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Revisiting a lower starting dose of alectinib in ALK-Positive non-small cell lung cancer

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ABSTRACT

We present here a case of ALK-positive lung adenocarcinoma that has been started on Alectinib. Treatment has been initiated at the recommended initial dose, but it subsequently required a dose adjustment following adverse drug events. Alectinib is a second-generation, CNS-active, tyrosine kinase inhibitor used in the treatment of ALK-positive non-small cell lung cancer. Its efficacy as a first-line treatment and as a second-line agent after Crizotinib has been proven across several trials both in terms of overall response rate and progression-free survival. The use of Alectinib is associated with side effects that occasionally lead to treatment discontinuation, interruption, or dose adjustment. Several studies have used two starting doses – 300 mg and 600 mg twice daily – across different populations and have consistently shown efficacy of Alectinib for both treatment doses. Results of these studies have also revealed that body weight, rather than race, affect the pharmacokinetics of Alectinib. Randomized trials have shown that the 600 mg dose is associated with more grade ≥3 adverse events and more changes in treatment in contrast to the 300 mg dose. A lower dose of Alectinib may limit treatment disruptions and dose reductions particularly for specific patient populations—particularly those with a lower body weight.

Introduction

Three to six percent of non-small cell lung cancers (NSCLC) exhibit re-arrangements in the anaplastic lymphoma kinase (ALK) gene. ALK-positive NSCLC is seen more frequently in young, female, never- or light-smokers and in individuals with a diagnosis of adenocarcinoma. In addition, it appears to be more common among Asians. [1] Treatment of ALK-rearranged disease using tyrosine kinase inhibitors, beginning with the first generation agent Crizotinib, is superior to chemotherapy in the first or subsequent lines of treatment. [2,3] Following the development Crizotinib, additional ALK-inhibitors have emerged: Alectinib, Ceritinib, Brigatinib, and Lorlatinib. [1,4]

Alectinib is a second-generation, ATP-competitive, ALK tyrosine kinase inhibitor that also has activity against rearranged during transfection (RET) kinase. Alectinib is also effective against gate-keeper mutations such as Leu1196Met that impart resistance to Crizotinib. [1,4,5] Alectinib is mainly metabolized by cytochrome P450 3A (CYP3A) to its active metabolite, M4. Additionally, potent CYP3A induction or inhibition results in only minor effects on the combined exposure of Alectinib and M4. Excretion is primarily by the fecal route in which unabsorbed Alectinib is the most abundant component. [6,7] Because of its lipophilicity and because it is not a substrate of *p*-glycoprotein efflux pumps expressed in the blood-brain-barrier, Alectinib is effective in the management of CNS metastases. [1,8,9] Current guidelines prefer Alectinib in the first-line treatment of ALK-rearranged NSCLC. [10] Following progression on Crizotinib, Alectinib is also superior to chemotherapy as second-line treatment. [11]

Data for the efficacy of Alectinib in the first-line setting were provided by three randomized trials. The J-ALEX trial was conducted in Japan and included 207 patients. This study showed a final progression free survival (PFS) advantage with Alectinib. [12] In the international ALEX trial that included 303 patients in 29 countries (46% Asian and 54% non-Asian population), better PFS was also seen for Alectinib vs. Crizotinib. [13] The third trial, ALESIA, was a randomized, open-label study comparing Alectinib with Crizotinib at 21 investigational centers in East Asia (China, South Korea) and in Southeast Asia (Thailand) that enrolled 187 patients. In this study, PFS favored Alectinib over Crizotinib as well (Table 1). [14] OS results for J-ALEX, ALEX, and ALESIA were still immature as of this writing[12–14].

Following progression on Crizotinib, Alectinib performed better in

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the second line setting compared to chemotherapy based on data from the Alur trial. This study enrolled 107 patients who were randomized 2:1 to receive Alectinib or a platinum-doublet. Participants were from 13 countries across Europe and Asia. Alectinib showed superior PFS compared to chemotherapy. [11] Further data on the effectiveness of Alectinib across treatment lines were provided by two recent meta-analyses by Fan et al. [9,16]

