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Safety issues with the ALK inhibitors in the treatment of NSCLC: A systematic review

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ABSTRACT

Introduction: Oral tyrosine kinase inhibitors targeting the chromosomal rearrangements of the anaplastic lymphoma kinase gene (ALK) in non-small cell lung cancer (NSCLC) were associated with superior clinical outcome. Tyrosine Kinase inhibitors (TKIs) are known to have peculiar toxicity profile, hence, increasing awareness to the safety profile of ALK inhibitors is essential.

Methods: A comprehensive systematic review of literature has been conducted to include prospective trials that used the ALK inhibitors Crizotinib, Ceritinib, Alectinib, Brigatinib and Lorlatinib in patients with advanced NSCLC and have available efficacy and toxicity results.

Results: A total of 14 studies including 2793 patients were considered eligible for our review and included two phase IB, seven phase II and five phase III studies. The most common adverse events (AEs) observed with ALK inhibitors were gastrointestinal (GI) toxicities as nausea (up to 83%), vomiting (up to 67%) and diarrhea (up to 86%), elevation of liver enzymes occurred in up to 60% and fatigue (up to 43%). There were differences in the toxicity patterns between the different ALK inhibitors with more GI and hepatic toxicities with Ceritinib, more visual disorders with Crizotinib, more dysgeusia with crizotinib and Alectinib and possibly more respiratory complications with Brigatinib. Most of the AEs were low grade and treatment-related deaths were associated with ALK inhibitors in 0–1% of patients.

Conclusion: Most of adverse effects of ALKi can be managed efficiently via dose modifications or interruptions. Timely identification of each ALKi pattern of toxicity can prevent treatment-related morbidity and mortality in this palliative setting.

1. Introduction

ALK inhibitors are one of the breakthrough advances in non-small cell lung cancer (NSCLC) and in cancer treatment in the last decade. ALK fusions were first reported in NSCLC in 2007 in a small subset (7%) of Japanese patients (Soda et al., 2007). The fusion partner was the echinoderm microtubule associated protein like-4 (EML4) gene, which is normally involved in microtubule formation (Inamura et al., 2008). The resultant fusion gene EML4-ALK, that occurs from an inversion rearrangement inv(p21;p23), has tyrosine kinase activity which causes increased cell proliferation as a result of activation of the ALK signaling pathway (Inamura et al., 2008). Other fusion partners were also detected with most of them providing a promoter that keeps constitutive expression of the fusion protein.

The first ALK inhibitor (ALKi) to be used in metastatic NSCLC was Crizotinib (CRZ). It is an oral, small molecule TK inhibitor (TKi) of ALK, c-MET and ROS^{-1} that causes the arrest of the cell cycle at G1/S phase and the induction of apoptosis (Christensen et al., 2007). Around one third of ALK-rearranged NSCLC patients develop resistance to CRZ due to mutations in the TK domain, amplification of ALK fusion gene or activation of bypass oncogenic signals. Some of these bypass signaling mediate also resistance to 2nd generation ALKi (Lucena-Araujo et al., 2016).

Moreover, CRZ has a limited CNS penetration. Next-generation ALK inhibitors were developed to combat the resistance to CRZ. Ceritinib is a more potent oral ALK inhibitor than CRZ, it can inhibit other kinases such as, IGF1R and insulin receptor but not c-MET (Katayama et al., 2015). In addition, it inhibits several CRZ-resistant mutations ((e.g.,

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Interestingly, most of the next-generation inhibitors are structurally-distinct apart from lorlatinib that shares a structural basis with crizotinib. Alectinib can effectively overcome more resistance mutations than ceritinib. Brigatinib has a 10-fold greater potency than CRZ and showed activity for most secondary resistant mutations reported in patients with disease progression on CRZ, ceritinib and alectinib (Wilson et al., 2015). Ceritinib has moderate CNS penetration, but alectinib and brigatinib have good CNS penetration. Spectrum of inhibition of other tyrosine kinases, potency against various resistant mutants of ALK and CNS efficacy may be the mechanistic underpinnings that make alectinib and brigatinib appearing more effective than crizotinib and ceritinib (although not compared head to head).

Introduction of Crizotinib (and other drugs of the same class as ceritinib) in the management of ALK-rearranged advanced NSCLC resulted in superior tumor response rates and better progression-free survival in addition to relatively less toxicity than conventional chemotherapy (Shaw et al., 2013; Solomon et al., 2014). but requires daily treatment and so patients may be potentially exposed to side effects over a longer period of time. We are lacking overall survival data comparing ALKi versus chemotherapy, one study on small cohort of patients with brain metastases from ALK-rearranged NSCLC, has reported median OS after development of brain metastases of 49.5 months (Johung et al., 2016). Another report on 26 patients with advanced disease received CRZ as the first ALK inhibitor to achieve an estimated 5-year OS of 36% (Rangachari et al., 2017). Both of which are far superior overall survival outcomes when compared to chemotherapy cohorts.

However, being less toxic shall not avert the practitioners from its peculiar toxicity profile. The use of these drugs is associated with a different profile of adverse events and such difference from the conventional chemotherapy should be clearly recognized by the treating physician. Moreover, introduction of ALKi has nearly doubled the progression-free survival of those patients making them more exposed to active treatment (Shaw et al., 2013; Solomon et al., 2014; Soria et al., 2017; Scagliotti et al., 2016). Recognizing both the early and late adverse effects is crucial for proper monitoring of such patients. It was anticipated that each ALKi might have a peculiar toxicity profile because they can inhibit other tyrosine kinases for instance, crizotinb can inhibit MET and ROS1, Lorlatinib can inhibit ALK and ROS1, but does not affect c-MET, Alectinib can inhibit ALK as well as RET.

