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Research paper

Evaluating dose-limiting toxicities of MDM2 inhibitors in patients with solid organ and hematologic malignancies: A systematic review of the literature

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ABSTRACT

Introduction: Mouse double minute 2 protein (MDM2), a negative regulator of the p53 tumour suppressor gene, is frequently amplified in malignancies. MDM2 antagonists have shown efficacy in treating malignancies with MDM2 overexpression and can overcome chemoresistance in acute myeloid leukemia. We systematically evaluated the safety profile of MDM2 inhibitors in the treatment of solid organ and hematologic malignancies.

Materials and Methods: We searched Medline and EMBASE from January 1947 to November 2018 for prospective clinical studies, in English or French, investigating any MDM2 inhibitor in pediatric or adult cancers, and reporting dose and toxicity outcomes. Primary outcome was dose-limiting toxicity (DLT) and secondary outcome was death.

Results: The search yielded 493 non-duplicate citations. Eighteen studies of 10 inhibitors met inclusion criteria (total N = 1005 patients). Two-thirds of included studies did not define DLTs and the reporting of toxicities was highly variable. The most commonly reported DLTs were cytopenias, gastrointestinal toxicity, metabolic disturbances, fatigue and cardiovascular toxicity; there was one death attributed to treatment toxicity.

Conclusion: MDM2 antagonists have been studied in a variety of malignancies with toxicities similar to other commonly used chemotherapy agents and may represent a safe adjuvant treatment for further study in in acute leukemia.

1. Introduction

The E3 ubiquitin ligase mouse double minute 2 (MDM2) protein is encoded in the human genome on chromosome 12 and serves as a negative regulator of the p53 tumour suppressor transcription factor that protects cells from malignant transformation [1]. MDM2 has been shown to bind to the p53 N-terminal alpha-helix through creation of a deep hydrophobic cleft within the MDM2 molecule, thereby masking the p53 transactivation domains and inhibiting its transcriptional activity [2]. MDM2 also functions as an E3 ubiquitin ligase for p53 (*via* its C-terminal RING domain), leading to the proteolytic degradation of p53 through the p53 C-terminal lysine components [3]. The MDM2 protein has been found to be frequently amplified in a variety of solid organ and hematologic malignancies [4,5], and MDM2 overexpression has been universally associated with a poor response to conventional chemotherapy.

MDM2 antagonists block the p53-MDM2 interaction, leading to reactivation of the p53 tumour suppressor protein and restoring the apoptotic pathway in tumours with wild type p53 [1]. To date, multiple MDM2 inhibitors have been investigated [6]. Nutlin-3a was the first specific small-molecule inhibitor discovered to target the p53-MDM2 complex [7], displacing the p53 protein from MDM2 through its *cis*-imidazoline core structure. Since then, other MDM2:p53 inhibitors have been developed to enhance specificity and efficacy [8]. These studies of

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLT, dose limiting toxicity; MDM2, mouse double minute 2; MDS, myelodysplastic syndromes; MTD, maximal tolerated dose; MTF2, metal response element binding transcription factor 2

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MDM2 antagonists have shown encouraging anti-tumour activity in both *in vitro* and *in vivo* studies, which has led to studies of treatment with MDM2 inhibitors in patients with p53 wild-type tumours.

Recently, studies in our institution have shown that Metal Response Element Binding Transcription Factor 2 (MTF2) represses MDM2 in hematopoietic cells, and that loss of MTF2 expression elicits chemoresistance in cell lines extracted from patients with refractory acute myeloid leukemia (AML) through increased MDM2-mediated degradation of the p53 protein [9]. However, use of MDM2 inhibitors in *in vivo* studies has been shown to target this signalling pathway and to restore sensitivity of MTF2-deficient refractory AML cells to standard induction chemotherapy.

Together, these studies show an important role of MDM2 inhibition as a treatment modality for sensitizing solid organ and hematologic malignancies to conventional chemotherapy. The objective of this systematic review of clinical trials was therefore to examine the safety and tolerability profile of MDM2 inhibitors (both alone or in combination with conventional chemotherapy) in patients with solid organ and hematologic malignancies, in order to inform the development of early phase clinical trials of MDM2 inhibitors in patients with AML.

