

Critical risk-benefit assessment of the novel anti-cancer aurora a kinase inhibitor alisertib (MLN8237): A comprehensive review of the clinical data

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Critical Risk-Benefit Assessment of the Novel Anti-Cancer Aurora A Kinase Inhibitor Alisertib (MLN8237): A Comprehensive Review of the Clinical Data

Abstract

Background: Many current anticancer chemotherapeutics suffer from significant side effects, which have led to the exploration of more targeted therapies. This resulted in the exploration of inhibitors of Aurora A kinase as a potential anti-cancer treatment. Alisertib (MLN8237) has proven to be a potent Aurora A kinase inhibitor that had the highest safety profile among its therapeutic family. Phase I/II/III clinical trials with Alisertib have been carried out and reported promising efficacy, yet serious side effects. This article attempts to assess the clinical effect of Alisertib administration in various cancer phenotypes while describing the reported side effects.

Methods: Alisertib clinical data were systematically retrieved from Medline, CINAHL, PubMed, and Cochrane Central Register of Controlled Trials and analyzed for quality, relevance, and originality in three stages prior to inclusion.

Results: Overall, seven studies met inclusion criteria and enrolled a total of 630 patients. The reported “potential” clinical effect of Alisertib in various tumours is promising as it improved time to disease progression, progression-free survival, and the duration of disease stability. The achieved improvement therefore rationalizes its further investigation as a novel anticancer therapy. However, the administration of the drug was associated with serious haematological disturbances in a relatively high percentage of patients.

Conclusion: The evidence of the anti-tumour effect of Alisertib administration is compelling in various types of malignancies. The reported side effects were serious but manageable in many cases. Topical or more targeted routes of administration are suggested when possible to overcome off-target events with systematic administration of the drug.

Keywords

Chemotherapy complication, Alisertib, Aurora A Kinase, systematic review, risk-benefit assessment

1. Introduction

Cancer remains a major health priority area with the global burden increasing from 14.1 million in 2012 (1) to 14.9 million cases in 2013(2). Mortality rates were 8.2 million in these consecutive years (1, 2). On average, cancer claimed more than 22,000 lives daily throughout 2013(2). The significant burden of cancer suggests a flaw in the current strategies of treatment and probably, screening, prophylaxis, and the diagnostic procedures. However, other factors related to the increase in population and the lack of proper treatment in the developing countries may contribute as well.

Current treatment practice includes surgery (3-5), chemotherapy (6) and radiotherapy (7) in the majority of the cases. Despite the efficacy of some treatments in early cancer stages, they are usually nonspecific in nature, associated with side effects on normal tissues and prone to develop resistance (8). Moreover, the accompanied harsh and invasive side effects of such treatments significantly affect the patient's quality of life, which may subsequently leave the patient susceptible to new cancers (9, 10). Therefore, there is a pressing need for the development of novel cancer treatments to improve the survival rates and decrease the burden of the disease.

Indeed, a range of new highly specific treatments have entered the market recently or are in clinical trial. Blocking angiogenesis from/in the tumour stroma (11), targeting specific oncogenic proteins and their subsequent inhibition of tumour suppressor factors (12) and targeting cell cycle regulators (13) are all strategies that have the potential to significantly increase the specificity and efficacy of cancer treatment (11-13).

In this paper, we examine the critical cell cycle regulator belonging to the Aurora Kinase family, Aurora A Kinase (AURKA) (14). AURKA, AURKB, and AURKC are involved in numerous cell cycle events including chromosome alignment, cytokinesis (15), centrosome function, and spindle formation, and assembly during the mitosis stage of cell cycle (16-18). AURKA also acts as a gate keeper for the G2-M check point in cell cycle and its deregulation was reported to induce G2-M arrest followed by apoptosis (19), in addition to severe mitotic abnormalities resulting in selective lethality for many types of solid and haematological malignancies (20, 21).