In the last decade, several new agents were approved for the treatment of advanced and metastatic NSCLC such as: monoclonal antibodies (e.g. bevacizumab) or EGFR TKIs (e.g. erlotinib and gefitinib) and most recently ALK inhibitors (e.g. crizotinib). Clinicians should be aware of the new designation of safety profiles of targeted therapies. It is either a class-related toxicity such as hypersensitivity reactions of monoclonal antibodies or target-related toxicity which depends mainly on the target itself, for example targeting VEGF is known to cause hypertension, bleeding and proteinuria.

To adequately describe the exact safety profile of each of those agents we conducted a systematic review of prospective trials testing various ALK inhibitors (ALKi) in NSCLC. We compare common AE with each ALKi along with clinical approach to management.

2. Methods

2.1. Search strategy

We conducted a thorough review of PubMed database, ASCO library database, ESMO, IASLC and ELCC meeting abstract databases from January 2005 to August 2017 using the following keywords in the titles or abstracts searched: ‘Crizotinib’ OR ‘Alectinib’ OR ‘Ceritinib’ OR 'Brigatinib' OR 'Lorlatinib' OR 'Entrectinib' OR 'X-396′ OR ‘ALK inhibitor’ AND ‘Lung Cancer’. The search was limited to prospective clinical trials published in English. An independent search of the Google scholar and clinicaltrials.gov was performed to ensure that no additional clinical trials had been missed. In case of duplicate publications, the most recent and updated report that included full safety data of the clinical trial was included. Trials were selected and reviewed according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement (Moher et al., 2009).

2.2. Study selection criteria

2.2.1. Inclusion criteria

i) Prospective clinical trials in patients with non-small cell lung cancer

ii) Participants have to be assigned to at least one arm containing one of the aforementioned ALK inhibitors.

iii) Sample size and safety results (for the common AEs) should be reported.

2.2.2. Exclusion criteria

i) Dose-finding phase I trials

ii) Incomplete reporting of the safety data either in the meeting abstract or in the full publication.

iii) Studies on other types of cancers not including NSCLC.

2.3. Data extraction

Two assigned reviewers (KSS, SL) independently performed the data extraction. Any conflicts were resolved by a third reviewer (LK). The following information was recorded for each study in a table form (Table 1); First author’s name, year of publication, trial phase, number of patients, treatment arms, prior chemotherapy, prior targeted therapy, primary outcome measure and number of events of all-grade (grade 1–4) and high-grade (grade 3–4) of the selected AEs.

2.4. Risk of bias judgment

We could not use the Cochrane risk of bias tool for assessing the risk of bias across the included studies as the majority of them were non-randomized.

3. Results

3.1. Selection of studies

Fig. 1 shows the PRISMA diagram for the included studies; 13 potentially relevant studies were obtained from the MEDLINE search and 16 studies from other databases. Of the initial retrieved results, eleven studies did not meet the inclusion criteria and were excluded. Thus, a total of 14 studies with 2793 patients were included in the final analysis: two phase IB trials, seven phase II trials and five phase III trials (Tables 1 and 2). Data were extracted from full-text publications, full-text of ASCEND-3 trial (Felip et al., 2016; Park and Tan, 2015; Felip, 2015) was not published at the time of this review.

3.2. Studies and patients characteristics

The majority of NSCLC patients treated in the included studies were metastatic. Patients with locally advanced (stage III) disease weren't eligible for local therapy. ALK inhibitors were used as a monotherapy in all studies. Three studies used crizotinib, three studies used alectinib, five studies used ceritinib, two studies used brigatinib (Kim et al., 2017; Gettinger et al., 2016), and one study randomized crizotinib versus alectinib (Hida et al., 2017). Four of the included studies compared an ALK inhibitor to chemotherapy while one compared 2 ALK inhibitors to each other. The median age of the included patients ranged from 48 to 61 years. Most of the included studies allowed prior platinum based chemotherapy for advanced disease (Table 1).

Table 1
Baseline characteristics of eligible studies.