2. Material and methods

2.1. Eligibility criteria

We included prospective clinical studies, including full length or conference proceedings, in English or French, investigating any MDM2 inhibitor in pediatric or adult cancer populations, and reporting dose and toxicity outcomes. Reviews, pre-clinical, observational and retrospective studies, case series or case reports, and studies in non-cancer populations were excluded, as were studies not reporting dose and toxicity outcomes. We included studies that reported on MDM2 inhibitors both as a single agent or in combination with conventional chemotherapy but excluded those that reported only on MDM2 inhibitors in combination with other small molecule-based therapies.

2.2. Literature search

A systematic search was performed by an information specialist using a search strategy subjected to a peer review of electronic search strategies [10]. We searched Medline and EMBASE from January 1947 to November 2018, inclusive. If updates to clinical trials were published separately, only the most complete report was included.

2.3. Article screening and data extraction

Two reviewers (LP and JR) independently performed title, abstract and full-text screening for study inclusion, and independently performed data extraction on dosing regimen, maximum tolerated doses (MTDs), dose limiting toxicities (DLTs), mortality rates and grade I-II toxicity rates. Decisions on article inclusion were reconciled between the two reviewers, and conflicts were resolved by consensus or a 3rd reviewer (GC).

Key data was extracted using a standardized data extraction form designed in Jotform (Jotform, Inc.) which was piloted on five records before use. Details that were extracted from each study included study size, treatment indication, interventions, dosing and DLTs reported, as well as study traits such as location, recruitment period, funding source and year of publication.

2.4. Quality assessment

Quality of each full-text study was assessed using the Newcastle-Ottawa Scale [11].

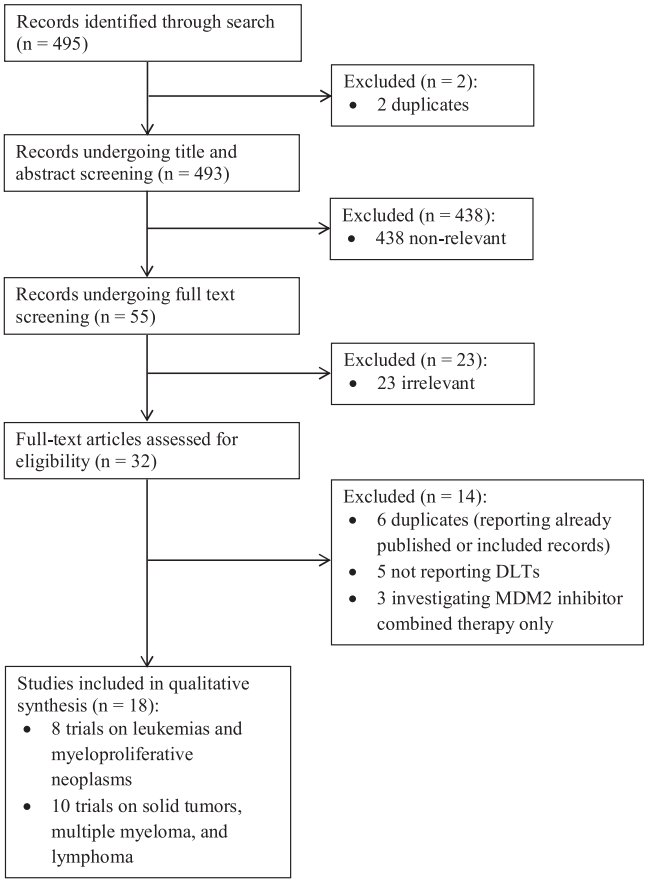


Fig. 1. PRISMA flow diagram of study selection process.

2.5. Meta-analysis

The I^2 statistic was calculated as a test of heterogeneity for the four full-length studies and pooled estimates of toxicity rates were calculated using a random effects model only where $I^2 < 75\%$.

