Cancer Treatment Reviews 54 (2017) 34–42

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Systematic or Meta-analysis Studies

Immune checkpoint inhibitors and targeted therapies for metastatic melanoma: A network meta-analysis

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ARTICLE INFO

Article history:
Received 16 September 2016
Received in revised form 14 January 2017
Accepted 16 January 2017

Keywords:
Melanoma
Metastatic
Network meta-analysis
Targeted therapy
Immune checkpoint inhibitor

ABSTRACT

Background: Immune checkpoint inhibitors and targeted therapies, two new class of drugs for treatment of metastatic melanoma, have not been compared in randomized controlled trials (RCT). We quantitatively summarized the evidence and compared immune and targeted therapies in terms of both efficacy and toxicity.

Methods: A comprehensive search for RCTs of immune checkpoint inhibitors and targeted therapies was conducted to August 2016. Using a network meta-analysis approach, treatments were compared with each other and ranked based on their effectiveness (as measured by the impact on progression-free survival [PFS]) and acceptability (the inverse of high grade toxicity).

Results: Twelve RCTs enrolling 6207 patients were included. Network meta-analysis generated 15 comparisons. Combined BRAF and MEK inhibitors were associated with longer PFS as compared to anti-CTLA4 (HR: 0.22; 95% confidence interval [CI]: 0.12–0.41) and anti-PD1 antibodies alone (HR: 0.38; CI: 0.20–0.72). However, anti-PD1 monoclonal antibodies were less toxic than anti-CTLA4 monoclonal antibodies (RR: 0.65; CI: 0.40–0.78) and their combination significantly increased toxicity compared to either single agent anti-CTLA4 (RR: 2.06; CI: 1.45–2.93) or anti-PD1 monoclonal antibodies (RR: 3.67; CI: 2.27–5.96). Consistently, ranking analysis suggested that the combination of targeted therapies is the most effective strategy, whereas single agent anti-PD1 antibodies have the best acceptability. The GRADE level of evidence quality for these findings was moderate to low.

Conclusions: The simultaneous inhibition of BRAF and MEK appears the most effective treatment for melanomas harboring BRAF V600 mutation, although anti-PD1 antibodies appear to be less toxic. Further research is needed to increase the quality of evidence.

Introduction

Metastatic melanoma is considered one of the most chemoresistant neoplasms [1,2] and Dacarbazine, though referred as the reference drug, has never been proven to confer any survival advantage as compared to best supportive care [3,4]. Over the last decades, neither conventional cytotoxic drugs nor different immunotherapy and biochemotherapy regimens have shown to perform better than Dacarbazine [5,6].

This scenario has been rapidly evolving since the introduction of two new classes of systemic therapies, immune checkpoint inhibitors and targeted drugs [7–9].

The immune checkpoint inhibitors are a group of monoclonal antibodies that block co-inhibitory molecules such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA4, which is expressed on activated CD4+ and CD8+ effector T-cells and regulatory T-cells), programmed-death-1 (PD1, which is also expressed on activated effector T-cells) and its ligand PDL1 (which is expressed on dendritic cells, activated T-cells, and tumor cells) [10–12]. Ipilimumab, a first in class anti-CTLA4 monoclonal antibody [9,13,14], can have a long-term benefit in about 10–20% of patients [15–18]. Other two monoclonal antibodies, Nivolumab and Pembrolizumab, which target PD1, have shown greater efficacy than Ipilimumab [19–22], although long-term efficacy results are lacking.

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http://dx.doi.org/10.1016/j.ctrv.2017.01.006
0305-7372/

The inhibitors of the mitogen-activated protein kinase (MAPK) pathway are another class of drugs effective for metastatic melanoma harboring BRAF V600 mutations [23,24]. BRAF inhibitors (Vemurafenib and Dabrafenib) specifically target these driver mutations, while MEK blockade (Trametinib and Cobimetinib), inactivates the MAPK pathway by targeting the downstream signaling molecule MEK [25,26]. Drugs targeting BRAF only have been shown to be effective, although patients usually develop resistance in 6–7 months [27,28]. MEK inhibitors improve the effectiveness of BRAF inhibitors and reduce the incidence of secondary skin cancer, one of the most relevant adverse events of anti-BRAF drugs [29–32].

The clinical implementation of these novel anticancer agents, which is surrounded by a fully justified enthusiasm, is generating new issues in the therapeutic management of metastatic melanoma, with special regard to which drug, or combination of drugs, should be the first line treatment. The relative efficacy and toxicity of each one of the five treatments currently used (anti-PD1 antibodies, anti-CTLA4 antibodies, anti-PD1 antibodies plus anti-CTLA4 antibodies, BRAF inhibitors, and BRAF inhibitors plus MEK inhibitors) has not yet been formally investigated [33–36]. Since BRAF wild type melanoma is basically resistant to targeted agents, this dilemma concerns patients with BRAF mutant melanoma, who represent up to 50% of all cases [37]. Immune checkpoint inhibitors and targeted therapies have not yet been compared in these patients within the frame of a RCT.

