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Resistance to immune checkpoint inhibitors. Next steps and combinational approaches

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Summary Immuno-oncology and in particular checkpoint inhibitor (CPI) treatment has become a novel promising cancer therapy strategy in recent years. However, still a minority of patients respond to checkpoint blockade. Primary and secondary resistance to CPI is a challenge in the daily clinical routine. Combination strategies have been tested in various clinical trials in order to address this issue. Data available from these trials indicate improved activity depending on the tumor type. This review article focuses on the molecular background for resistance to CPI, gives an overview of current clinical data of CPI combination studies and points out potential strategies to overcome CPI resistance depending on the immune phenotype.

Keywords Immunotherapy · Checkpoint inhibitor · Primary resistance · Secondary resistance · Immune phenotype

Introduction

Immune checkpoint inhibitors (CPI) have entered the clinical routine during the last couple of years and CPI therapy is considered as the standard of care for a wide range of malignancies. A recent analysis of 262 patients treated with CPI and suffering from 19 different malignancies demonstrated an objective response rate (ORR) of 29% across all tumor types and a long-term survivor rate (i.e. longer than 2 years) of 11.8% [1]. Despite these advances, response to single agent CPI varies markedly between highly sensitive tumors such as Hodgkin's lymphoma (ORR >65%) and resistant ones such as microsatellite stable colorectal cancer (ORR <10%) [2, 3]. Apart from that, it has been observed that—while the majority of responses to CPI are durable—disease recurrence during immunotherapy or after (early) discontinuation occurs as reported in head and neck squamous cell carcinoma or non-small cell lung cancer patients [4, 5]. Therefore, it is obvious that understanding the mechanisms of resistance to CPI therapy is crucial in order to turn non-responsive tumors into responsive ones and prevent relapse during or after treatment with CPI. Overcoming resistance and rational combinatorial approaches have to be based on the molecular understanding of the underlying resistance mechanisms:

Resistance to CPI therapy can be divided into primary resistance (i.e. no upfront response to immunotherapy) and secondary (or acquired) resistance (i.e. after initial response to immunotherapy tumor recurrence/progression is observed) [6]. Both tumor-intrinsic and -extrinsic (or host) factors can contribute to either primary or secondary resistance mechanisms [6].

Primary resistance

Primary resistance to CPI is partially based on adaptive mechanisms. Either the tumor is not recognized by the immune system at all or adaptive mechanisms facilitate immune escape [6]. As mentioned above various host and/or tumor intrinsic factors contribute to primary resistance. Host factors comprise the tumor microenvironment (TME), endocrine and metabolic factors, environmental factors such as dysbiosis or antibiotic or steroid use and other nonmodifiable factors such as age, chronic disease or unfavorable host genetics [7].

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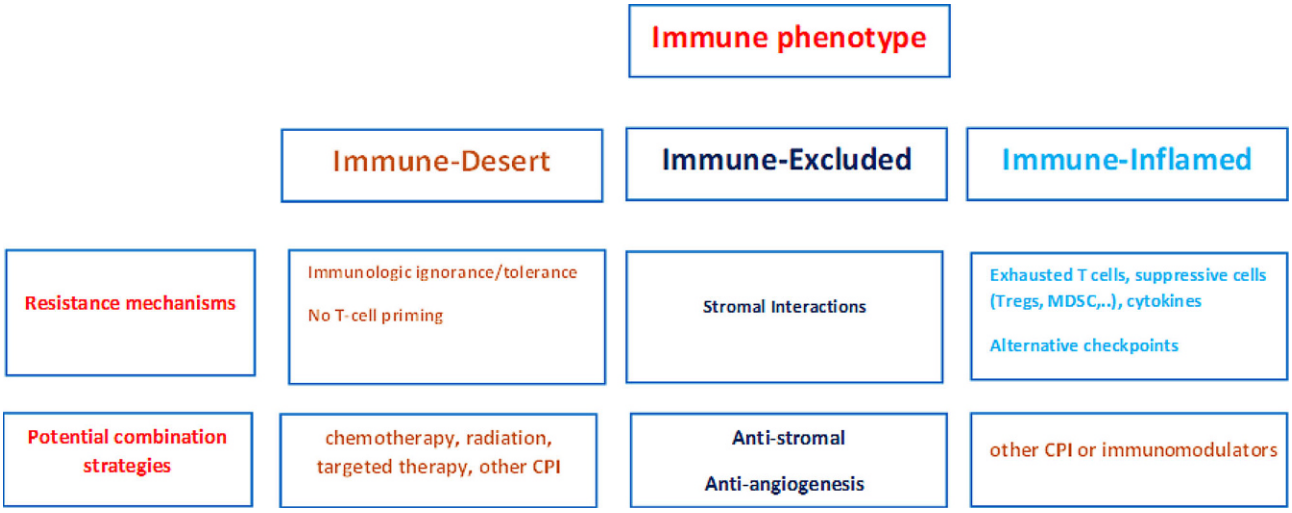