3. Results

A total of 493 non-duplicate citations were identified by the electronic search. Following title and abstract screening, 55 articles were selected for further review (Fig. 1). Full-text review identified 18 full-length English language articles for inclusion in our systematic review. Twenty-three of the studies excluded by full-text review were deemed not relevant. Five studies did not report dosing or toxicity outcomes and three studies reported on MDM2 inhibitors in combination with other agents. Six studies were found to be duplicates or were updates to previously published studies, in which case only the most recent and comprehensive report was included. Of the 18 articles that met inclusion criteria, 4 studies were full-text and 14 studies were abstracts; all studies were phase 1 clinical trials.

3.1. Patient demographics and malignancies

The total sample size was 1005 adult patients across 18 studies (Table 1); there were no studies in the paediatric population. Twelve studies reported on age with a median age ranging from 58 to 75 years, and an overall age range of 19 to 88 years across studies. Nine studies reported on the sex distribution, which ranged from 44% to 77% males. Seven studies pertained only to leukemias (AML, acute lymphoblastic leukemia [ALL], chronic myeloid leukemia [CML], or chronic lymphocytic leukemia [CLL]) and high risk myelodysplastic syndrome

Table 1
Patient characteristics and malignancies for corresponding MDM2 inhibitors.

MDM2 Inhibitor	Author & Year	Sample Size	Sex (% males)	Median age (range)	Malignancies	Prior treatments	Dosing Regimen (starting dose, with MTD in bold)
RG7112	Andreeff (2016)	116	57%	62 (19-85)	AML (excluding APL), ALL, CML, CLL, sCLL	Mean 3.6 regimens (SD 2.2)	20 mg/m^2 daily (10/28) (**1500 mg BID, or 1920 mg/m^2 BID**)
	Kurzrock (2012)	106	55%	58 (22-84)	Relapsed/refractory solid tumours	N/A	20 mg/m^2 daily (10/28) (**2500 mg daily (10/28), or 1440 mg/m^2 daily (10/28)**)
NVP-CGM097	Bauer (2016)	48	N/A	N/A	P53 wild type solid tumours	N/A	Arm 1: 10 mg 3x/week (28/28) (**400 mg 3x/week (28/28)**) Arm 2: 300 mg 3x/week (14/21) (**700 mg 3x/week (14/21)**)
SAR405838	DeJonge (2017)	74	49%	61 (22-82)	Advanced solid tumours (liposarcoma, GI, melanoma, NSCLC, other)	Median 2 (range 1-7)	Arm 1: 50 mg daily (**300 mg daily**) Arm 2: 400 mg BID q weekly (**not reached**)
DS-3032b	DiNardo (2016)	38	63%	68.5 (30-88)	Relapsed/refractory AML, high risk MDS	Not available	60 mg daily (21/28) (**160 mg daily (21/28)**)
	Gounder (2016)	34	44%	59.5 (no range given)	Advanced solid tumours (liposarcoma, DLBCL, melanoma, lymphoma)	3 or more treatments (in 62%)	Arm 1: 15 mg daily (21/28) interrupted (**120 mg daily (21/28) interrupted**) Arm 2: 15 mg daily (21/28) continuous (**90 mg daily (21/28) continuous**)
AMG 232	Erba (2017)	26	Not available	68 (26-86)	Relapsed/refractory AML	N/A	60 mg daily (7/14) (**360 mg daily (7/14)**)
	Langenberg (2016)	39	67%	64 (41-84)	Advanced p53 wild type solid tumours	N/A	15 mg daily (7/21) (**240 mg daily (7/21)**)
NVP-HDM201	Hyman (2017)	85	N/A	N/A	P53 wild type solid tumours	N/A	Arm 1: high dose intermittent (**no MTD available**) Arm 2: low dose continuous (**no MTD available**)
	Stein (2017)	37	N/A	N/A	Relapsed/refractory AML, ALL	N/A	Arm 1: high dose intermittent (day 1 of 3-week cycle) (**dose escalation ongoing, no MTD available yet**) Arm 2: high dose intermittent (days 1 and 8 of 4-week cycle) (**dose escalation ongoing, no MTD available yet**) Arm 3: low dose extended (daily, 14/28) (**dose escalation ongoing, no MTD available yet**) Arm 4: low dose extended (daily, 7/28) (**dose escalation ongoing, no MTD available yet**)

