Clinical efficacy of nivolumab and ipilimumab combination therapy for the treatment of advanced melanoma: systematic review and meta-analysis of clinical trials.

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Abstract

Background

Advanced melanoma accounts for the majority of skin cancer death due to its poor prognosis. Nivolumab and ipilimumab are monoclonal antibodies targeting on programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocytes antigen 4 (CTLA-4). Nivolumab and ipilimumab combination therapy has been proven to be effective for advanced melanoma. This systematic review and meta-analysis is to evaluate its clinical efficacy and adverse events.

Method

A systematic search was done on databases (Pubmed, Embase, Medline, Cochrane) on 21 June 2020. Search keywords were nivolumab, ipilimumab, melanoma, and randomised controlled trials. Clinical trials fulfilling the inclusion criteria were selected to evaluate the efficacy of combination therapy in terms of prolongation of progression-free survival (PFS), overall survival (OS) and objective response rate (ORR). The odd ratios and distributions of grade 3 or above adverse events were documented. Subgroup analysis was performed based on PD-L1 expression-status and BRAF-mutation status.

Results

Compared with nivolumab monotherapy, the hazard ratios of PFS, OS and odd ratio of ORR in combination therapy were 0.64 (95% CI, 0.48-0.85; p=0.002), 0.84 (95% CI, 0.74-0.95; p=0.007) and 1.76 (95% CI, 1.51-2.06; p<0.001), respectively. Compared with ipilimumab monotherapy, the hazard ratios of PFS, OS and odd ratio of ORR were 0.46 (95% CI, 0.37-0.57; p<0.001), 0.54 (95% CI, 0.48-0.61; p<0.001) and 6.18 (95% CI, 5.19-7.36; p<0.001), respectively. In combination therapy, the odd ratios of grade 3 or above adverse events were 4.71 (95% CI, 3.57-6.22; p<0.001) compared with nivolumab monotherapy, and 3.44 (95% CI, 2.49-4.74; p<0.001) compared with ipilimumab monotherapy, respectively. High PD-L1

expression level and BRAF mutation were associated with better clinical outcomes in patients receiving combination therapy.

Conclusion

Combination therapy is effective for the treatment of advanced melanoma. Adverse events were common but manageable. Better clinical outcomes were observed in patients with high PD-L1 expression level and positive BRAF-mutation.

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Conflict of interest

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Ethics Approval

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Availability of data and material

All data were directly retrieved from databases (Pubmed, Embase, Medline, Cochrane).

Code availability

Review manager, version 5.3 and SPSS (IBM)

Author's contributions

Literature search was done by Zhipeng Yan and Prof.Ching-Lung Lai. Study design was done by Zhipeng Yan and Janice Wing-Tung Kwong. Figures, data collection, data analysis, data interpretation and manuscript writing were done by Zhipeng Yan, Janice Wing-Tung Kwong and Prof. Ching-Lung Lai.

Introduction

Melanoma is the cancer of pigment-producing cells, with over 280,000 new cases and over 60,000 deaths annually[1]. Advanced melanoma accounts for the vast majority of skin cancer death. Advanced melanoma refers to melanoma of stage III or beyond , with 5-year survival rate of 63.6% and 22.5% in stage III and IV melanoma patients, respectively[2].

Nivolumab is a program cell death protein (PD-1) monoclonal antibody for the treatment of melanoma[3]. Ipilimumab is a monoclonal antibody targeting on cytotoxic T-Lymphocytes Antigen 4 (CTLA-4) protein, which is also an effective treatment for melanoma[4]. The combination of nivolumab with ipilimumab has been used as the first line treatment for inoperable melanoma without BRAF mutation, the signalling pathway for cellular growth and spread of cancer[5]. Better clinical outcomes have been observed with nivolumab and ipilimumab combination therapy [6-9].

A previous meta-analysis of the combination therapy included only 6 clinical trials[10]. This systematic review and meta-analysis includes more recent clinical trials to review the efficacy and serious adverse events of combination therapy, compared with its monotherapy.