Author-year	Study Type	Regimen	No patients	Pts evaluable for safety	Disease stage/Biology	Phase	Median Age (yrs)	Prior chemotherapy, n (%)	Prior targeted therapy, n (%)	1ry outcome measure*
A) Crizotinib (CRZ) trials										
Camidge et al. 2012 PROFILE 1001	Open label, single arm	CRZ 250 mg bid	149	149	III or IV NSCLC	IB	52	127 (84%)	No	ORR, PFS
(Shaw et al., 2013) PROFILE 1007	Randomized, open label	CRZ 250 mgbid Vs pemetrexed or docetaxel	347	343	Locally adv. or met. ALK + ve NSCLC	III	51 Vs 49	One Platinum containing regimen	none	PFS
(Solomon et al., 2014) PROFILE 1014	Open label, Randomized	CRZ 250 mg bid Vs PEM/Cis or PEM/ Carbo	343	172 Vs 171	Locally adv., recurrent or metastatic ALK + ve NSCLC	III	52	none	none	PFS
J-Alex (Crizotinib arm) Hida et al. 2017	Randomized open label	ALC 300 mg bid Vs CRZ 250 mg bid	104	104	IIIB-IV	III	59	No	No	PFS
B) Alectinib (ALC) trials										
(Seto et al., 2013) AF-001JP	single arm	ALC 300 mg bid	46	46	IIIB, IV, or recurrent NSCLC	I/II	48·0	45 (99)	none	ORR
(Ou et al., 2018 NP28673, Global	Single arm	ALC 600 mg bid	138	138	Advanced CRZ-Refractory (ALK+) NSCLC	II	52	80%	CRZ (100%)	ORR
(Shaw et al., 2016) NP28761, North America	Single arm, open label	ALC 600 mg bid	87		IIIB-IV	II	54	74%	CRZ (100%)	ORR
J-Alex (Alectinib arm) (Hida et al., 2017)	Randomized open label	ALC 300 mg bid Vs CRZ 250 mg bid	103	103	IIIB-IV	III	61	No	No	PFS
C) Ceritinib (CRT) trials:										
(Kim et al., 2016a) ASCEND-1	Single arm	CRT 750 mg/d	246	246	ALK + locally advanced or metastatic NSCLC	IB	52	93.5% received chemotherapy	163 (66.2% received CRZ	ORR, PFS
Crino et al., 2016, ASCEND-2	Single arm	CRT 750 mg/d	140	140	ALK-rearranged metastatic NSCLC	II	51	140 (100) received 2 or more lines	140 (100) received CRZ	ORR
Soria et al., 2017 (ASCEND-4)	Randomized, open label	CRT 750 mg/d Vs Platinum based chemo	376	189 Vs 187	IIIB-IV	III	55	0 (0%)	0	PFS
ASCEND-3 (Felip et al., 2016; Park and Tan, 2015; Felip et al., 2016	Abstract, single arm, open label	CRT 750 mg/d	124	124	ALKi naïve pts	II	56	122 (98.4%) [31 (25) receiving ≥3 lines]	none	Whole body and intracranial ORR
Shaw et al., 2017 (ASCEND-5)	Randomized, open label	CRT 750 mg/d Vs Pem or Docetaxel	231	115 Vs 116	IIIB-IV	III	54 vs 54	100% (1-2 lines)	100% CRZ	PFS
D) Other ALK inhibitors:										
Gettinger et al., 2016	Single arm open label	Brigatinib	137	137	locally advanced/metastatic ALK + NSCLC	I/II	54	Yes (47% had ≥ 2 lines)	90% CRZ, 20% erlotinib,	ORR
Kim et al., 2017	Randomized open label	Brigatinib 90 mg/d Vs 180 mg/d	222	112 Vs 110	locally advanced/metastatic ALK + NSCLC	II	50.5 Vs 56.5	Yes (74%)	100% CRZ	ORR

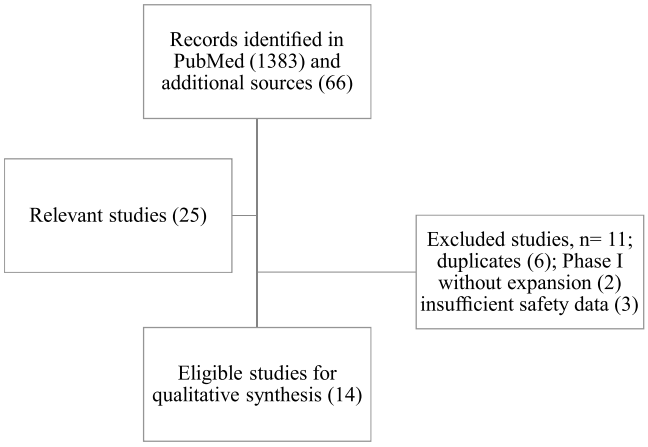

Fig. 1. Flowchart of the systematic review process.

3.3. Gastrointestinal toxicities

The most common GIT toxicities were nausea, vomiting, constipation and diarrhea. All grade nausea ranged from 10.7% to 83%. Incidence of nausea was highest with Ceritinib (ranged from 66% to 83%) and was lowest with Alectinib (ranged from 10.7 to 21.8%). Grade 3–4 nausea was generally uncommon (ranged from 0% to 8%) and with the exception of Ceritinib studies, incidence of high-grade nausea did not exceed 2%. All grade vomiting ranged from 4% to 67% with highest incidence occurring in Ceritinib studies (52% to 67%) and lowest incidence with Alectinib (4% to 11.5%). Grade 3–4 vomiting ranged between 0 to 8%.

All-grade diarrheas ranged from 4% to 86% of cases. It was highest in Ceritinib treated patients (ranged from 72% to 86%) and lowest in Alectinib treated patients (ranged from 4% to 20.7%) with intermediate risk of diarrhea with Crizotinib and Brigatinib. However, the risk of high grade diarrhea was negligible (between 0 and 6.4%).

Finally, Constipation occurred in 19% to 44.2% of patients receiving ALK inhibitors and was rarely a high-grade AE (< 2%). It appeared that constipation occurred more with Crizotinib and Alectinib (ranged from 24% to 44.2%) than with Ceritinib and Brigatinib (ranged from 19% to 30%), however, there was no reliable statistical comparison to confirm such observation. The rest of GIT toxicities were lower than the reporting threshold of most of the studies.

3.4. Hepatic toxicities

Regarding liver injury, most of the studies reported only changes in the biochemical liver profile without clear description of the clinical implications of such laboratory changes. The most common AE encountered was elevation of ALT and/or AST levels which ranged from 10.7% up to 60%. Increased ALT and/or AST was more common in patients receiving Ceritinib and Crizotinib than in those receiving Alectinib and Brigatinib. Grade 3–4 elevated liver enzymes ranged from 0% to 31% and was also much more common in Ceritinib-treated patients (3% to 31%). Acute liver injury with clinical implications ranged from 0% to 6% across the few studies that gave a separate description from the biochemical changes.