(*continued on next page*)

Table 1 (*continued*)

MDM2 Inhibitor	Author & Year	Sample Size	Sex (% males)	Median age (range)	Malignancies	Prior treatments	Dosing Regimen (starting dose, with MTD in bold)
RG7388	Mascarenhas (2017)	12	42%	63.5 (32-83)	Polycythemia vera and essential thrombocytosis	83.3% prior hydroxyurea therapy	100 mg daily (5/28) (**150 mg daily (5/28)**)
	Siu (2014)	95	N/A	N/A	Solid tumours	Not available	Arm 1: 100 mg weekly x 3 weeks (**1600 mg BID weekly x 3 weeks**) Arm 2: 100 mg daily x 5 days (**500 mg daily x 5 days**) Arm 3: 1000 mg daily x 3 days (**500 mg BID x 3 days**)
	Yee (2014) (+/-cytarabine, ara-C)	86	N/A	Dose escalation group: 68.5 (28-83); dose extension group: 75 (66-83); dose escalation (+ara-C): 64 (32-76); dose extension (+ara-C): N/A	AML	Dose escalation group: median 2 (range 0-4); dose extension group: not available; dose escalation (+ara-C): median 1.5 (range 0-5); dose extension (+ara-C): N/A	Arm 1 (dose escalation): 400 mg daily (5/28) (**600 mg BID (5/28)**) Arm 2 (dose extension): 600 mg BID (5/28) (**N/A**) Arm 3 +ara-C (dose escalation): 400 mg daily (5/28) (**600 mg BID (5/28)**) Arm 4 +ara-C (dose extension): 600 mg BID (5/28) (**not available**)
ALRN-6924	Meric-Bernstam (2017)	69	N/A	61 (25-78)	Solid tumours or lymphoma	N/A	0.16 mg/kg q weekly (21/28) (**3.1 mg/kg q weekly (21/28)**)
MK-8242	Ravandi (2016)	26	77%	66 (29-81)	Refractory/recurrent AML	N/A	30 mg daily (7 on/7 off, 28-day cycle) (**not established**)
	Wagner (2017)	47	60%	Mean 61.6 (SD 10.6)	P53 wild type solid tumours	N/A	60 mg BID (7/21) (**400 mg BID (7/21)**)
RO6839921	Razak (2016)	41	N/A	Not available	Solid tumours	N/A	14 mg daily (5/28) (**110 mg daily (5/28)**)
	Yee (2017)	26	N/A	Not available	Relapsed/refractory AML	(Range 1-4)	120 mg daily x 5 days (**250 mg daily x 5 days**)

(N/A = Not applicable).

(MDS), 1 pertained to myeloproliferative neoplasms (polycythemia vera [PV] and essential thrombocytosis [ET]), and 10 pertained to non-leukemia malignancies, including solid tumours and lymphoma

3.2. MDM2 inhibitors

There were 10 different MDM2 inhibitors studied. Seven of these were studied in both leukemias and non-leukemia cancers, while the remaining 3 inhibitors were studied only in non-leukemia cancers. Sixteen studies looked at the MDM2 inhibitor alone, 1 study looked at the MDM2 inhibitor alone and in combination with another small molecule inhibitor (the MEK inhibitor, trametinib) for which only patients in the MDM2 inhibitor alone arm were included for analysis [12], and 1 study looked at the MDM2 inhibitor alone and in combination with a chemotherapy agent (intravenous cytarabine, dosed at 1 g per square-meter for 6 days, every 28 days) for which patients in both the MDM2 inhibitor and combination arms were included for analysis [13]. The 4 full-text studies looked at 3 different MDM2 inhibitors, including RG7112 in relapsed/refractory AML (excluding acute promyelocytic leukemia [APL]), ALL, CML and CLL/small cell lymphocytic lymphomas (sCLL) [14]; SAR405838 in locally advanced or metastatic solid tumours [15]; and MK-8242 in refractory/recurrent AML [16] and advanced solid tumours [17].