A striking difference between the studies was the dose of Alectinib used. In J-ALEX, it was 300 mg twice daily, while in ALEX and ALESIA, it was 600 mg twice daily. This difference in dosing was the result of the first-in-human AF-001JP done in Japan which evaluated Alectinib using the maximum investigated dose of 300 mg twice daily. In this study, 43/46 treated patients (93•5%) had an objective response, supporting a recommended dose of 300 mg twice per day. [17] Given that the overall safety profile of Alectinib is favorable, the question of whether higher doses would lead to higher tumor penetration and clinically to longer progression-free survival was raised. Subsequently, the phase 1–2 study AF-002JG was conducted in the USA to identify the maximum tolerated dose of Alectinib. [5] This trial provided the current recommended dose of 600 mg twice daily. This higher dose was identified and approved based on a model-informed drug development (MIDD) approach that considered safety, tolerability, efficacy, and pharmacokinetic data. Exploratory population pharmacokinetic (PopPK) analyses showed that body weight, but not race, was a major statistically significant covariate influencing Alectinib PK. As the US population had a higher distribution of body weights compared with the Japanese population, the 600 mg twice daily dosing regimen would ensure that the US population achieved drug exposures that were not inferior to those achieved in the Japanese population in J-ALEX. [4,18]

As toxicity is related to drug dose, not surprisingly, fewer toxicities were noted with the 300 mg dose than with the 600 mg dose of Alectinib. As an example, anemia (all grades) was reported in only 6% patients in J-ALEX, compared with 31% of patients in ALESIA. [4] Overall, grade ≥3 adverse events (AEs) occurred in 52%, 29%, and 36.9% of patients in ALEX, ALESIA, and J-ALEX, respectively. [12–14] Additionally, safety data from ALEX showed that 4.6% of patients suffered a fatal adverse event, while 14.5% experienced AEs that led to treatment discontinuation. Meanwhile, 20.4% and 26.3% of patients experienced AEs that led to dose reductions and dose interruptions, respectively[13]. Data from ALESIA showed that AEs leading to deaths, discontinuations, dose reductions, and dose interruptions affected 2%, 7%, 24%, and 26% of patients, respectively[14]. J-ALEX meanwhile reported that serious AEs leading to treatment withdrawal occurred in 7% of patients, while AEs leading to dose interruptions occurred in 34% of patients. Importantly, there were no fatal adverse events reported in J-Alex (Table 2). [12]

The most common adverse events cited across the three first-line studies were constipation, nasopharyngitis, upper respiratory tract infection, interstitial lung disease, increased creatinine phosphokinase, increased alanine aminotransferase, increased blood bilirubin, bradycardia, myalgia, dysgeusia, diarrhea, and rash. Furthermore, the most common grade ≥3 adverse events cited were increased levels of alanine and aspartate aminotransferase, increased creatinine phosphokinase, and increased blood bilirubin. Rates of increased laboratory parameters were higher in the ALEX trial compared to the ALESIA and J-ALEX trial. [12–14]

Up to two dose reductions are recommended for Alectinib in patients unable to tolerate the full 600 mg twice daily (BID) dose – an initial reduction to 450 mg BID and a second reduction to 300 mg BID. For patients who cannot tolerate the 300 mg BID dose, discontinuation of Alectinib is recommended. Table 3 summarizes the recommended dose reductions for specific adverse events. [19]

We present below an illustrative case that shows the efficacy of Alectinib in the treatment of ALK-positive NSCLC but also the challenges that come with managing its adverse events.

Case and methods

A 69/F with a history of pharmacologically controlled hypertension was diagnosed with metastatic non-small cell lung adenocarcinoma after presenting with hemoptysis. The tumor specimen from the right lung stained positive for the ALK (D5F3). Her baseline laboratory parameters were all within normal limits. The patient was started on Alectinib 600 mg twice daily as first-line treatment for her cancer. Resolution of hemoptysis within the first week of starting treatment was noted. The earliest AE noted was constipation, which was managed with increased hydration, dietary fiber, and laxatives. Beginning on her third week of treatment, the patient noted myalgia. Laboratory evaluation at this time revealed multiple abnormalities: muscle-specific creatine kinase (CKMM) (10x elevated ULN), hyperbilirubinemia (27x ULN), and her AST and ALT were both <2x ULN. The patient's estimated glomerular filtration rate also dropped from 91 mL/min/1.73 m^2 to 49 mL/min/1.73 m^2. On the basis of these findings, Alectinib was discontinued. Following a hiatus of three weeks, the patient's CKMM, bilirubin levels, AST, and ALT all returned to within normal limits (WNL). The patient's GFR likewise improved to 53 mL/min/1.73m^2. CT evaluation revealed a partial response by RECIST criteria with a 55% reduction in the primary tumor size.