In addition to its mitotic roles, AURKA contributes to acquiring resistance to standard treatments through its non-mitotic functions. More specifically, AURKA provides cells with stem-like properties by transforming them from epithelial to mesenchymal type (22, 23). This transformation aids in potentiating the progression of the tumour, metastasising, and increasing the resistance towards treatments (23-25).

Interestingly, a growing body of literature has shown over-expression of AURKA in numerous types of cancers including colorectal, ovarian, gastric (21), and haematological cancers (20). This suggests that these types of cancers may be dependent on AURKA to survive (15, 26, 27). Due to its important roles in maintaining chromosomal integrity, cell cycle regulation, and its up-regulation in various types of tumour models, it was considered a strong potential candidate for anti-cancer targeted interventions.

Accordingly, many AURKA inhibitors were developed. During the last 10 years, more than 13 different inhibitors of the Aurora kinases have been tested in phase I clinical trials in patients with hematologic and solid tumours. The majority of these agents were inhibitors of all Aurora-A, -B, and -C indiscriminately. However, only a few inhibitors made it through to phase II clinical trials. Several trials were suspended or not completed due to serious cytotoxic side effects observed upon administration of clinically effective doses, while others

were discontinued due to inadequate anti-tumour activity (28-30). Despite the fact that there were several proposed selective inhibitors for AURKA such as MLN 8054 (31), TAS-119 (22), MK-5108, ENMD-2076, and MLN 8237 (32), only MLN 8237 (also known as Alisertib) progressed to phase III evaluation (33). Alisertib was developed as a structurally improved generation of a previously established inhibitor, MLN 8054. The latter was the first AURKA inhibitor to be evaluated in human phase I clinical trial due to its encouraging pharmaceutical characteristics, such as reliable absorption and prolonged half-life in preclinical models. However, upon clinical administration, patients suffered from central nervous system (CNS) side effects due to its structural similarity to the benzodiazepine family, particularly somnolence due to GABAA α -1 benzodiazepine off-targeting(34). Subsequently, a change in the structure of MLN 8054 led to the development of MLN 8237 (apyrimidobenzazepines), which showed less affinity to GABAA α -1 and therefore, less CNS side effects (35).

In preclinical data, Alisertib has been able to achieve robust anti-tumour efficacy that rationalized its further advancement to clinical trials (36-41). Growth inhibition was achieved in a wide range of cell cultures, including cells originating from HTLV-1 infected adult T-cell leukemia (42), peripheral T-cell lymphomas (37), multiple myeloma (38), human tongue squamous cell carcinoma (39), malignant bladder cancer (40), and cervical cancer (36) cell lines. The latter were able to be completely cured in mouse xenograft models (36).

Despite its efficacy, its safety profile is still concerning. Severe drug-related side effects like neutropenia and anaemia were reported in Phase I/II clinical trials (43-52). Hence, this systematic review examines the therapeutic potential and safety profile of Alisertib from the publically data available.

2. Methods

This review was undertaken according to the PRISMA guideline for systematic reviews. All published human trials testing Alisertib for any cancer type were considered for inclusion with the most recent database search performed on 25 August 2016. Medline database via EBSCO HOST, CINAHL database via EBSCO HOST, PubMed and Cochrane Central Register of Controlled Trials were searched for articles using the terms [Alisertib OR mln8237 OR "MLN 8237" OR "mln-8237"] in the TITLE field. This was limited to human trials only in the last 10 years that are written in English. Articles from the authors' database and bibliographic references cited by original and review articles identified as part of the literature search were also explored and cross-referenced against the search results.

A design of inclusion criteria for this systematic review was generated to include the most robust clinical trials undertaken on adults in various types of cancer. The studies were analyzed in three stages prior to inclusion in the final review. To be included in this review, the article had to report both efficacy and side effects of Alisertib systematic administration in adult patients diagnosed with any type of cancer. Animal or basic science

research articles, studies testing Alisertib in combination with other drugs, and studies that had less than 40 patients were excluded.