3.5. Fatigue, Visual disorders and peripheral edema

In our review, fatigue was one of the most encountered AEs. All-grade fatigue ranged from 15% to 43% while grade 3–4 fatigue ranged from 0 to 6.4%. There were no or little differences in the incidence of fatigue across different ALK inhibitors. Visual disorders occurred almost only with Crizotinib ranging from 54.8% to 82%. Visual disorders included diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters. The majority were grade 1–2 with almost no high-grade visual disorders observed with Crizotinib. Peripheral edema occurred in the Crizotinib and Alectinib studies in the range of 25% to 49%. It was not reported in the Ceritinib and Brigatinib studies denoting its very low incidence. Almost all cases of peripheral edema were grade 1–2 with no high-grade events.

3.6. Hematological toxicities

The most common haematological toxicities observed with ALK inhibitors were neutropenia and anemia. In general neutropenia was much lower than observed with chemotherapy. All grade neutropenia ranged from 3.5% to 21% and grade 3–4 neutropenia ranged from 0% to 13% in the included studies. Of note, neutropenia did not reach the reporting threshold (of 10%) in many of the included studies. All-grade anemias ranged from 12% to 18.3% with only 0–2% being high grade. Like neutropenia, anemia was not fully reported in all the included studies.

3.7. Miscellaneous toxicities

Upper respiratory infections were reported only with Crizotinib and Alectinib ranging from 10% to 32% with a limited description of the group of symptoms used to define such broad AE. In CRZ studies, the upper respiratory infection includes nasopharyngitis, rhinitis, pharyngitis, and upper respiratory tract infection (Pfizer Labs, 2015). In particular, the incidence of all-grade nasopharyngitis was 10% either with ceritinib (Shaw et al., 2017) or alectinib (Tamura et al., 2017). Dysgeusia was also observed in Crizotinib and Alectinib studies in the range of 11% to 52%. Such non-specific AE was not consistently reported in most of the studies. Similarly, dizziness was reported in the range of 10.3% and 22% but the majority of the included studies didn't report it.

Finally, in the 2 studies using Brigatinib, early onset of pulmonary complications occurred in 6–7% of the included patients. With the early use of the drug, such major AE should be clearly described to differentiate treatment-related from disease-related pulmonary symptoms. Myalgia tends to be common with alectinib ranging from 14.5% to 24% with only 1.2% having G3 myalgia. Elevation of serum creatine phosphokinase (CPK) was reported with both Alectinib and brigatinib ranging from 11% to 30% for any grade and from 3% to 9% for grade 3–4. Hypertension was unique to Brigatinib with incidence of 5% to 6% of Grade 3–4. Two patients in the phase I/II trial of brigatinib required dose reductions due to hypertension (Gettinger et al., 2016).

3.8. Serious AEs (SAEs) and treatment-related deaths

Serious adverse events (SAEs) occurred in the range of 0% to 25% across all studies. The discrepancy across different studies is mostly due to inconsistent definition of treatment-related versus disease-related SAEs. Treatment interruptions due to AEs were common with ALK inhibitors reaching up to 80% in some studies. However, treatment discontinuation due to AEs was less common ranging from 2% to 20%. Most of the studies did not report the exact numbers of dose interruptions/modifications rates by each specific adverse event.

The most common causes of SAEs with brigatinib were respiratory events including dyspnea (7%), pneumonia (7%) and hypoxia (5%). In one of alectinib studies, five patients developed one of the following SAEs: brain edema, radius fracture, tumour haemorrhage, sclerosing cholangitis, and allergic alveolitis (Seto et al., 2013). Treatment-related deaths (TRD) were infrequent with ALK inhibitors ranging from 0 to 1% of the included patients. In brigatinib phase I/II trial there were 3 TRDs due to hypoxia, sudden death or unknown cause (Gettinger et al., 2016). Two TRDs were reported with alectinib due to haemorrahge and intestinal perforation (Ou et al., 2018; Shaw et al., 2016). Meanwhile, the two deaths with ceritinib were due to interstitial lung disease and

Table 2
incidence of common adverse effects of ALK inhibitors.

