Is There Room for Immune Checkpoint Inhibitors in Patients Who Have NSCLC With Autoimmune Diseases?

COMMENTARY

Is There Room for Immune Checkpoint Inhibitors in Patients Who Have NSCLC With Autoimmune Diseases?

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Immune checkpoint inhibitors (ICIs) have changed the treatment paradigm and prognosis in advanced NSCLC.[1] However, some subgroups of patients with NSCLC are usually not enrolled in clinical trials because of their disease status (i.e., brain metastasis) or underlying conditions such as a history of autoimmune disease (AID). The major concerns preventing enrollment of patients with AID were the risk of unacceptable immune activation in the form of AID symptom exacerbation (flares) or the occurrence of new autoimmune manifestations, in particular through inhibition of cytotoxic T-lymphocyte antigen 4 and programmed death 1/programmed death ligand 1 axes, which are the main targets of ICI treatment, with preclinical evidence data suggesting that these axes may also play a role in AID.[2] Immune dysregulation may be associated with heightened risk of immune-related adverse events (ir-AEs), especially among those patients with higher titers of autoimmunity.[3-5] AID cases are relevant in NSCLC because 14% of patients with NSCLC (especially females) have a concurrent AID, the most common ones being rheumatoid arthritis, psoriasis, and polymyalgia.[6] A history of AID in patients with NSCLC does not influence other treatment possibilities and is not associated with lung cancer–specific and all-cause mortality.[7] As ICIs improve survival in advanced NSCLC, there is an urge to explore the safety and efficacy of ICIs in this population.

Real-world data reported that up to 22% of all patients with advanced NSCLC receiving ICIs have a history of AID.[8,9] Only four retrospective cohorts have assessed the efficacy and safety of ICIs in NSCLC patients with AID. Two cohorts focused on NSCLC patients, whereas the other two enrolled patients with different solid tumors including NSCLC, mainly enrolling patients with non-symptomatic rheumatologic, dermatologic, and endocrine disorders without baseline-specific treatment (Table 1).[8,10-12] Regarding safety, patients with AID had a higher incidence of ir-AEs, but these were mostly mild with an incidence of grade greater than or equal to 3 ir-AEs similar to those reported in the whole population without AID, and sometimes associated to AID flare.[8,10-12] These toxicities rarely required therapy discontinuation and were manageable with standard treatment algorithms (Table 1).[11,12] More specifically in patients

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Table 1. Cohorts of Cancer Patients With Autoimmune Disease Treated With Immune Checkpoint Inhibitors

	Investigator			
	Leonardi et al.[10]	Khozin et al.[8]	Danlos et al.[11]	Cortellini et al.[12]
N/tumor types	56/NSCLC	2402/NSCLC Real-world data	397/Multiple (NSCLC: 16.3%)	751/Multiple (NSCLC: 66%)
Patients with AID	56	531 (22%)	45 (6 NSCLC, 13%)	85
Active AID	18%	NR	56%	17%
Treatment for AID	20%	NR	16%	17%
Flare AID	23%	NR	24.4%	47.1%
Ir-AEs/grade ≥3 ir-AEs	38%/11%	27.1% /NR (26.0%/NR for non-AID)	44% / 11% (29% / NR for non-AID)	66%/9.4% (40%/9% for non-AID)
Discontinued	14%	NR	11.1%	7% (7.2% for non-AID)
RR	22%	NR	38% (28% RR for non-AID, $p = 0.098$)	38% inactive-AID, 50% active-AID (35% for non-AID)[a]
PFS, months	NR	$p = 0.74$	NR	6.8 active-AID, 14.4 inactive-AID, 8.0 no-AID[a]
OS, months	NR	11.5 vs. 12.8, $p = 0.13$	$p = 0.38$	9.8 active-AID, 15.7 inactive-AID, 16.5 no-AID[a]