Duplicate articles were removed, followed by screening titles and abstracts as per the criteria previously outlined. The search strategy is outlined in Figure 1. The full text of the articles was retrieved and the methods were analyzed.

Quality Assessment Tool for Quantitative Studies was utilized to assess the quality of the included studies(53). Briefly, this tool addresses eight criteria (selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis appropriate to question) to appraise study quality (table 2). The final global rating classifies studies into strong (no weak rating in all the eight areas), moderate (one weak rating), or weak (two or more weak ratings). Discrepancies in quality assessment were resolved by inviting an expert opinion.

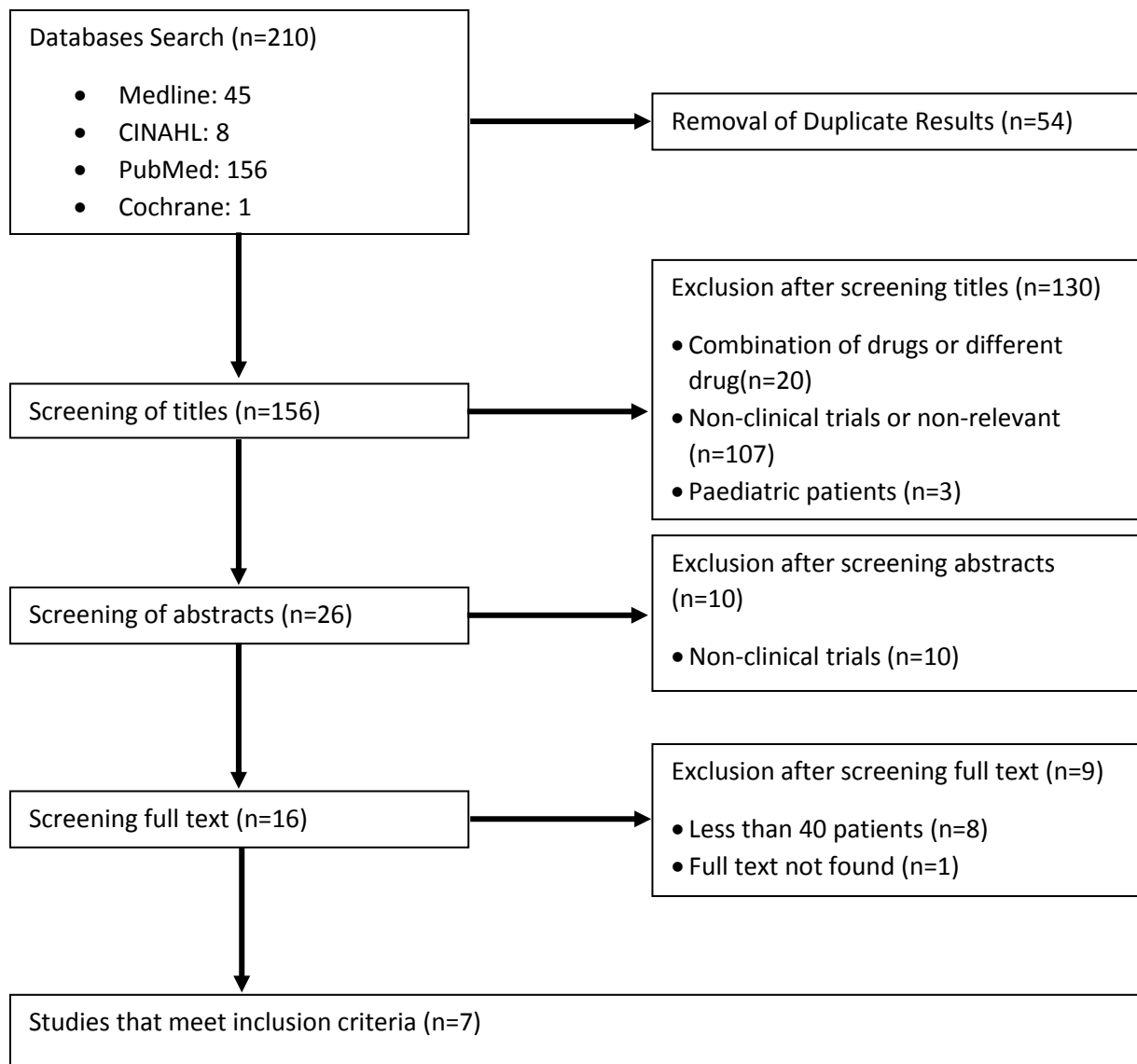


Figure 1. Study flow chart. Searching strategy and databases hits

3. Results

3.1 Description of the included studies

A total of 210 articles were identified following removal of duplicates and application of initial filters, with 16 articles nominated, and their methods were assessed in greater detail. That resulted in a further exclusion of nine articles and therefore, seven articles were included in this review for the final qualitative synthesis (table 1).

This comprised 3 phase I and 4 phase II clinical trials. These studies form the basis for the following analysis of efficacy and safety of Alisertib

Table 1. Human trials included in the current systematic review after following the search strategy outlined in figure 1. PFS: progression-free survival, OS: overall survival, DOR: duration of response, RR: response rate, ORR: overall response rate PO: per oral, BID: twice a day, QD: once a day, d: day, PIC: powder-in-capsule, ECT: enteric-coated tablet. DLTs: dose-limiting toxicities, MTD: maximum tolerated dose, PK: pharmacokinetics, PD: pharmacodynamics