Study	Grade	Fatigue	nausea	vomiting	edema	Constipation	Diarrhea	Visual disorders	Dizziness	Upper respiratory infections
A) Crizotinib (CRZ) trials										
Camidge et al., 2012	All G	24 (16)	84 (56)	58 (39)	44 (30)	41 (28)	74 (50)	96 (64)	31 (21)	NR
	G 3-4	2 (1)	1 (< 1)	1 (< 1)	0 (0)	1 (< 1)	1 (< 1)	0 (0)	0 (0)	NR
Shaw et al., 2013	All G (for CRZ)	46 (27)	94 (55)	80 (47)	54 (31)	73 (42)	103 (60)	103 (60)	37 (22)	44 (26)
	G 3-4	4 (2)	2 (1)	2 (1)	0	4 (2)	0	0	1 (1)	0
Solomon et al., 2014	All G	49 (29)	95 (56)	78 (46)	83 (49)	74 (43)	105 (61)	122 (71)	31 (18)	55 (32)
	G 3-4	5 (3)	2 (1)	3 (2)	1 (1)	3 (2)	4 (2)	1 (1)	0	0
J-Alex (Crizotinib arm) (Hida et al., 2017)	All G	NR	77 (74)	60 (57.7)	NR	46 (44.2)	76 (73)	57 (54.8)	NR	24 (23.1)
	G3-4	NR	2 (1.9)	2 (1.9)	NR	1 (1)	2 (1.9)	0 (0)	NR	0 (0)
B) Alectinib (ALC) trials										
Seto et al., 2013	All G	n/a	6 (13)	2 (4)	NR	11 (24)	2(4)	2 (4)	NR	NR
	G 3-4	n/a	0	0	NR	0	0	0	NR	NR
Ou et al., 2018	All G	36 (26)	16 (12)	15 (11)	34 (25)	45 (33)	14 (10)	NR	NR	NR
	G 3-4	2 (1)	0	1(1)	0	0	1(1)	NR	NR	NR
Shaw et al., 2016	All G	29 (33.3)	19 (21.8)	10 (11.5)	20 (23.0)	31 (35.6)	18 (20.7)	NR	9 (10.3)	9 (10.3)
	G 3-4	0	0	0	0	0	0	NR	NR	0
J-Alex (Alectinib arm) (Hida et al., 2017)	All G	NR	11 (10.7)	6 (5.8)	NR	36 (35)	9 (8.7)	NR	NR	21 (20.4)
	G3-4	NR	0 (0)	0 (0)	NR	1 (1)	0 (0)	NR	NR	0 (0)
C) Ceritinib (CRT) trials:										
ASCEND-1 (2627)	All G	106 (43)	205 (83)	150 (61)	NR	75 (30)	213 (86)	60%	31 (13)	NR
	G 3-4	12 (5)	15 (6)	11 (4)	NR	0	15 (6)	NR	0	NR
(Camidge et al., 2012) ASCEND-2	All G	51 (36.4)	114 (81.4)	88 (62.9)	NA	40 (28.6)	112 (80.0)	NA	NA	NR
	G 3-4	9 (6.4)	9 (6.4)	6 (4.3)	NA	3 (2.1)	9 (6.4)	NA	NA	NR
Soria et al., 2017 (ASCEND-4) (11)	All G	55 (29)	130 (69)	125 (66)	NR	36 (19)	160 (85)	NR	NR	NR
	G 3-4	8 (4)	5 (3)	10 (5)	NR	0 (0)	10 (5)	NR	NR	NR
Shaw et al., 2017 (ASCEND-5)	All G	31 (27)	76 (66)	60 (52)	NR	22 (19%)	83 (72)	NR	NR	NR
	G 3-4	6 (5.2)	9 (8)	9 (8)	NR	0	5 (4.3)	NR	NR	NR
D) Other ALK inhibitors										
(Gettinger et al., 2016) (Brigatinib)	All G	(42)	(52)	(21)	NR	(20)	(40)	NR	NR	NR
	G3-4	(4)	(1)	(0)	NR	(0)	(1)	NR	NR	NR
(Kim et al., 2017)(Brigatinib)	All G	(27)	(40)	(23)	NR	NR	(38)	NR	NR	NR
	G3-4	(0)	(1)	(0)	NR	NR	(0)	NR	NR	NR

Study	Dysgeusia	Alopecia	Liver injury	Elevated AST or ALT	neutropenia	Anemia	Others G 3-4	Serious AEs n (%)	ttt interruptions/ discontinued	ttt-related deaths
A) Crizotinib (CRZ) trials										
Camidge et al., 2012	16 (11)	NR	NR	18 (12)	NR	NR	HypoP.	N/A	10 (7)/3 (2)	0 (0)
	0	NR	6	6 (4)	9	NR	6 (4)			
Shaw et al., 2013	44 (26)	14 (8)	0	66 (38)	NR	NR	NR	12% Vs 14%	NA/6%	3 Vs 1
	0	0	1	27 (16)	23 (13)	4 (2)	NR			
Solomon et al., 2014	45 (26)	NR	1 (1)	61 (36)	36 (21)	15 (9)	stomatitis	NR	NR/12%	0
	0	NR	0	24 (14)	19 (11)	0 (0)	1 (1)			
J-Alex (Crizotinib arm) (Hida et al., 2017)	54 (51.9)	NR	NR	33 (31.7)	NR	NR	NR	NR	(74%)/(20 %)	
	0 (0)	NR	NR	13 (12.5)	NR	NR	NR	NR		
B) Alectinib (ALC) trials										
Seto et al., 2013	14 (30)	n/a	0	13 (28)	8 (17)	NR	Stomatitis	5 (11)	22(48) /4(9)	
	0	n/a	0		2 (4)	NR	7 (15)			
Ou et al., 2018	NR	NR	NR	16 (12%)	NR	NR	NR		29 (21)/11 (8)	1
	NR	NR	NR	NR	NR	NR	NR			

(*continued on next page*)

Table 2 (*continued*)