Methods

A systematic search was performed on electronic databases (Pubmed, Embase, Medline, Cochrane) on 21 June 2020. The keywords were nivolumab, ipilimumab, melanoma, and randomised controlled trials. All studies fitting the inclusion criteria were selected and analysed. The inclusion criteria were clinical trials with a specific focus on the use of nivolumab and ipilimumab combination therapy for the treatment of advanced melanoma. All patients in the pooled studies fulfilled the following criteria: 1) histologically confirmed American Joint Committee on Cancer stage III or IV melanoma; 2) age of patients at least 18 years; 3)with an Eastern Cooperative Oncology Group (ECOG) performance of 0-2; 4) no history of severe autoimmune diseases; 5)previous BRAF inhibitor therapy with or without MEK inhibitor therapy; 6)measurable disease as assessed by means of computed tomography or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Exclusion criteria includes: 1)pregnant or breastfeeding patients; 2)patients with ocular melanoma; 3)patients who have received previous systemic anti-cancer therapy.

Standard dosage regimen is summarised as follows. Patients in combination therapy groups received nivolumab 1mg/kg and ipilimumab 3mg/kg every 3 weeks for 4 doses, followed by nivolumab 3mg/kg every 2 weeks and beyond until disease progression, withdrawal of consent or occurrence of unacceptable adverse events. Patients in nivolumab monotherapy groups received nivolumab 3mg/kg and ipilimumab-matched placebo every 2 weeks. Patients in ipilimumab monotherapy groups received ipilimumab 3mg/kg plus nivolumab-matched placebo every 3 weeks for 4 doses. Dosages varied in some selected studies focusing on the dose-response effect of the treatment regimen. (Refer to table 1)

Data analysis

The primary aim was to evaluate the improvement in prognosis of patients receiving combination therapy for the treatment of advanced melanoma in terms of hazard ratios of progression-free survival (PFS), overall survival (OS) and odd ratios of objective response rate (ORR), compared with their monotherapy groups. PFS is defined as time from randomisation to the first documentation of disease progression by independent radiological review or to death, in the intention to treat population (all patients who underwent randomization). Overall survival refers to the time from randomization until death from any cause. ORR is defined as the best objective response [complete or partial] according to RECIST version 1.1. Secondary outcomes included effects of Programmed death-ligand 1 (PD-L1) expression status and BRAF-mutation status on the clinical outcomes of melanoma patients receiving combination therapy. Odd ratio and distribution of grade 3 or above adverse events were documented.

The titles, abstracts and full articles were independently screened by two authors (ZY and CLL). Following the PRISMA guidelines in PRISMA flow diagram, the study profile is shown in **Figure 1**. Duplicate articles were removed and reasons for exclusions were reviews articles, and studies without primary therapeutic data or not fitting the inclusion criteria.

Data extraction was performed by ZY and CLL with specific focus on study design, population demographics and therapeutic outcomes. Bias assessment was performed by Cochrane collaboration for randomised controlled trials (RCT). Bias or quality issues were minimized by cross-checking between authors.

Review manager, version 5.3 and SPSS (IBM) were used in data analysis. Dichotomous data were pooled in random-effect model as odd ratio using Mantel-Haenszel method with 95%

confidence interval; while overall survival and progression-free survival data were pooled as weighted hazard ratio using generic inverse-variance method, random-effect model with 95% confidence interval. Heterogeneity was assessed with chi-square (χ^2) test, with p-value smaller than 0.1 as statistically significant. Its extent was measured with I^2-test. As the number of studies included in each outcome measure was less than 10, Egger's test for funnel plot asymmetry could not be performed.

Results

As of 21 June 2020, 8913 studies were retrieved from databases. After deleting duplicates and screening of titles and abstracts, 40 articles were identified for full text review. Eventually 25 articles were selected for meta-analysis. Articles which do not fit the inclusion criteria (N=6), reviews (N=5) or contain only monotherapy group data were excluded (N=4).

Of the 10582 patients in the pooled studies (N=25), the mean age was 59.1 years (excluding studies with mean age not reported). Patients receiving combination therapy had better prognosis, compared with monotherapy groups. Compared with nivolumab monotherapy, combination therapy groups had better PFS (hazard ratio 0.64; 95% CI, 0.48-0.65; p=0.002), OS (hazard ratio 0.84; 95% CI, 0.74-0.95, p=0.007), and ORR (odd ratio 1.76; 95% CI, 1.51-2.06; p<0.001) as shown in **Figure 2**. The efficacy of combination therapy was more promising when compared with ipilimumab monotherapy as shown in **Figure 3**. The pooled PFS hazard ratio was 0.46 (95% CI, 0.37-0.57; p<0.001) and OS hazard ratio was 0.54 (95% CI, 0.48-0.61; p<0.001). The odd ratio of ORR was 6.18 (95% CI, 3.09-5.28; p<0.001).