ID	Author (year)	Initial dose (treatment/rest)	Primary end point(s)	Secondary end point(s)	Patient Characteristic			
					N	Age (y) Med (range)	Male %	Cancer Type (%)
1	Dickson <i>et al</i> (2016) (54)	50 mg PO BID (7d/14d)	RR	PFS OS	72	54.5 (20-84)	54	Liposarcoma (17), Leiomyosarcoma (non-uterine) (14), Undifferentiated sarcoma (15), Malignant peripheral nerve sheath tumour (14), Other (40)
2	Melicharet <i>et al</i> (2015) (55)	50 mg PO BID (7d/14d)	RR	DOR Time to progression PFS	249 ¹ /212 ²	60.1 ³ (49-73)	54.72 ²	Breast Cancer (23) ² , Small-cell lung cancer (23) ² , Non-small-cell lung cancer (11) ² , Head and neck squamous-cell carcinoma (21) ² , Gastro-esophageal adenocarcinoma (22) ²
3	Kelly <i>et al</i> (2014) (56)	PIC: 25 or 35 mg/day ⁴ BID d1, QD d2-14 or 21 (14d/14d or 1d/7d) ECT: 40mg/day QD (14d/28d)	DLTs MTD PK	RR DOR AAK inhibition Gene amplification	58	61 (27-82)	47	Non-Hodgkin lymphoma (62), Multiple myeloma (33), Chronic lymphocytic leukaemia/ small lymphocytic leukaemia (5)
4	Friedberg <i>et al</i> (2014) (57)	50 mg PO BID (7d/14d)	RR	Safety DOR PFS PK and PD	48	67.5 (32-85)	73	B-cell lymphoma (83), Aggressive T-cell lymphoma (17)
5	Goldberg <i>et al</i> (2014) (58)	50 mg PO BID (7d/14d)	ORR	PFS DOR	57	72 (46-85)	56	Acute myelogenous leukaemia (80.7), Myelodysplastic syndrome (19.3)
6	Dees <i>et al</i> (2012) (59)	Various doses tested ⁵ (7d/14d, 14d/14d or 21d/14d)	DLTs MTD	PK AAK inhibition Bioavailability Antitumor activity	87	60 (36-83)	51	Colorectal cancer (17), NSCLC (11), Ovarian cancer (11) Soft tissue sarcoma (9), Head and neck cancer (7), Other (44)
7	Cervantes <i>et al</i> (2012) (60)	Various doses tested ⁶ (7/14d)	DLTs MTD	PK AAK inhibition Antitumor activity	59	61 (30-78)	63	Colorectal cancer (46), Soft tissue sarcoma (14), Head and neck cancer (5), Ovarian cancer (5), Renal cell carcinoma (5), Other (25)