Study	Dysgeusia	Alopecia	Liver injury	Elevated AST or ALT	neutropenia	Anemia	Others G 3-4	Serious AEs n (%)	ttt interruptions/ discontinued	ttt-related deaths
Shaw et al., 2016	NR	NR	1 (1.1)	18 (20.7)	4 (4.5)	16 (18.3)	HypoP.	13(15)	31 (36)/2(2)	1
	NR	NR	1 (1.1)	0 (0)	0 (0)	1 (1.1)	2 (2.3)			
J-Alex (Alectinib arm) (Hida et al., 2017)	19 (18.4)	NR	NR	11 (10.7)	NR	NR	NR	NR	(29.1%)/(8.7%)	NR
	0 (0)	NR	NR	1 (1)	NR	NR	NR	NR		
C) Ceritinib (CRT) trials:										
ASCEND-1 (2627)	NR	NR	0	109 (45)	NR	30 (12)	NR		0/9(3.6)	2 cases
	NR	NR	0	7 (3)	NR	0 (0)				
(Camidge et al., 2012) ASCEND-2	NR	NR	4 (2.9)	61 (43)	NR	22 (15.7)	NR	17.1%	75.7%/7.9%	NR
	NR	NR	3 (2.1)	24 (17)	NR	3 (2)				
Soria et al., 2017 (ASCEND-4) (11)	NR	NR	0 (0)	114 (60)	9 (5)	28 (15)	NR	NR	152 (80)	0
	NR	NR	NR	58 (31)	1 (1)	4 (2)	NR			
Shaw et al., 2017 (ASCEND-5)	NR	6 (5.2)	NR	49 (42.6)	4 (3.5)	NR	NR	13 (11)	84 (73)/6 (5.2)	NR
	NR	0 (0)	NR	24 (21)	1 (1)	NR	NR			
D) Other ALK inhibitors										
(Gettinger et al., 2016) (Brigatinib)	NR	NR	NR	(18)	NR	NR	Early onset pulmonary events (6-7%)	(25%) mostly pulmonary	NR	NR
	NR	NR	NR	(1)	NR	NR			NR	NR
(Kim et al., 2017)(Brigatinib)	NR	NR	NR	(15)	NR	NR	Early onset pulmonary events (6%)	NR	(36)/(8)	1
	NR	NR	NR	(0)	NR	NR				

multiorgan failure (Shaw et al., 2014; Kim et al., 2016a).

4. Discussion

ALK inhibitors are very effective in treating ALK positive NSCLC compared to chemotherapy but with different spectrum of adverse events. Although generally tolerated, their toxicity should be closely monitored in order to maximize their safety and reduce dose if necessary.For simplicity of data presentation and summary we categorized the selected adverse effects into the following categories:

4.1. Gastrointestinal AEs

Among ALK inhibitors, Ceritinib was associated with highest risk of nausea, vomiting and diarrhea (60–80%) followed by Crizotinib (40–60%) with G3–4 toxicity in range 3–8% and 1–2% respectively, while Alectinib was associated with the lowest risk with no reported cases with G3–4 GI AEs. Such toxicities might be overlooked by many practitioners not expecting significant increase in nausea and vomiting with TKIs. In fact, in the 4 studies comparing ALK inhibitors (Crizotinib and Ceritinib) to chemotherapy, the ALK inhibitor carried more risk of all-grade nausea and vomiting than chemotherapy with equal risk of high-grade nausea and vomiting (Shaw et al., 2013; Solomon et al., 2014; Johung et al., 2016; Rangachari et al., 2017; Soria et al., 2017; Scagliotti et al., 2016). Of note, 2 of these comparative studies compared ALK inhibitor to a platinum-based doublet (acknowledging the fact that in these trials no routine anti-emetics were used with ALK inhibitors on contrary to chemotherapy) (Solomon et al., 2014; Johung et al., 2016; Rangachari et al., 2017; Soria et al., 2017). Based on these findings, NCCN guidelines categorized Ceritinib and Crizotinib as drugs with moderate emetic risk necessitating daily anti-emetics while Alectinib was categorized as drug with low emetic risk with anti-emetics on demand. However, the choice of optimal therapy for nausea and vomiting that occurs with ALK inhibitors is quite challenging due to the drug interactions usually encountered with such a class of drugs. For example, drugs that elevate the gastric pH as H2 receptor blockers and proton pump inhibitors may decrease the solubility and hence absorption of ALK inhibitors and might reduce their efficacy (however, little data is available on the clinical implication of this interaction) (Pfizer Labs, 2015). Moreover, co-administration of some anti emetics like 5-HT_3 receptor antagonists or metoclopramide with ALK inhibitors might increase the risk of QT interval prolongation. Therefore, baseline assessment and careful monitoring of ECG changes is critical when using such combinations. It is noteworthy that alectinib was not associated with any clinically significant QTc prolongation that allows using 5-HT_3 antagonists safely (Genentech, Inc, 2015).

In addition, diarrhea and constipation were found to be variable between different ALK inhibitors. While Crizotinib and Ceritinib were associated with diarrhea rather than constipation (with G3–4 diarrhoea in 1–2% and 4–7% respectively), Alectinib was associated with more constipation but with no G3–4 AE. Furthermore, ASCEND-8 study (Cho et al., 2017) was developed to investigate the safety of lower doses of ceritinib at 450 or 600 mg with a low fat meal in comparison to the standard 750 mg in a fasted state. The 450 mg fed showed more GI tolerability than the 750 mg fasted.

4.2. Hepatic AEs

ALK inhibitors tend to cause elevations of liver enzymes but less commonly to cause acute liver injury. Proving drug-induced liver injury (DILI) is a daunting task, even in clinical trials. Two liver toxicity grading system were devised; the one from the Drug-Induced Liver Injury Network (DILIN)that is commonly used by hepatologists in daily practice. The second one that is almost exclusively used in clinical trials of cancer therapeutics is the Common Toxicity Criteria for Adverse Events, version 4.0: CTCAEv4 (National Cancer Institute Cancer, 2018).

Table 3
Clinical approach to some selected adverse effects of ALK inhibitors.