Shared decision-making with the patient and her family led to resumption of Alectinib at the lowest dose adjustment of 300 mg twice daily. Follow-up laboratory tests done at three weeks following resumption showed CKMM, AST, and ALT WNL. Hyperbilirubinemia was also noted (1.4x ULN). Meanwhile the patient's GFR decreased to 43 mL/min/1.73m^2 and had remained between 40 and 50 mL/min/1.73m^2 on subsequent determinations. Her second CT scan at four months of treatment showed partial response by RECIST with a further decrease in the size of the primary tumor to 31% of the baseline size (69% reduction) and resolution of all bilateral satellite lung nodules as well as all paratracheal and para-esophageal lymphadenopathies. She is currently being given Alectinib 300 mg BID.

Table 1
Overall investigator-reported response rate and progression-free survival for Alectinib trials in ALK-positive NSCLC.

Trial	Sample Size	ORR (95% CI)		PFS in months (95% CI)		HR (95% CI)	Reference
ALK-treatment naïve		**Alectinib**	**Crizotinib**	**Alectinib**	**Crizotinib**		
ALEX	***N* = 303; $N_{Alectinib}$=152/ $N_{Crizotinib}$=151**	126 (82.9%; 76.0–88.5%)	114 (75.5%; 67.8–82.1%)	34.8 (17.7-NE)	10.9 (9.1–12.9)	0.43 (0.32–0.58)	(13)
ALESIA	***N* = 187; $N_{Alectinib}$=125/ $N_{Crizotinib}$=62**	114 (91%; *not reported*)	48 (77%; *not reported*)	*Not Estimable* (16•7–NE)	11.1 (9.1–13.0)	0.22 (0.13–0.38; p<0•0001)	(14)
J-ALEX	***N* = 207; $N_{Alectinib}$=103/ $N_{Crizotinib}$=104**	76 (92%; 85.6–97.5%)	71 (79%; 70.5–87.3%)	*Not Estimable* (17.5–NE)	10.2 (8.3–13.9)	0.31 (0.17–0.57)	(12,15)
Second line after Crizotinib		**Alectinib**	**Chemotherapy**	**Alectinib**	**Chemotherapy**		
ALUR	***N* = 107; $N_{Alectinib}$=72/ $N_{Chemotherapy}$=35**	27 (37.5%; 26–50%)	1 (2.9%; 0–15%)	9.6 (6.9–12.2)	1.4 (1.3–1.6)	0.15 (0.08–0.29)	(11)

Table 2
Adverse events in first-line Alectinib trials.

Trial	Population	Adverse Events Fatal Adverse Event	Leading to Discontinuation of Treatment	Leading to Interruption of Treatment	Leading to Dose Reduction	All Grade ≥3	References
ALEX (600 mg BID)	**$N_{Alectinib}$=152**	7 (4.6%)	22 (14.5%)	40 (26.3%)	31 (20.4%)	79 (52%)	(13)
ALESIA (600 mg BID)	**$N_{Alectinib}$=125**	2 (2%)	9 (7%)	32 (26%)	30 (24%)	36 (29%)	(14)
J-ALEX (300 mg BID)	**$N_{Alectinib}$=103**	0 (0%)	12 (11.7%)	35 (34%)	NA	38 (36.9%)	(12)

Table 3
Recommended dosing modifications for adverse events. ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal; ILD = interstitial lung disease; CPK = blood creatine phosphokinase. Bradycardia is defined as a HR <60 bpm. (Adapted from Alectinib Prescribing Information).

CRITERIA(19)	DOSE MODIFICATION(19)
Alanine Transaminase (ALT) or Aspartate Transaminase (AST) elevation of greater than 5X upper limit of normal (ULN) with total bilirubin ≤2 times ULN	Withhold temporarily until return to baseline or to less than or equal to 3 times ULN and then resume at lower dose.
ALT or AST elevation greater than 3X ULN with total bilirubin elevation greater than 2X ULN in the absence of cholestasis or hemolysis	Permanently discontinue Alectinib.
Total bilirubin elevation of >3X ULN	Withhold temporarily until recovery to baseline or to less than or equal to 1.5 times ULN and then resume at lower dose.
Any grade treatment-related interstitial lung disease (ILD)/ pneumonitis	Permanently discontinue Alectinib.
Grade 3 renal impairment	Withhold temporarily until serum creatinine recovers to less than or equal to 1.5X ULN and then resume at lower dose.
Grade 4 renal impairment	Permanently discontinue Alectinib.
Symptomatic bradycardia	Withhold Alectinib until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume Alectinib at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. Otherwise, resume Alectinib at lower dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia (life-threatening consequences, urgent intervention indicated)	Permanently discontinue Alectinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume Alectinib at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently discontinue Alectinib in case of recurrence.
CPK elevation >5X ULN	Withhold temporarily until recovery to baseline or to less than or equal to 2.5X ULN and then resume at same dose.
CPK elevation >10X ULN or second occurrence of CPK elevation of >5X ULN	Withhold temporarily until recovery to baseline or to less than or equal to 2.5X ULN and then resume at lower dose.