¹ Total number of patients

² Patients assessable for response

³ Patients assessable for response, Calculated as weighted median from all types of cancers

⁴ Escalated to 45, 65, and then 90 mg QD if dose-limiting toxicity were observed in no more than 0/3 or 1/6 patients.

⁵ Ranged between 5-150 mg QD and between 40-60 mg BID

⁶ Ranged between 5-150 mg QD and between 50-100 mg BID

3.2 Risk of bias assessment

All the included studies were assessed according to the Quality Assessment Tool for Quantitative Studies. The results showed that all the included studies are of a “moderate” global rating. Given that all these studies were open-label phase I or II trials, blinding was not possible, and therefore all these studies were downgraded to a “moderate” quality (one weak rating in the blinding criterion). In addition, Melicharet *al* (2015) and Friedberg *et al* (2014) scored “moderate” in the withdrawal criterion as both studies reported a certain percentage of dropout due to side-effects or other reasons (55, 57).

Table 2: The quality assessment of the included studies

Studies	Selection Bias	Study Design	Confounders	Blinding	Data collection	Withdrawals and dropouts	Intervention integrity	Analysis appropriate to question	Global rating
Dickson <i>et al</i> (2016) (54)	2	2	1	3	1	1	1	1	2
Melicharet <i>al</i> (2015) (55)	2	2	1	3	1	2	1	1	2
Kelly <i>et al</i> (2014) (56)	2	2	1	3	1	1	1	1	2
Friedberg <i>et al</i> (2014) (57)	2	2	1	3	1	2	1	1	2
Goldberg <i>et al</i> (2014) (58)	2	2	1	3	1	1	1	1	2
Dees <i>et al</i> (2012) (59)	2	2	1	3	1	1	1	1	2
Cervantes <i>et al</i> (2012) (60)	2	2	2	3	1	1	1	1	2

1: strong; 2: moderate; 3: weak.

3.3. The anti-tumour activity of Alisertib administration in different types of malignancies

In order to evaluate the clinical effect of Alisertib, various drug doses and formulations were tested in patients with advanced tumours. In most phase I or II trials, the clinical effect was described according to the evidence of Aurora A Kinase inhibition, achieving a clinical response (which was assessed by validated scales), time to disease progression, progression-free survival, and the duration of disease stability after the administration of Alisertib (55-59). Although the primary end-point in the included studies was to assess the toxicity and the safety of administration of Alisertib, and therefore they lacked a valid comparator for the purpose of efficacy assessment of the treatment, the reported improvement in the clinical response was promising. For example, a study by Melicharet *al* (2015), which utilized the revised version of Response Evaluation Criteria in Solid Tumours (RECIST) scale to assess the clinical response to treatment (61), reported a partial response rate of 18% in patients with breast cancer, and a 21% response rate in patients with small-cell lung cancer when Alisertib was administered in 21-day cycles, at a 50 mg per dose, twice daily, for 7 days followed by a 14-day washout period (the mean duration of response was 5.6 and 4.1 months, respectively) (55). Similarly, Dees *et al*

