,58] Our exploratory subgroup analyses show that the effect of DC-based vaccination is significant in advanced melanoma. Possible explanations include that tumour cells evade the surveillance of immune cells via multiple mechanisms and are unable to mobilize the antitumour immune response, which destroys the dynamic balance between immunological activation and inhibition, thus leading to systemic immunosuppression and local immune dysfunction.[59] Immunization with in vitro-cultured DCs, mainly derived from monocytes, can generate vigorous CTL-induced specific immune responses and non-specific NK cell responses. It is now well established that tumours of diverse

antigenic aetiologies are susceptible to DC-based therapy. Currently, some studies emphasize on optimizing DC products with novel technologies to overcome the problems associated with MHC-negative cells and antigenic heterogeneity in patients with melanoma.

Peptide-based vaccines consist of single or multiple peptide antigens that can be recognized by T lymphocytes and activate CTLs reactive towards cancer cells.[60,61] However, the use of peptide antigens as cancer vaccines is MHC-restricted, targeting only one or a few antigenic epitopes, which in turn limits extrapolation and results in heterogeneity in clinical benefits. Generally, peptide vaccines are administered with an adjuvant to enhance the antitumour response. Our results show that the peptide vaccine combined with an immune modulator is effective for improving survival.

Increasing evidence illustrates that sex is a crucial biological variable in the pathogenesis and prognosis of malignancies.[62–65] Notably, our findings show that females with melanoma are more likely to improve survival after vaccination, suggesting sex-specific survival benefits between specific and non-specific immunotherapies and the propensity for sex-dependent effects in patients with melanoma treated with cancer vaccines. It is unequivocal that sex-based initiation and adaptive immune response differences are caused by multiple factors, including genes, steroid hormones and environmental factors.[66,67] Our analysis underlines the role of sex differences in clinical efficacies in patients treated with cancer vaccines. Future trials highlighting the treatment type and dosage associated with the sex-based differences should be conducted.

This network meta-analysis, which synthesizes all evidence to date, is the first to evaluate autologous or allogeneic tumour cell vaccines, autologous dendritic cell-based vaccines, peptide-based vaccines and combinations with immunomodulators or chemotherapeutic agents separately, which provides new insight into this issue with implications for future research and practice choices. The present study has several strengths. As an expansion of conventional pairwise meta-analysis, network meta-analysis allows us to make full use of available evidence and perform a simultaneous analysis of all potential interventions by indirect comparisons based on a common comparator across studies, thus providing strengthened and precise evidence. Furthermore, the application of a Bayesian framework implemented with MCMC algorithms is flexible and allows the computation of models with complex data sets due to its ability to incorporate prior information and summarize the information about all treatment options studied by the use of the posterior distribution, which is not possible using frequentist statistics. To circumvent potential selection bias, we incorporated all data on survival endpoints across trials within a single network meta-analysis. Overall survival is still the gold standard endpoint to assess the efficacy of therapeutic options in oncologic intervention trials. Since the previous study suggested that toxicity might not be associated with overall survival in cancer treatments, we evaluated both outcomes to provide a comprehensive insight into the benefit and risk balance of the different treatment strategies. We separately verified the presence of publication bias within pairwise and network meta-analyses because the funnel plots in the network meta-analysis needed to account for the fact that summary estimates in each study were derived from different comparisons. The potential publication bias of the network meta-analysis can be more accurately screened after adjusting for comparison.

The limitations of our study should be stated. First, blinding of several trials was not feasible because of ethical issues, especially for patients with terminal-stage disease, which inevitably increases the risks for detection and performance bias. Second, subgroup analysis could not be conducted in detail due to data sparseness across studies. The statistical analyses based on existing evidence were interpreted with caution and conservation, and we deemed that the original results were reliable for providing effective estimates. Third, unavoidable confounding factors remain imbalanced at the individual level across comparisons.

Conclusions

Our network meta-analysis suggests that allogeneic tumour cell vaccines alone or in combination with immune modulators and autologous dendritic-based vaccines appear to be the optimum treatments for patients with melanoma. Peptide vaccines plus immune modulators are effective for improving survival but have more toxic effects. Combination strategies for cancer vaccines are more likely to be associated with increased toxicity risk than vaccine therapy alone. These findings could fill an important knowledge gap regarding cancer vaccines and aid the development of clinical guidelines.

Authors' contributions

HL, XC, YC and JZ conceived the study project. PL and MS designed the study, collected literatures and accessed the quality of trials. FM and HL performed the data extraction and checking. JZ and PL did the statistical analysis and created the figures and tables. All authors contributed to interpretation of results. PL and XC wrote the first draft of the report and all authors revised the final manuscript. JS, YC and PL revised and reviewed the manuscript. MS, HL, YC and JS supervised the study.

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Ethical approval and consent to participate

All analyses were based on previous trials and literature; thus, no ethical approval or patient consent was required.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.
Appendix S2. Network of eligible comparisons.
Appendix S3. Forest plots of traditional meta-analysis and Bayesian network meta-analysis for overall survival and any-grade toxic effects.
Appendix S4. Heterogeneity test results of pairwise and network meta-analysis for each outcome.
Appendix S5. Assessment of model fit and inconsistency for each outcome.
Appendix S6. Treatment cumulative ranking plot.
Appendix S7. Subgroup analysis.
Appendix S8. Sensitivity network meta-analysis including trials with 1:1 allocation.
Appendix S9. Sensitivity network meta-analysis removing multi-arm trials.
Appendix S10. Funnel plot for each outcome from pairwise meta-analysis.
Appendix S11. Comparison-adjusted funnel plot for each outcome from the network meta-analysis.
Appendix S12. PRISMA NMA checklist.