All studies were retrospective.
AID types according to the cohorts were as follows:
Leonardi et al.[10]: rheumatologic disorder (45%), dermatologic disorder (29%), endocrine disorder (16%), inflammatory bowel disease (11%), neurologic condition (5%), rheumatic fever (3%), and autoimmune hemolytic anemia (2%). Seven patients had more than one autoimmune disease.
Khozin et al.[8]: glucocorticoid deficiency (3.9%), rheumatoid arthritis (5.8%), and sacroiliitis (3.9%).
Danlos et al.[11]: Thirty-six patients had a pre-existing AID other tan vitiligo: cutaneous psoriasis (n = 12, including 1 case with psoriatic arthritis), autoimmune thyroiditis (Hashimoto disease or Grave's disease; n = 7), primary Sjögren's syndrome (n = 4), rheumatoid arthritis (n = 2), immune thrombocytopenic purpura (n = 1), spondyloarthritis (n = 1), multiple sclerosis (n = 2), hidradenitis suppurativa (n = 1), myasthenia gravis (n = 1), polymyalgia rheumatica (n = 1), polyarteritis nodosa (n = 1), sarcoidosis (n = 1), chronic cutaneous lupus (n = 1), and type 1 diabetes (n = 1). Two concomitant AID cases were reported in 18% of cases.
Cortellini et al.[12]: thyroid disorders (60%), dermatologic (16.4%), rheumatologic (11.8%), gastrointestinal/hepatic (4.7%), neurologic/ nephrologic (~1%), and multiple sites (4.7%).
[a]Differences were not statistically significant (AID vs. non-AID).
AID, autoimmune disease; ir-AEs, immune-related adverse events; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate.

with NSCLC, the incidence of grade 3 ir-AEs and discontinuation rate were 11% and 14%, respectively.[10] This was similar to what has been reported in randomized trials in previously treated NSCLC patients (grade ≥3 ir-AEs ranging from 5% to 16%, and up to 8% of treatment discontinuation).[13] An observational study has reported that pre-existing AID was not associated with time to any hospitalization after initiating ICI therapy, but it was associated with a modest increase in hospitalizations with ir-AE diagnoses and with corticosteroid treatment.[14] Furthermore, 25% to 47% of AID patients treated with ICI may experience an exacerbation of their underlying AID, being the cause of grade 3 ir-AEs in some cases.[10-12] The majority of these flares are detected within the first 3 months of ICI treatment, without late occurrence, with a trend toward risk of flare among patients with pre-existing thyroid, dermatologic, or gastrointestinal/hepatic disorders.[10,12] However, it remains unknown whether this hypothetical correlation is truly organ-specific, or whether it is only related to the fact that these ones are ones of the most frequent AID cases.

Besides safety, ICI efficacy in this population was similar to those without AID, with a response rate ranging from 22% in the NSCLC cohort to up to 39% in the other two cohorts.[10-12] Previous data have reported contradictory results regarding the role of baseline autoimmunity in NSCLC patients treated with ICI and outcome, despite the fact that increased risk of ir-AEs has been correlated with better outcome.[4,5] In three of four current cohorts, outcome was similar for AID and non-AID patients, but patients with active AID had a shorter survival.[8,10,11] In the reported AID cohorts, between 20% and 56% of patients were symptomatic at the time of ICI initiation, and up to 20% were receiving immunosuppressant or immunomodulatory treatments for their AID.[10-12] It has been previously reported that concurrent administration of steroids during the first cycle of ICI as well as within 30 days of the start of ICIs correlates with decreased outcome.[15,16] However, this correlation seems linked to the dose and duration of steroids[16] and to the use of corticoesteroids for palliative conditions.[17] Use of immunosuppressant drugs in patients with active AID may potentially explain the shorter outcome with ICI in this population as compared with patients with inactive AID and with non-AID patients (Table 1).[12] All these cohorts have the limitations that they were retrospective and enrolled mild-symptomatic AID patients without any life-threating AID. Therefore, we cannot extrapolate the current evidence to more severe AID patients. Prospective evaluation of the ICI strategy in patients with AID remains challenging. Two phase I clinical trials with the

anti–programmed death 1 antibody nivolumab in lung cancer (NCT03656627) and across tumor types (NCT03816345) are ongoing in this population.

In conclusion, current data suggests that ICIs are a reasonable strategy in patients with some quiescent AID and life-threatening malignancies, without effective alternative treatments. There is a risk of AID exacerbations in up to half of cases, which usually are manageable without increased risk of hospitalizations. However, a discussion about risk-benefit with the patient, as well as a close monitoring of these patients by a multidisciplinary team are necessary to identify AID flares and implement an early therapeutic intervention. In addition, before broadly applicability of ICI in all patients with AID, larger studies are necessary to identify risk of ICI in case of more severe and symptomatic AID or in patients with specific AID subtypes, very few represented in the current retrospective cohorts.

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