(2012) utilized the RECIST guidelines (the older version)(62), to assess the effect of this treatment on various, refractory to standard therapy, metastatic solid tumours, and reported a partial response rate of 23%, which was sustained for more than 3 months (59). Alisertib treatment also seemed effective when administered to various haematological malignancies; with partial responses varying between 13% and 27% of the enrolled patients for at least 2 months (56-58). Goldberg *et al* (2014) described the requirement of multiple treatment cycles to demonstrate the anti-tumour effect of Alisertib (58). After four cycles, Alisertib treatment resulted in a median of 51 days of progression-free survival in patients diagnosed with acute myelogenous leukaemia (AML) (56). However, the effect of Alisertib is obviously disparate when administered in different types of malignancies. Even when given at the same dose and schedule, being 50 mg/day twice daily for seven days followed by a 14-day recovery, Alisertib administration showed modest effects in patients with non-small-cell lung cancer, head and neck squamous cell carcinoma and gastro-esophageal adenocarcinoma (55). Unlike patients with AML, Alisertib administration did not show any effect in patients with myelodysplastic syndromes (MDS) (58). One possible explanation is the difference in the pathogenesis between AML and MDS. The failure in the haematopoiesis in MDS is caused by increased apoptosis, rather than bone marrow suppression by proliferation as in AML. Thus, Alisertib administration may have been able to suppress abnormal proliferation in AML, but was not able to reverse apoptosis in MDS (58). Therefore, future investigation of the anti-tumour effect of Alisertib should take in consideration the tumour type and attempt to explain the mechanism of action of Alisertib in that specific context. Such understanding would certainly help to characterize more effective cancer therapeutics and deliver more patient-specific treatment options.

In addition, the anti-tumour activity of Alisertib was also assessed according to the inhibition of Aurora A Kinase in the skin and tumour specimens. Cervantes *et al* (2012) demonstrated an Alisertib-exposure-dependent increase in the number of mitotic cells with characteristic spindle abnormalities, which supported AURKA inhibition in tumour biopsies (60). Dees *et al* (2012) also collected skin biopsies pre-treatment and 6 and 24 hours after treatment. The results showed a significant increase in the mitotic cells in the basal epithelium following treatment, reflecting a consistent AURKA inhibition by Alisertib (59). However, one trial showed that the AURKA inhibition might not correlate with achieving a clinical response in some patients (56). The latter evidence highlights the possibility of a multi-factorial effect and the involvement of multiple molecular mechanisms to achieve a clinically quantifiable effect. In other words, the inhibition of AURKA per se may not be enough to achieve the desired anti-tumour effect in certain types of cancers.

Although the reported preclinical and clinical data on the effect of Alisertib in various malignancies seem exciting, such results should be interpreted with caution owing to several limitations in the design and reporting of these studies. Firstly, all the reported studies lacked a valid comparator, which means it is not possible to infer the causal relationship between the treatment and the observed clinical effect. Sure, as the included

patients were end-of-life patients who failed every other therapy, it may not be ethical to include a valid control group at this stage (phase I or II trials), and the comparator was historical data, however, the findings of these trials should be described as a “potential” effect of Alisertib at best. Secondly, the exact mechanism of action of Alisertib should be thoroughly investigated in different cancer types. The fact that Alisertib exhibited an inconsistent effect across a range of different tumours sheds the light on the importance of mapping all the factors involved in the cancer development. Apart from assessing the effect of Alisertib on AURKA inhibition regardless of cancer phenotypes, it is perhaps helpful to also investigate its effect on other cancer-specific epigenetic/key oncogenes expression. Nevertheless, the reported “potential” clinical effect of Alisertib on various tumours is promising, and therefore rationalizes its further investigation as a novel anticancer therapy. Hence, many clinical trials are currently planned and recruiting patients.