Grade 3 or above severe adverse events were documented in accordance with Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 for oncology drugs. Adverse events were common during combination therapy. Patients receiving combination therapy had a higher chance of grade 3 or above adverse events, compared with nivolumab monotherapy (odd ratio 4.71; 95% CI, 3.57-6.22, p<0.001) and ipilimumab monotherapy (odd ratio, 3.44; 95% CI, 2.49-4.74; p<0.001), respectively (as shown in **Figure 4**).

Patients receiving nivolumab monotherapy had better clinical outcomes than those receiving chemotherapy with dacarbazine (as shown in **Figure 5**)[11-14]. The pooled PFS hazard ratio was 0.61 (95% CI, .39-0.94, p=0.03), and the OS hazard ratio was 0.58 (95% CI, 0.33 to 1.01; p=0.05). The odd ratio of ORR was 4.04 (95% CI, 3.09-5.28; p<0.001).

Adverse events were common but manageable. Sznol et al showed that the median times for resolution of treatment-emergent adverse events (TEAE) were 10.9 weeks (range, 0.1 to more than 101.3 weeks) for skin-related, 3.0 weeks (range, 0.1 to 78.7 weeks) for gastrointestinal-related, 4.6 weeks (range, 0.1 to more than 53.1 weeks) for hepatic related, 42.7 weeks (range, 0.4 to more than 93.9 weeks) for endocrine related, 6.1 weeks (range, 0.3 to more than 46.9 weeks) for pulmonary related, and 1.9 weeks (range, 0.3 to 42.6 weeks) for renal related[15]. In terms of discontinuation of treatment due to TEAE, Schadendorf et al showed that the median PFS were 8.4 months (95% CI, 5.9 to 23.0) for patients who discontinued treatment during induction phase due to TEAEs and 10.8 months (95% CI, 5.9 to 23.0) for patients who did not discontinue treatment despite TEAE. (hazard ratio 0.99, 95% CI, 0.72 to 1.37, p=0.966). PFS rates at 18 months were 38% and 49% for patients who discontinued treatment during induction phase and patients who did not discontinue treatment despite TEAE, respectively. There was no difference in OS between the 2 groups, with the median OS not reached in both groups (hazard ratio 0.79, 95% CI, 0.54 to 1.17; p=0.2344). OS rates at 18 months were 67% and 62% for patients who discontinued treatment during induction phase and patients who did not discontinue treatment despite TEAE, respectively. The ORR was 58.3% (95% CI, 47.8 to 68.3) for patients who discontinued during the induction phase, and 50.2% (95% CI, 43.6-56.8) for patients who did not discontinue despite of TEAE[16].

Several studies investigated the different regimens of combination therapy. Clinical outcomes of standard disease "nivolumab 1mg/kg plus ipilimumab 3mg/kg (NIVO1+IPI3) " and "nivolumab 3mg/kg plus ipilimumab 1mg/kg (NIVO3+IPI1)' were similar. Rozeman et al showed that the radiological ORR were 63% (95% CI, 44-80) and 57% (95% CI, 37-75) in the "NIVO1+IPI3" and "NIVO3+IPI1" groups, respectively. The pathological ORR were 80% (95% CI, 61-92), 77% (95% CI, 58-90) in the two groups, respectively. But TEAE was lower in "NIVO3+IPI1" group (20%) than in the "NIVO1+IPI3" group (40%)[17]. This is supported by Lebbe et al, who showed that a similar ORR were observed in the two groups regardless of baseline LDH levels, BRAF mutation and PD-L1 status, but patients receiving "NIVO3+IPI1" had a lower rate of grade 3 or above TEAE[18].

Concurrent treatment was better than sequential treatment when prescribing combination therapy[19,20]. Lower grade 3 or above TEAE was observed in concurrent treatment (49%), compared with the sequential treatment (73%). The ORR were 40% (95% CI, 27 to 55) and 20% (95% CI, 8 to 39) in the concurrent treatment group and sequential treatment group, respectively[19]. The ORR was further increased to 53% (95% CI, 28 to 77) in patients receiving the maximum dosage associated with an acceptable level of adverse events in concurrent treatment. The survival rates were consistently higher in concurrent treatment group. The one -year OS rates were 85% (95% CI, 72-92) and 75% (95% CI, 59-86) and the two-year OS rates were 79% (95% CI, 65-88) and 63% (95% CI, 46-76) in concurrent treatment group and sequential treatment group, respectively[20].