Fig. 1 Potential combination strategies of an immune checkpoint inhibitors (CPI) in order to overcome resistance based on the immune phenotype. *MDSC* myeloid-derived suppressor cells (Modified and adapted, [14, 25])

The complex interplay between the TME and the tumor itself determines if an effective antitumor immune response can take place. FoxP3+ T cells (Tregs) can dampen the immune response by direct cell–cell contact or the secretion of inhibitory cytokines such as IL-10, IL-35 or TGF-beta [6, 8]. Apart from that T-cell exhaustion, which is a state where T cells are exposed to continuous antigen signals and lose their effector function, contributes to primary resistance [8, 9]. It was demonstrated that PDL-1 high exhausted CD8+ T cells respond poorly to PDL-1 blockade [10]. Besides T cells, myeloid-derived suppressor cells (MDSC) and tumor-associated M2 macrophages (TAMs) play a role in negative immune regulation [6, 8, 11]. Finally, adaptive upregulation of alternative immune checkpoints such as TIM-3 or Lag-3 was shown to be responsible for primary CPI resistance [6, 12].

Intrinsically, tumors can modulate their gene expression and pathways ultimately resulting in a lack of immune cell infiltration or suppression of an adequate antitumor immune response. Epigenetic modifications of immune-related genes or mutations in the interferon gamma pathway, the JAK pathway or constitutive PDL-1 expression also lead to a negative immune-response [8]. Additionally, low antigenicity of the tumor cell, which is mediated by a low tumor mutational burden or alterations in the antigen-presenting machinery, results in a lack of immune cell recognition [11].

Secondary resistance

Contrary to primary resistance, secondary resistance develops over time subsequent to constant pressure of the immune system on the tumor cells. Likewise, the immune-related gene expression profile of the tumor can be altered. Interferon gamma pathway mutations and loss of antigen presentation proteins leading to a lack of T cell recognition have been described [11]. In melanoma patients, who initially responded to CPI, but relapsed, a truncating beta 2 microglobulin mutation was detected by whole exome sequencing. This mutation resulted in the loss of surface expression of major histocompatibility complex class I [13].

Immune phenotype

Based on these considerations antitumor immunity can be classified into three main phenotypes as suggested by Chen and Mellman [14]: The inflamed tumor, the immune excluded tumor and the immune desert tumor. Each of this phenotype is associated with multiple mechanisms for primary/secondary resistance to avoid response antitumor immune response [14]. While immune-desert tumors exhibit immunological ignorance, tolerance or lack of T-cell priming, stromal factors such as mechanical barriers, vascular factors or an immune-suppressive chemokine state are the predominate cause for immune evasion in immune-excluded tumors [14]. Finally, all types of mechanisms for resistance to immunotherapy described above can be detected in inflamed tumors. Translating these immune phenotypical findings into molecular signatures seems to be crucial for the elucidation of resistance. Although the pan cancer initiative, which analyzed more than 10,000 tumors in 33 cancer types employing comprehensive sequencing techniques, reported six types of immune signatures, which correlated with OS, the significance for predicting resistance to CPI or immunotherapy in general is still unclear [15].

Table 1 Selected combination trials in order to overcome resistance to CPI

Author	Indication	Regimen	Number of Patients	HR for death	HR for progression/death	ORR %
Wolchock et al. [17]	Untreated advanced melanoma	Nivo and Nivo/Ipi vs. Ipi alone	945	HR 0.55, 95% CI 0.45–0.69 for Nivo/Ipi vs. Ipi	HR 0.43, 95% CI 0.35–0.52 for Nivo/Ipi vs. Ipi	57.6 for Ipi/Nivo
Motzer et al. [18]	Untreated advanced renal cell cancer	Nivo/Ipi vs. Sunitinib	1096	HR 0.63, 99.8% CI 0.44–0.82	HR 0.82, 99.1% CI 0.64–1.05; not significant	42 for Ipi/Nivo
Motzer et al. [19]	Untreated advanced renal cell cancer	Axitinib/Ave vs. Sunitinib	886	Final data not available yet	HR 0.61, 95% CI 0.475–0.790	62 for Axitinib/Ave
Antonia et al. [22]	Stage III NSCLC	Chemorad/Durva vs. Chemorad	709	HR 0.86, 95% CI 0.54–0.86	HR 0.52, 95% CI 0.42–0.65	28.4 for Chemorad/Durva
Socinski et al. [24]	Stage metastatic non-squamous NSCLC	Chemo/Atezo/Bev (and Chemo/Atezo) vs. Chemo alone	1202	HR 0.78, 95% CI 0.64–0.96 For EGFR/ALK: HR 0.54, 95% CI 0.29–1.03 (not significant)	HR 0.62, 95% CI 0.52–0.74	63.5 for Chemo/Atezo/Bev