3.4. Safety assessment and its implications

Phase I studies (56, 59, 60) were mainly interested in determining dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of Alisertib, and subsequently suggest a recommended phase II dose (RP2D) and treatment cycle. The three papers reported neutropenia as the highest frequent DLT, followed by other haematological side effects as leucopenia, anaemia, and thrombocytopenia. Kelly *et al* (2014) suggested that administering higher daily doses of Alisertib within shorter period of treatment (7d) is more tolerable than longer treatment cycles and will result in less frequent adverse events. Dees *et al* (2012) and Cervantes *et al* (2012) results aligned with this finding and therefore, they abandoned more than 7 days duration dosing schedules. It was also found that CNS side effects are related to high, once-daily dose, and dividing the dose into twice a day schedule decreased both the frequency and severity of these adverse events. Interestingly, 50 mg twice a day for 7 days of treatment followed by 14 days of recovery in a 21 day cycle was suggested by the three studies as RP2D.

Kelly *et al* (2012) and Dees *et al* (2012) were also interested in comparing two oral formulations of Alisertib, namely; powder in capsule (PIC) and enteric-coated tablets (ECT). Both studies reported similar bioavailability and pharmacokinetics properties for both PIC and ECT. However, Kelly *et al* (2012) suggested ECT for future development, as it allows Alisertib to bypass the acidity of the stomach and delay dissolution to the delivery site in the small intestine.

Overall, 630 patients were assessed in the seven studies. Only severe, life-threatening, and fatal adverse events (grade ≥ 3 according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE)) related to the systematic administration of Alisertib were extracted individually from each study and summarized in table 3.

Table 3. Most frequently reported drug-related grade ≥ 3 adverse events in all papers (Papers ID as in table 1). All adverse events and serious adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), the values in the table represent n (%) and is visually grouped according to the percentage of occurrence as follows: 1%-9%, 10%-19% and $\geq 20\%$.

Side Effect	Study ID	1	2	3	4	5	6	7	Total
	(n)	(n=72)	(n=249)	(n=58)	(n=48)	(n=57)	(n=87)	(n=59)	
Neutropenia	30 (42%)	107 (43%)	26 (45%)	30 (63%)	7 (12%)	26 (30%)	20 (34%)	246 (39%)	
Leukopenia	16 (22%)	53 (21%)	14 (24%)	26 (54%)	2 (4%)		13 (22%)	124 (20%)	
Anaemia	10 (14%)	26 (10%)	11 (19%)	17 (35%)	5 (9%)	7 (8%)	6 (10%)	82 (13%)	
Thrombocytopenia	10 (14%)	18 (7%)	16 (28%)	16 (33%)	5 (9%)	5 (6%)	7 (12%)	77 (12%)	
Fatigue and Asthenia	3 (4%)	15 (6%)	2 (3%)	4 (8%)	7 (12%)	3 (3%)		34 (5%)	
Stomatitis		19 (8%)	1 (2%)	7 (15%)	2 (4%)	1 (1%)	4 (7%)	34 (5%)	
Febrile neutropenia	7 (10%)		5 (9%)	6 (13%)	6 (11%)	7 (8%)		31 (5%)	
Lymphopenia	7 (10%)		4 (7%)	2 (4%)			4 (7%)	17 (3%)	
Diarrhea	1 (1%)	3 (1%)	1 (2%)	1 (2%)	1 (2%)	6 (7%)		13 (2%)	
Mucositis oral	9 (12%)							9 (1%)	
Somnolence		3 (1%)		1 (2%)	2 (4%)	2 (2%)		8 (1%)	
Nausea	2 (3%)	2 (1%)		1 (2%)		1 (1%)		6 (1%)	
Vomiting	1 (1%)	3 (1%)				1 (1%)		5 (1%)	
Palmar-Plantar Erythrodysesthesia Syndrome	3 (4%)							3 (<1%)	
Pneumonia				3 (6%)				3 (<1%)	
Pancytopenia				3 (6%)				3 (<1%)	
Sepsis	1 (1%)				1 (2%)			2 (<1%)	
Decreased Appetite		1 (1%)		1 (2%)				2 (<1%)	
Dehydration				2 (4%)				2 (<1%)	
Leukocytosis	1 (1%)							1 (<1%)	
Anal mucositis	1 (1%)							1 (<1%)	
Typhlitis	1 (1%)							1 (<1%)	