Discussion

As shown by the case above, the period of uncertainty following the recognition of AEs leads to anxiety for both the patient and the oncologist. During this time, questions arise as to when clinical parameters will return to normal – or if they will at all – and how AEs will impact treatment going forward. These questions are often difficult to answer. Such a scenario is cause for at least some consideration of ways to mitigate treatment toxicity without compromising efficacy. The case of Alectinib is distinctive in that there are data showing that a lower starting dose is still effective in the treatment of NSCLC. As a direct clinical comparison of the activity of Alectinib 300 mg versus 600 mg twice daily does not exist at present, a formal conclusion as to the best dose is yet to be reached[4]. Another question worth exploring is whether a weight-based dose stratification strategy can be a compromise going forward?

Exposure-response (ER) analyses suggested that lower dosing could result in suboptimal exposure to Alectinib possibly diminishing treatment efficacy. [20] However, efficacy data from J-ALEX showed that the lower dose of 300 mg twice daily did not produce a markedly different primary outcome (PFS) compared with ALEX or ALESIA wherein the higher 600 mg twice daily dosing was used. The safety and efficacy of the 300 mg BID dose is further supported by real world data reported by Masuda et al. This Japanese study included 1251 patients (of whom 1221/1251 patients formed the safety population and 1194/1251 patients formed the effectiveness population) from 519 study sites in Japan. Follow-up in this prospective cohort was from enrolment until discontinuation of Alectinib or until completion of 18 months of treatment. Notably, this study enrolled a population with a median age similar to that of J-ALEX but older than those in ALEX and ALESIA. [14,15,21,22] Incidence of adverse drug reactions (ADRs) was the primary endpoint of this study which found that grade ≥3 ADRs occurred in 123 (10.1%) of patients. Efficacy as measured by OS was the secondary endpoint. Median OS for the study was not estimable. Eighteen-month cumulative OS was found to be better for patients who had better performance status (ECOG ≤1), were without prior Crizotinib, were on first-line Alectinib, and were free of brain metastases at the time of enrolment. [21] Meanwhile, real-world data on the safety of the 600 mg BID dose of Alectinib were described by Bedas et al. This small cohort of 21 patients that received Alectinib across several lines of treatment stratified data based on age (<65; $N = 12$ v. ≥65; $N = 9$). Adverse events leading to dose reductions were seen in 33% of the younger compared to 44% of the older group. No grade ≥3 ADRs were seen in this population. Moreover, no adverse events leading to treatment discontinuation nor fatal adverse events were noted in this study. [23]

While the 600 mg twice daily dose of Alectinib may produce higher therapeutic levels of this drug, it is accompanied by more adverse events. Some of these AEs can lead to discontinuation of treatment. In addition, treatment interruptions that may ensue subtract from the therapeutic benefit of a higher dose of Alectinib. Moreover, a fraction of these patients will also receive a reduced dose of Alectinib following a period of treatment interruption. Starting Alectinib at a lower dose of 300 mg twice daily will produce fewer AEs and result in fewer treatment interruptions and thus makes it an attractive approach during treatment

initiation considering the proven efficacy of the TKI at this dose.

Conclusion

Alectinib is the preferred first-line treatment of ALK-rearranged NSCLC and is also superior to chemotherapy in the second-line setting. Data on its efficacy and safety are beyond question, but due to disparities in the dosing regimens used in Alectinib trials, the possibility of adopting a lower starting dose of this TKI and consequently reducing the incidence of adverse drug events, without sacrificing efficacy, appears feasible and merits consideration in the clinic.

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Authorship statement

The authors contributed equally to this work.

Ethical statement

The patient provided verbal consent for the purposes of this work. This work does not contain identifiable patient data, nor does it involve human tissue, biological samples, or data. It is exempted from ethical review based on the National Ethical Guidelines for Health and Health-Related Research of the Republic of the Philippines published in 2017.

CREDIT

Author contributions based on CREDIT are the following:

DBS and JAL contributed equally to this work

DS: Conceptualization; Methodology; Investigation; Resources; Formal Analysis; Writing, OD/R&E; Project Administration; Supervision

JAL: Conceptualization; Methodology; Investigation; Formal Analysis; Writing OD/R&E; Supervision; Project Administration

Declaration of Competing Interest

This study received no external funding. All the authors declare that they have no conflict of interest arising from this paper

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