The order and timing of receiving combination therapy also played a role in clinical recovery. Receiving nivolumab prior to ipilimumab and combination therapy was beneficial to clinical outcomes. Weber et al showed that a consistently higher ORR rate was achieved with

nivolumab-first regimen, regardless of PD-L1 status. The overall ORR were 56% (95% CI, 43.3 to 67.0) and 31% (95% CI, 20.9-43.6) in nivolumab-first group and ipilimumab-first group, respectively[21]. Among patients with PD-L1 positive tumour, a higher ORR was observed in nivolumab-first group (42%, 95% CI, 24.5-60.9) , compared with ipilimumab-first group (18%, 95% CI, 6.8-34.5). The ORR in nivolumab-first group (73%, 95% CI, 49.8-89.3) was higher than that in the ipilimumab first group (60%, 95% CI, 26.2-87.8) for patients with PD-L1 negative tumour. With regards to timing, receiving combination therapy in neoadjuvant form was better than adjuvant therapy. The grade 3 or above TEAE were both 90% in both treatment arms; but a higher tumour response was observed in neoadjuvant arm[22].

Within combination therapy group, subgroup analysis was performed based on PD-L1 expression status, BRAF mutation status and brain metastases. High PD-L1 expression level refers to a more than 5% tumour cell membrane immunochemistry staining. Patients with a higher PD-L1 expression level were associated with higher chance of ORR (odd ratio 1.84; 95% CI, 1.07-3.17; p=0.03). The median PFS was 14.0 months (95% CI, 9.7-not reached) and 11.2 months (95% CI, 8.0-not reached) in the high PD-L1, and low PD-L1 expression level, respectively[23]. The 4-year OS was 61% (95% CI, 48-71) and 52% (95% CI, 45-58) in the high, and low PD-L1 expression level, respectively[24]. This is consistent with Tawbi et al who showed that combination therapy was associated with a higher rate of clinical benefit among patients with high tumour PD-L1 expression than those with low PD-L1 expression (76% vs 48%)[25]. However, Wolchok et al showed that the OS was independent of PD-L1 status, with OS hazard ratio 0.59 in low expression group and 0.56 in the high expression group[26].

BRAF mutation was associated with a better PFS and OS, compared with BRAF wild type. PFS ranged from 11.7 months to 16.8 months in BRAF-mutated groups, and 11.2 months in

BRAF-wild groups[23,27]. The OS were more than 60 months (95% CI, 50.7-not reached) and 39.1 months (95% CI, 17.9-31.0) in BRAF-mutated and BRAF-wild groups, respectively[27]. The rates of 3-year, 4-year and 5-year OS were 68% (confidence interval unreported), 62% (95% CI, 52-71) and 60% (confidence interval unreported) in the BRAF-mutated group; and 56%, 49% (95% CI, 42-55) and 48% in the BRAF-wild groups, respectively[24,26,27]. However, Hodi et al showed that there was no difference in 2-year OS between BRAF-mutated and BRAF-wild groups[28]. In terms of ORR, Postow et al showed that the BRAF-wild groups were with better ORR, compared with BRAF-mutated groups. The ORR were 61% (95% CI, 49 to 72) and 52% (95% CI, 31-73) in BRAF-wild and BRAF-mutated groups[29].

Patients with brain metastases had the worst prognosis, compared with melanoma metastases to other sites. Combination therapy was shown to be more efficacious than monotherapy for melanoma patients with brain metastasis[30]. In a study involving melanoma patients with brain metastases, promising ORR were observed in intracranial response (46%, 95% CI, 29-63) and extracranial response (57%, 95% CI, 37-75) in patients receiving combination therapy, compared with nivolumab monotherapy patients whose intracranial (20%, 95% CI, 7-41) and extracranial response (29%, 95% CI, 11-52) were much worse. The intracranial PFS and extracranial PFS in combination therapy were not reached (95% CI, 2.9-not reached) and 13.8 months (95% CI, 4.9-not reached), compared with 2.5 months (95% CI, 1.7-2.8) and 2.6 months (95% CI, 1.8-13.8) for intracranial and extracranial PFS in patients receiving nivolumab monotherapy, respectively.