Lung infection	1 (1%)	1 (<1%)
Alanine aminotransferase increased	1 (1%)	1 (<1%)
Aspartate aminotransferase increased	1 (1%)	1 (<1%)
Skin and subcutaneous tissue disorder	1 (1%)	1 (<1%)
Hypertension	1 (1%)	1 (<1%)
Confusion	1 (2%)	1 (<1%)
Dyspnoea	1 (2%)	1 (<1%)

The single most obvious observation from the safety data was the haematological disturbance in a relatively high percentage of the patients, which aligns with the characteristics of cytotoxic agents (63). On top of the list, severe neutropenia occurred in 246 (39%) patients, followed by leucopenia, which was reported in 124 (20%) patients. Severe anaemia and thrombocytopenia were also reported in 13% and 12% of the patients, respectively. Less frequent severe side effects included fatigue, stomatitis and febrile neutropenia and were reported in 5% of the total number of patients.

4. Discussion and Conclusions

Although it might be too early to make conclusions based on phase I/II trials, the evidence of the anti-tumour effect of Alisertib administration is compelling in various types of malignancies. Nevertheless, such treatment is associated with several serious side effects that might limit its future clinical use. However, several considerations should be seriously taken while assessing the efficacy/safety profile of Alisertib administration as an anticancer therapy. First, the reported heterogeneity of its clinical effects in different cancer types raises a red flag that Alisertib works differently in different disease contexts. Understanding the mechanism of action of Alisertib in different malignancies is therefore critical to mitigate or precisely profile potential life-threatening side effects. Moreover, it may not be wise to evaluate the efficacy/safety profile of Alisertib treatment in a group of patients with different types of malignancies. It is understandable that testing a new therapeutic molecule can be challenging in terms of recruiting patients and obtaining the ethical approval. However, segregating patients based on the cancer phenotype would represent the effect of Alisertib in a more precise way. From a statistical point of view, and given that most cancers are drastically different in terms of the pathogenesis and the molecular interactions involved in the cancer development, combining the effect of Alisertib administration on different types of cancer would be similar to comparing apples to oranges(64).

Certainly, the total effect size from such studies might over-estimate or under-estimate the actual effect of Alisertib.

In addition, one study reported that the clinical effect of Alisertib administration did not necessarily correlate with AURKA inhibition (56). That has to say, the molecular changes being induced by Alisertib may not necessarily result in an anti-tumour effect. This finding implicates the involvement of other, more prominent, molecular pathways that determine the outcome of cancer. If this is the case, the analysis of other key cancer drivers while administering Alisertib treatment is imperative to evaluate to what extent such a treatment would impact the inter-pathway interactions and networking. Since the first mention of the oncogene-addiction theory (65), it has become evident that many cancer types depend on the continuous expression of certain genes to survive, and therefore many important gene-gene interactions were characterized as key drivers of carcinogenesis(66). While the included papers have only focused on the inhibition of AURKA as the primary indicator of Alisertib action, it would be worthwhile to also investigate its effect on other well-described key pathways.

More importantly, the safety profile of the systemic administration of Alisertib is worrisome as it needs careful dose scheduling and considerable washout periods. Given its cytotoxic nature, one should expect that Alisertib would cause these serious side effects. Therefore, exploring alternative routes of administration when possible can be the answer. Cervical cancer is an example, knowing that inhibiting Aurora A kinase was established as a strong potential target in this cancer (36), intravaginal delivery systems are therefore a recommended alternative. Indeed, local delivery systems have proven effective in reducing the serious side-effects associated with chemotherapeutics through avoiding systemic uptake and retention of these toxic agents in healthy tissues (67). Such systems can be exploited to deliver Alisertib to the site of interest with minimal systemic exposure, and thus help to reduce its side effects.

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