3.3. Quality assessment

Quality assessment of the 4 full-text articles using the Ottawa-Newcastle Scale [11] revealed a mean score of 5 out of 6 stars (with all 4 studies scoring 5 stars).

3.4. Toxicities

The overall toxicities observed are summarized in Table 2 . DLTs were defined in 5 of 18 studies generally as any toxicity of grade 3 or above (with 2 studies including grade 2 toxicities). Four of the studies that defined DLTs *a priori* were full-text articles, and one was abstract only. The remaining studies did not report pre-defined DLTs; these studies were all abstract form only. Although these studies did not explicitly define DLTs at the outset, toxicities were explicitly reported as "dose-limiting toxicities" and non-dose limiting toxicities. The most commonly reported DLTs were cytopenias (12 studies), followed by gastrointestinal toxicities (mainly defined as nausea, vomiting, diarrhea, and abdominal discomfort) (7 studies). Metabolic disturbances including tumour lysis syndrome were reported in 5 studies, and fatigue and

cardiovascular toxicity (including pericarditis, QTc prolongation and hypotension) were both reported in 3 studies each. Overall, the way in which DLTs were reported was highly variable.

Several studies reported non-dose limiting toxicities (defined as any adverse events, regardless of grade) related to MDM2 inhibitor treatment. The most common non-dose-limiting toxicities were gastrointestinal toxicity (reported in 14 studies), cytopenias (11 studies), fatigue (10 studies), infectious complications (including pneumonia, febrile neutropenia, and stomatitis) (6 studies), and metabolic disturbances (5 studies). Cardiovascular, neurologic and infectious complications were the most poorly reported with only 7 studies reporting on cardiovascular and infectious complications each, and 5 studies reporting on neurologic complications. There was only 1 reported death due to treatment toxicity in a study of MK-8242 in a patient with AML [16] attributed to fungal pneumonia secondary to bone marrow aplasia. One study investigating the use of AMG 232 in patients with AML reported no DLTs [12]. Another study investigating the use of NVP-HDM201 in patients with relapsed/refractory AML and ALL specifically reported no gastrointestinal toxicities [18].

In studies investigating MDM2 inhibitors in leukemias, the most common DLTs encountered amongst patients were gastrointestinal toxicity (3 studies), and metabolic disturbances (3 studies). Other reported DLTs included cytopenias (2 studies), infectious complications (2 studies), cardiovascular toxicity (2 studies), fatigue (1 study), and neurologic toxicity (1 study).

In studies investigating MDM2 inhibitors in non-leukemia cancers, the most common DLTs were cytopenias (10 studies), gastrointestinal toxicity (4 studies), metabolic disturbances (2 studies), fatigue (2 studies), and cardiovascular toxicity (1 study). There were no reports of neurologic or infectious DLTs.

Across the four full-text articles, the most common DLTs were cytopenias (3 studies) and gastrointestinal toxicities (3 studies). The most consistently reported toxicities within these categories were thrombocytopenias, nausea, vomiting, and diarrhea. Due to the highly variable study designs, pooled estimates using a random effects model could only be reliably estimated for vomiting ($I^2 < 75\%$). The pooled rate for vomiting was 32.1% (95% CI 24.5–39.7). Diarrhea rates varied from 23 to 56%, nausea rates were 42–68% and thrombocytopenia rates were 4–24% (Figs. 2a–d).

3.5. Maximal tolerated dose

Given the number of different inhibitors used, no meaningful estimation of a maximal tolerated dose could be made (Table 1).

4. Discussion

Our systematic review has identified a number of different MDM2 inhibitors used in patients with a variety of solid organ and hematologic malignancies. Overall, the results indicate that MDM2 inhibitors have an acceptable safety and tolerability profile.