Network meta-analysis offers the unique opportunity to perform indirect comparisons between treatments never directly compared in RCTs but compared to a common treatment (e.g. comparison of treatment B versus treatment C, using data from trials comparing treatment A versus treatment B and treatment A versus treatment C), as well as to rank multiple treatments [38,39].

We used this novel biostatistical tool to compare both progression-free survival (PFS, which is considered the appropriate drug efficacy measure in this setting [40,41]) and high-grade toxicity across RCTs testing immune checkpoint inhibitors or targeted therapies.

The ultimate aim of the present study was to better inform the decision-making process of physicians involved in the therapeutic management of patients with metastatic melanoma.

Methods

Literature search

The protocol of this meta-analysis was registered with the Prospective Register of Systematic Reviews, PROSPERO (identification code CRD42016036332).

A systematic review of RCTs reporting on currently used novel systemic treatments strategies (i.e., anti-PD1 antibodies, anti-CTLA4 antibodies, anti-PD1 antibodies plus anti-CTLA4 antibodies, BRAF inhibitors, and BRAF inhibitors plus MEK inhibitors) in patients with metastatic melanoma was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for network meta-analysis [42] and Cochrane guidelines [43].

The two endpoints were efficacy (as measured by PFS) and toxicity (as measured by high grade toxicity).

A search of Embase, Ovid MEDLINE and the Cochrane library was conducted by two investigators (SM and SP) using the following algorithm: "melanoma [Title] AND (Vemurafenib OR PLX4032 OR Dabrafenib OR GSK-2118436 OR LGX818 OR Trametinib OR GSK-1120212 OR Cobimetinib OR GDC-0973 OR Ipilimumab OR MDX-010 OR Tremelimumab OR CP-675,206 OR Nivolumab OR MDX-1106 OR Pembrolizumab OR MK-3475) AND clinical trial NOT review" (Algorithm A), and with the algorithm "(BRAF [ti] OR NRAS [ti]) AND melanoma [ti] AND survival" (Algorithm B), respectively. The literature search was restricted to articles published between January 1990 and August 2016 in the English language.

The following inclusion criteria were used: (1) experimental treatment: currently used treatment strategies based on immune checkpoint inhibitors (anti-CTLA4, anti-PD1 monoclonal antibodies, or their combination) or targeted drugs (BRAF inhibitor alone or in combination with, MEK inhibitors); (2) study design: phase III RCTs and randomized phase II trials reporting on PFS and toxicity; and (3) the majority of enrolled patients (>60%) had to be previously untreated. No language restriction was applied. The search ended in May 2016. Manual searching of reference lists from original articles was also performed. Only trials described in full text articles were included; if multiple publications of the same trial were retrieved, the most recent publication was utilized. Subsequent updates of included trials available only in abstract form were also considered, when available.

The abstracts and full-text were reviewed independently by two investigators (SM and SP) and conflicts resolved by a third author (VCS).

Risk of bias assessment and evidence grading

All articles were assessed for risk of bias by SM and SP using the Cochrane Risk of bias tool for RCTs [44]. Included RCTs were classified into one of three categories: low risk, high risk or unclear risk. The data were extracted by SM and SP using predefined data collection forms. The extracted data were verified independently (VCS).

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system adapted to network meta-analysis was employed to grade the quality of evidence into four levels: high, moderate, low, and very low [45].

The quality can be downgraded by one (serious concern) or two levels (very serious concern) for the following reasons: study limitations (risk of bias, see above paragraph), evidence for small study effect (as assessed by means of a funnel plot dedicated to network meta-analysis [46]), indirectness (indirect population, intervention, control, outcomes; lack of transitivity assumption, see below), inconsistency (between-study statistical heterogeneity, as suggested by meta-analysis estimate of prediction interval crossing the null value), and imprecision (as suggested by meta-analysis estimate of confidence interval crossing the null value).

Finally, since different comparisons might be characterized by a different risk of bias, the relative contribution of each direct evidence was properly accounted for, using the data from the network contribution matrix [45].

Statistical analysis

The two study endpoints were PFS and high-grade toxicity. PFS survival was measured from the time of randomization to disease progression. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [47] and high grade toxicity (grades 3 and 4) were considered.

Regarding survival data, the outcome measure was the hazard ratio (HR) with its 95% confidence interval (CI). When HRs were unreported, they were estimated as per Parmar et al. [48,49]. For toxicity, the outcome measure was relative risk (RR) along with its CI.

For direct comparisons, standard pairwise meta-analysis was performed using the inverse variance DerSimonian-Laird random effects model [50]. If a direct comparison was based on two or