Nivo Nivolumab, *Ipi* Ipilimumab, *Ave* Avelumab, *Chemorad* Chemoradiation, *Durva* Durvalumab, *Atezo* Atezolizumab, *Bev* Bevazicumab

Next steps: combinatorial approaches to overcome resistance

In order to overcome resistance to single agent CPI, combination strategies have been suggested and multiple trials testing CPI combinations are currently being conducted. Unfortunately, the landscape of clinical immunotherapy combination trials is quite often driven by the specific pipeline of the industry and does not always follow rational combination strategies based on the molecular and immune phenotype considerations outlined above [16]. Obviously, the vast majority of combination trials is conducted with the five approved CPI [16]. In general, several combination strategies of CPI with other compounds are tested in clinical trials. The most promising ones comprise the combination of a CPI with (a) another immunotherapeutic approach (vaccines; dual checkpoint blockade and removal of co-inhibitory signals; activation of co-stimulatory signals; adoptive T-cell transfer; allogenic stem cell transplantation, …), (b) DNA damaging agents such as cytotoxic chemotherapy or radiation or (c) targeted therapies (monoclonal antibodies or a tyrosine kinase inhibitors). Ideally, the distinct combination strategy employed should be tailored to the tumor microenvironment as summarized in Fig. 1.

Clinical data

Multiple clinical immunotherapy trials evaluating CPI combinations have been conducted so far (Table 1). Dual checkpoint blockade with a programmed cell death protein 1 (PD-1) antibody plus a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) targeting agent proved to be a successful strategy in melanoma, renal cell carcinoma and non-small cell lung cancer (NSCLC). A positive nivolumab plus ipilimumab trial has led to the approval of this combination in metastatic melanoma patients, since the risk for death was decreased with nivolumab plus ipilimumab compared to ipilimumab alone (HR 0.55, 95% CI 0.45–0.69) [17]. Likewise it was demonstrated that in intermediate- or poor-risk advanced renal cell carcinoma patients, there was a significant improvement in OS with nivolumab plus ipilimumab compared to sunitinib (median not reached versus 26 months; HR 0.63, 99.8% CI 0.44–0.82) as demonstrated in the CheckMate 214 study, which resulted in FDA approval in this setting in 2018 [18]. Of note, dual checkpoint blockade significantly increases the rate of treatment-related adverse events and toxicity compared to single agent CPI therapy.

Overcoming primary resistance to CPI therapy can be achieved by the combination with targeted therapy. Axitinib plus the PD(L)-1 inhibitor avelumab (or pembrolizumab) is superior to sunitinib monotherapy in advanced renal cell carcinoma (PFS 13.8 vs 8.4 months; HR 0.69) [19]. Although the tolerability of this combination was similar between the groups, it has to be noted that the combination of a CPI with targeted agent can lead to major toxicity as well. Dose-limiting hepatotoxicity was observed for ipilimumab plus vemurafenib or nivolumab plus crizotinib for instance [20, 21].

A very interesting concept is the combination of radiotherapy and CPI. Radiotherapy triggers antigen release and might potentiate the efficacy of CPI therapy and turn an immune desert tumor into an inflamed one. Although the optimal radiation dose and fractionation is still under investigation, the PACIFIC study in stage III unresectable NSCLC patients, which evaluated platinum-based chemoradiation followed by checkpoint blockade via durvalumab vs. placebo, yielded positive results (HR for death 0.68, 95% CI 0.54–0.86) [22].

Finally, cytotoxic chemotherapy plus CPI is an effective strategy in order to overcome immunother-

apy resistance. Initial concerns that leukocyte depletion by chemotherapy might dampen the effect of CPI therapy turned out to be unjustified. On the contrary, numerous clinical trials such as the KEYNOTE-189 study in NSCLC stage IV patients showed that chemotherapy plus CPI is superior to chemotherapy alone and not associated with a higher number of immune-related adverse events [23].

Even the combination of chemotherapy, antiangiogenic (targeted) therapy with bevacizumab plus CPI seems to be more effective that this combination without a CPI. The IMpower150 trial demonstrated a trend towards survival advantage for the addition of a CPI in EGFR-mutated or ALK-positive NSCLC stage IV patients, which used to be resistant to single agent checkpoint blockade (OS not reached compared to 17.5 months; HR 0.54; 95% CI 0.29–1.03) [24]. However, the toxicity of this regimen is substantial and despite the OS benefit in this setting, the approach of a chemo/CPI/bevacizumab combination in the absence of an adequate biomarker seems questionable.

Conclusion

Primary and secondary resistance to single agent checkpoint blockade is an emerging problem in daily clinical routine given the increasing numbers of patients treated with immunotherapy. Knowledge about the reasons for resistance to immunotherapy is constantly expanding. Although results from immunotherapy combination trials are promising and resulted in approvals, future clinical immunotherapy combination trials should take the circumstances for resistance into account and select patients based on their specific host immune microenvironment.

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