Discussion:

This systematic meta-analysis specifically focuses on the improvement of prognosis of combination therapy for the treatment of advanced melanoma, supported by a prolonged PFS, OS and higher ORR compared with monoclonal antibodies alone and chemotherapy. One limitation of this study is the pooled PFS and OS stratified by mutation status could not be performed due to limited literature data.

Nivolumab was proven to be superior to chemotherapy by a prolonged PFS and OS, and higher odd ratio of ORR (Figure 5). This study further showed that combination therapy was more efficacious in the treatment of advanced melanoma with prolongation of PFS, OS and ORR, compared with monotherapy groups. The favourable prognosis is related to the disinhibition of immune T-cell inactivation pathway though 2 blockades [31] First there is the blockade of the binding between CTLA-4 receptor on T-cell surface and protein B7 on antigen-presenting cells; thus blocking the transduction of inhibitory signal to the T-cell nucleus. There is also the blockade of binding between PD-1 receptor on T-cell surface and PD-L1 on tumour tissues.

However, patients on combination therapy had higher likelihood of developing grade 3 or 4 adverse events. Adverse events were manageable. As documented in the appendix, the majority of the adverse events were gastrointestinal-related. A meta-analysis of the fatal toxicity effects showed that colitis and myocarditis were the major fatal side effects[32]. Hodi et al showed that addition of GM-CSF to the treatment regimen decreased toxicity from 58% to 45%, and gastrointestinal toxicity dropped from 27% to 16%[33]. The toxicity effect was likely to be immune-induced, because several studies have shown that those discontinued from the combination treatment could still benefit without additional treatment[16,24]. Meanwhile, Lebbe et al did a study to investigate the post-discontinuation benefits in the two combination

regimen[18]. It was shown that the lower discontinuation rate due to TRAEs in the "Nivolumab 3mg/kg plus Ipilimumab 1mg/kg" resulted in a higher rate of patients receiving nivolumab maintenance therapy.

Subgroup analysis showed that cancer patients with high PD-L1 expression had better prognosis when using combination therapy. This is consistent with Grosso et al who showed that PD-L1 positive tumours had better clinical outcome with nivolumab in advanced cancer[34]. An upregulation of PD-L1 expression may lead to a failed rejection of tumour cells by immune clearance, through tumour cell apoptosis and modulations of cytotoxic T-cell activities[35]. The better prognosis may be associated with the peripheral T cell responses, since an increased percentage of CD4 and CD8 expressing HLA-DR, ICOS and/or Ki67 was observed with combination therapy, without a rise in absolute lymphocyte counts[36].

Patients with BRAF-mutated melanoma had better prognosis after receiving combination therapy. However, for patients without BRAF-mutation, further research should be done, focusing on the use of MAPK-associated pathway inhibitors, nivolumab and ipilimumab as a combination therapy. Evidence has shown that MEK-inhibitors, an MAPK-associated pathway inhibitor, are efficacious in induction of melanocyte-inducing transcription factor and melanocyte-derived antigen expression, leading to an enhancement of T-cell infiltration to tumours[37].

Alternative addition of agent such as bevacizumab and interferon-alpha for multiple-therapy regimen should be explored. Bevacizumab is a monoclonal antibody targeting on vascular endothelial growth factor A (VEGF-A); thus slowing angiogenesis of tumour. A previous study of bevacizumab and ipilimumab combination therapy showed that bevacizumab could

be safely administered and displayed successful influences on inflammation, lymphocyte trafficking and immune modulation[38]. Combination therapy of interferon-alpha and ipilimumab was also associated with better therapeutic outcomes[31].

Conclusion:

Nivolumab and ipilimumab combination therapy was effective for the treatment of advanced melanoma, with a prolonged PFS, OS and higher ORR. Adverse events were common, but manageable. Better prognosis was observed in patients with high PD-L1 expression and positive BRAF mutation.

Author Contributions:

Literature search was done by ZY, JWTK and CLL. Searches screening, and article review was done by ZY, JWTK and CLL. Study designs were done by ZY,JWTK and CLL. Data extraction and analysis was done by ZY and CLL. Data interpretation was done by ZY and CLL. Manuscript writing was done by ZY, JWTK and CLL.

Declaration of interest:

Nil

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