Toxicity	Diagnosis	Precautions	Management
Late onset pneumonitis	Seen more with crizotinib, in the fourth week of intake, non-specific symptoms, definitive diagnosis via imaging and biopsy	Exclude other causes e.g. infection Serum biomarkers e.g. KL-6, SP-D	Drug discontinuation, corticosteroids
Early onset pneumonitis	Almost exclusive to brigatinib, in the first week of intake	Patient visit at days 2 and 8 of commencing of brigatinib.	Drug discontinuation, corticosteroids
Hypogonadism	Fatigue, decreased libido, depression	Inform the patient Early morning testosterone assay upon clinical suspicion	Testosterone supplementation (oral, gel, IM injections) No dose adjustment
Renal cyst	Accidental while doing imaging work-up	Screen for hematuria and proteinuria	Self-limiting Not to be confused with tumor progression
Peripheral edema	Delayed onset Multifactorial etiology	Compression stockings for high risk patients Diet advice Screen for albuminuria	Diuretics are not recommended due to potential electrolytes imbalance
Asymptomatic Sinus bradycardia	heart rate of < 60 bpm	Monitor HR and Blood pressure Initial drop of HR by 11-13 bpm is expected	No dose adjustment
Symptomatic Bradycardia	dizziness, angina, presyncope, syncope, and heart failure	Review concomitant medications e.g. antihypertensive	Withhold until HR $>$ 60 bpm or symptoms resolved. Discontinue permanently if life-threatening bradycardia
Dysguesia	Taste alteration (reduced, absent or bitter taste to any food) Loss of appetite	Monitor for weight loss Rule out zinc deficiency (especially with prior chemotherapy)	Dose reduction Switch to another ALKi

In both systems, the criteria used to diagnose and classify hepatotoxicity rely mainly on biochemical parameters such as bilirubin, ALT and Alkaline phosphatase (ALK P) serum levels.

Among the studies included in this review,9 studies reported the incidence of acute liver injury not only the mere elevations of liver enzymes. Three trials clearly depended on Hy's law when reporting acute liver injury (Shaw et al., 2013; Solomon et al., 2014; Kim et al., 2016a). Meanwhile one study (Crino et al., 2016) reported abnormal hepatic function without indicating the basis for "abnormal" and whether this is considered acute liver injury or not. In this study, the grade 3–4 abnormal hepatic function was 2.1% and G3–4 increase in ALT, AST, gamma-GT and Alk P were 17.1%, 5%, 12.1% and 2.9% respectively.

Interpretation of grade 3 and 4 liver toxicity should be taken cautiously. That is because firstly, not every elevation in liver aminotransferases or ALK P reflects a true liver injury, it might be an adaptive response to drugs. The CTCAEv4 tended to overestimate the liver toxicity. For instance, when ALT levels rise to 5–20 times the upper limit of normal (200–800 U/L) without any other salient symptoms, this is designated as high-grade (G3) toxicity which may prompt practitioners to discontinue the drug permanently and that was the case in the very early CRZ trial (Camidge et al., 2012). The data on the time to normalization of elevated liver enzymes and the effect of this interruption on drug efficacy is thoroughly investigated elsewhere (Schnell et al., 2012).

It is noteworthy that DILI was found to be dose-limiting toxicity in phase I study of ceritinib in Japanese patients (Nishio et al., 2015). On the other hand in a phase I trial of ceritinib (ASCEND-1) (Kim et al., 2016a), no cases of liver injury meeting Hy's law occurred despite the high incidence of elevated liver transaminases that was efficiently managed in almost all cases with dose interruption until resolution. After Grade 3–4 ALT and AST elevations, the decision either to permanently discontinue the drug or withhold to resolution and re-challenge at a modified dose must be taken on case by case basis (which should also be guided by changes in serum bilirubin level).

4.3. Visual disorders

Visual disorders were reported in two thirds of patients treated with Crizotinib but none with other ALK inhibitors. Electroretinography studies in rats showed a direct effect of crizotinib on retinal function, specifically a decreased rate of dark adaptation (Liu et al., 2015). This AE occurred mainly in first 2 weeks of treatment and resolved spontaneously with length of time on treatment. Again this was consistent with animal studies that showed no further worsening of dark adaptation of rats when the drug duration increased from 15 to 29 days (Liu et al., 2015). No impact on daily activity was observed but patients should be cautious when driving or operating machinery. An ophthalmological evaluation is not required before starting crizotinib treatment except if visual disturbances persist or worsen in severity in order to exclude unrelated retinal pathology, optic nerve pathology, or CNS involvement of underlying NSCLC (Matsumoto et al., 2011).

4.4. Respiratory AEs

Laryngitis, nasopharyngitis and rhinitis (collectively reported as upper respiratory infections) were observed in one third of patients receiving crizotinib and 10% of patients receiving alectinib. Most of the studies failed to clearly define when exactly was this AE considered treatment-related. On the other hand, interstitial lung disease (ILD) or pneumonitis was reported in a few cases receiving Alectinib (Ikeda et al., 2015), and was not reported in the phase 2 studies (Seto et al., 2013; Ou et al., 2018; Shaw et al., 2016) as separate adverse events but as dyspnoea in 10–15% of patients (which may not be all attributed to interstitial pneumonitis). It is noteworthy that an independent review of the four PROFILE trials have come to a conclusion that the incidence of de novo ILD, that can be definitely attributed to drug only, was 1.2% (Yoneda et al., 2017). Most respiratory events are typically very uncommon to be drug-related, but those which turn to be drug-related are fatal with mortality rate reached 50%. That is why every means must be asked for to know the cause of a respiratory event as immediate discontinuation of ALKi was associated with less mortality (Yoneda et al., 2017). The median time to onset of CRZ-induced ILD was 23 days (range 3–763 days). On the other hand, the median time to onset of pulmonary events with Brigatinib was 2 days that was fatal in 4% of patients (Gettinger et al., 2016). Moreover, in the phase 2 ALTA trial (Kim et al., 2016b), the incidence of early onset pulmonary events was 6% with onset range 1–9 days. This too early onset is unique to Brigatinib and warrants a patient visit on day 2 and 8 from the starting dayof the drug. There is a pressing need for investigating serum

