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Review

Survival of patients with advanced metastatic melanoma: The impact of novel therapies

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Abstract The survival of advanced metastatic melanoma has been greatly improved within the past few years. New therapeutic strategies like kinase inhibitors for BRAF-mutant melanoma and immune checkpoint blockers proved to prolong survival times within clinical trials, and many of them have already entered routine clinical use. However, these different treatment modalities have not yet been tested against each other, which complicate therapy decisions. We performed an explorative analysis of survival data from recent clinical trials. Thirty-five Kaplan–Meier survival curves from 17 trials were digitised, re-grouped by matching inclusion criteria and treatment line, and averaged by therapy strategy. Notably, the

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survival curves grouped by therapy strategy revealed a very high concordance, even if different agents were used. The greatest survival improvement was observed with the combination of BRAF plus MEK inhibitors as well as with Programmed-death-1 (PD1) blockers with or without cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) blockers, respectively, with these two treatment strategies showing similar survival outcomes. For first-line therapy, averaged survival proportions of patients alive at 12 months were 74.5% with BRAF plus MEK inhibitor treatment versus 71.9% with PD-1 blockade. This explorative comparison shows the kinase inhibitors as similarly effective as immune checkpoint blockers with regard to survival. However, to confirm these first trends for implementation into an individualised treatment of melanoma patients, data from prospective clinical trials comparing the different treatment strategies head-to-head have to be awaited.

1. Introduction

Systemic treatment of advanced metastatic melanoma has been an unmet medical need for decades. Chemotherapy with dacarbazine or other cytotoxic drugs resulted in median survival times of 7–9 months and no therapeutic regimen, either other chemotherapeutic agents, biochemotherapy, or immunotherapy proved to be superior to dacarbazine in terms of survival [1]. In these times, long-term survival of 5 years and more was only achieved in 5–10% of patients regardless of the specific therapy strategy used.

Recently, during the last few years, the treatment of metastatic melanoma has been rapidly evolving. Approximately 40–50% of metastatic cutaneous melanomas harbour a BRAF V600 mutation, constitutively activating the mitogen-activated protein kinase (MAPK) pathway [2]. The BRAF inhibitors vemurafenib and dabrafenib were developed to specifically target this driver mutation and further similar compounds like encorafenib are still under study [3,4]. Another target is the signalling molecule MEK downstream of BRAF, and its blockade can likewise inactivate the MAPK pathway [5]. Both, BRAF and MEK inhibitors showed superior activity in BRAF V600-mutated melanoma in comparison to dacarbazine, and led to a significantly increased progression-free (PFS) and overall survival (OS) in the respective patients. Even more efficacious is the combined inhibition of both targets, BRAF and MEK, and thus a simultaneous application of vemurafenib plus cobimetinib or dabrafenib plus trametinib led to a further prolongation of PFS and OS [6–9].

New immunotherapeutic approaches for metastatic melanoma are another promising approach, which developed simultaneously and in parallel to MAPK pathway inhibitors, resulting in two separate novel treatment strategies. Presently, targeting immune checkpoints, which normally terminate immune responses after antigen activation, is a main focus in the treatment of advanced melanoma. Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is an immunomodulatory molecule that down-regulates T-cell-activation. Ipilimumab, a fully human monoclonal antibody that blocks CTLA-4 was the first successfully developed drug of a new class of therapeutics named immune checkpoint inhibitors. Long-term survival of up to 20% of treated patients has been reported with ipilimumab [10–12]. Programmed-death-1 (PD1) is another immune checkpoint target expressed on activated T-cells mediating immunosuppression. Its ligands PD-L1 (B7-H8) and PD-L2 (B7-DC) are expressed on many tumour cells, stroma cells and other cell types including leucocytes. The immunosuppressive action of the PD1 receptor is activated in the effector phase of the interaction between T lymphocytes and tumour cells, and the blockade of this receptor seems to be more effective towards T-cell-activation than CTLA-4 blockade. Nivolumab (BMS-936558) is a fully human IgG4 monoclonal antibody directed against PD1. Pembrolizumab (MK-3475) is a selective, humanised monoclonal IgG4-kappa anti-PD1 antibody. The efficacy of both agents was studied in advanced melanoma and other solid tumours [13–15]. Other PD-1 and PD-L1 inhibitors are also under evaluation.

With regard to these new developments in the treatment of advanced melanoma, only few of these therapies have yet been compared to one another, and trials have not yet been conducted to evaluate the optimal sequence of therapies with rigorous, randomised designs. For BRAF-mutant patients, multiple therapy strategies with documented survival improvement exist from which to choose. However, there are no clear data as to which regimen should be administered in the first, second, or even third line, or whether there are patient characteristics or biomarkers helpful for treatment selection.

This work analyses selected clinical trials representative for the new treatment strategies in advanced melanoma and compares their survival outcome by digitisation of published Kaplan–Meier survival curves.