biomarkers that can predict drug-induced lung disease. Changes of circulating levels of KL-6 were found to be predicative of EGFR-TKIs induced ILD and useful tool for monitoring of severity (Kawase et al., 2011). One case report of Alectinib-induced ILD found elevated levels of KL-6, SP-D and LDH that on drug discontinuation were gradually improved (Ikeda et al. 2015). Moreover, it is crucial to identify the possible risk factors for development of pulmonary toxicity with each ALKi and the effect of prior chemotherapy or radiotherapy. Those points were properly addressed with immune checkpoint inhibitors (Shohdy and Abdel-Rahman, 2017).

4.5. Hematologic AEs

Despite that, neutropenia, anemia and thrombocytopenia occurred in a much lower frequency with ALK inhibitors compared to cytotoxic chemotherapy, however, such important (and sometimes life-threatening) toxicities should not be neglected. Generally, more neutropenia was observed with crizotinib while more anemia was observed with alectinib and ceritinib. In case of grade 1–2 neutropenia, no dose modification is required while in case of grade 3–4 neutropenia withholding the drug till recovery (to ≤ grade 2) then resuming the ALK inhibitor at the lower dose level is the preferred strategy.

4.6. Fatigue and dysgeusia

Fatigue is one of the most commonly reported symptoms among patients receiving anti-neoplastic agents (Barsevick et al., 2013). In our review, this proved to also be true for ALKIs; where the incidence of all grade fatigue ranged from 15 to 43%, however, high grade fatigue ranged from 0 to 6.4%. Being a multi-factorial symptom that may interfere with the patient's ability to work and perform daily activities, fatigue is a distressing symptom that negatively impacts patients' quality of life.

Dysgeusia is a prevalent problem among cancer patients either due to the disease itself or its treatment. Dysgeusia is closely linked to changes in olfaction; however the exact mechanism underlying changes in taste and olfactory sensations in cancer patients is not fully understood (Heckmann et al., 2005). In our review, dysgeusia was reported in only 6 of the included studies, with Crizotinib and Alectinib, and was in the range of 11% to 52%. It is worth noting that in a systematic review of dysgeusia induced by cancer therapies, the prevalence of dysgeusia among cancer patients receiving chemotherapy was reported to be 56.3% (Hovan et al., 2010), a number not far from what was reported in some of the ALKI studies, however, none of the included studies reported high-grade dysgeusia. Although it seems to be benign AE, this might be a cause of patient incompliance. One patient was intolerant to crizotinib in AF-002JG trial due to developing Grade 3 dysguesia leading to weight loss. In *J*-Alex trial CRZ was associated with higher incidence of Dysguesia than Alectinib. Moreover, one case developed CRZ-induced G3 dysguesia continued on Alectinib without further toxicity reflecting differential toxicity profile of both agents (Koizumi et al., 2015).

4.7. Miscellaneous AEs

Although peripheral edema was commonly reported with Crizotinib and Alectinib, it was usually of Grade 1 and of late onset with no impact on treatment. A clinical approach of some selected AEs is summarized in Table 3. The patient has to be assessed for muscle pain, weakness and creatine phosphokinase (CPK) assay. CPK elevations were found in a considerable number of patients on Alectinib and Brigatinib therefore might require regular monitoring. Serum CPK levels should be tested every 2 weeks for the first 1–2 months of Alectinib intake. No cases of rhabdomyolysis were documented so far with this class.

Interestingly, in the ALTA trial, the dose of 180 mg with lead-in of brigatinib was associated with higher grade 3–4 CPK elevation than the 90 mg daily (9% versus 3%).This approach of starting brigatinib at 90 mg for 7 days and escalating to 180 mg was introduced to mitigate the early-onset respiratory events reported in the phase I/II study of brigatinib, where the incidence of pulmonary events in those who started on 180 mg daily was 14% and none reported in those started on 90 mg and continued on 180 mg. It is noteworthy that other high-grade AEs were the same in both regimens such as, hypertension (6%) and back pain (2%).

5. Conclusion

Although ALK inhibitors seem to have common class safety issues, however, early observations in the next-generation inhibitors suggests that alectinib is more tolerable than ceritinib. This might drive some clinicians to favor one over the other where both drugs (in addition to crizotinib) are the 3 recommended options in the first line setting. Initially, Crizotinib was associated with more GI and visual AEs. Alectinib tends to be associated with more hepatic and musculoskeletal AEs while ceritinib safety profile appears as the most adverse among this class with significant GI AEs and laboratory abnormalities. Moreover, the most recently introduced agent, Brigatinib, has a unique profile of increased early onset pulmonary AEs and hypertension. The type of ALK inhibitors may help prediction of AEs and hence proper patient selection and management. The differential toxicity profile of each ALKi had encouraged some authors to adopt approach of switching to another ALKi when encountering an adverse effect requiring treatment discontinuation. It has to be noted however, that all of these conclusions are based mainly on cross study comparisons with weak comparative evidence between different ALK inhibitors. Thus, these early observations will need to be further supported by the reports of more and more randomized trials.

Conflicts of interest and source of funding

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