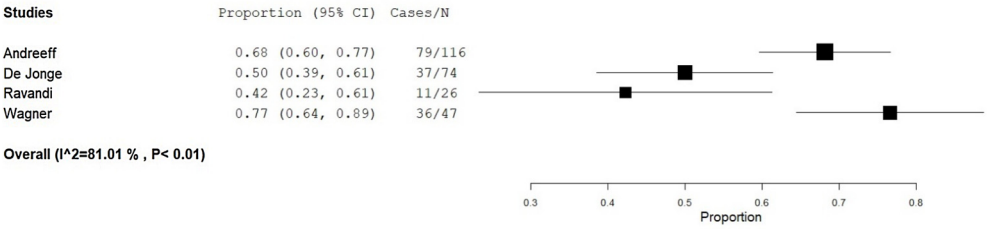
Commonly reported toxicities included bone marrow suppression, gastrointestinal toxicities (including nausea, vomiting and diarrhea), metabolic disturbances (such as electrolyte disturbances), fatigue and cardiovascular effects (such as pericarditis, QTc prolongation, and hypotension). Only one death was attributed to treatment with an MDM2 inhibitor out of 1005 treated patients. Of the 10 different MDM2 inhibitors included in our review, 7 inhibitors were studied in 2 or more trials, including: RG7112 [12,19], RG7388 [13,20,21], RO6839921 [22,23], DS-3032b [24,25], AMG232 [12,18], NVP-HDM201 [19,26], MK-8242 [17,27], NVP-CGM097 [28], SAR405838 [29] and ALRN-6924 [30] (Table 1). Comparison of the studies conducted on each of these molecules shows that the side effects and DLTs were not inhibitor-specific and are likely due to a class effect.

One limitation of our study is that, despite efforts to be as inclusive as possible, most studies were published in abstract form only, with only 4 full-text articles. Moreover, we found significant variability in

Table 2
Number of studies reporting MDM2 inhibitor toxicities by organ system.

	Cytopenia	Metabolic	GI	Fatigue	Cardiovascular	Infectious	Neuro
DLT	12	5	7	3	3	2	1
Non-DLT	11	5	14	10	4	6	3
None	1	1	1	1	1	1	1
Not reported	1	10	1	7	11	11	13

a)



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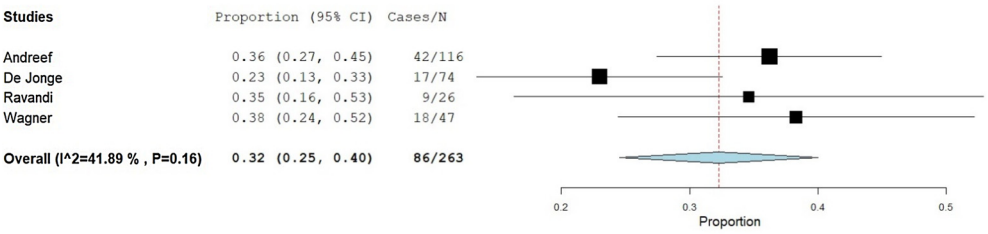

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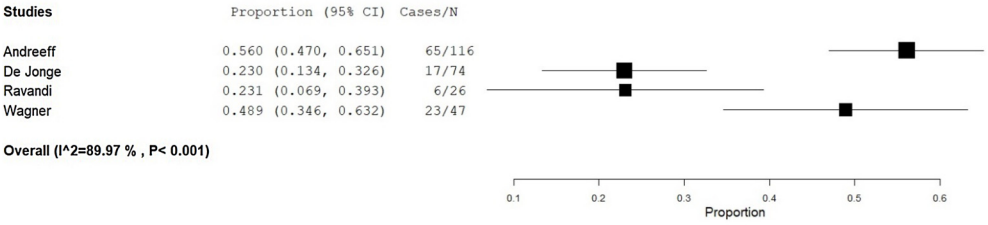

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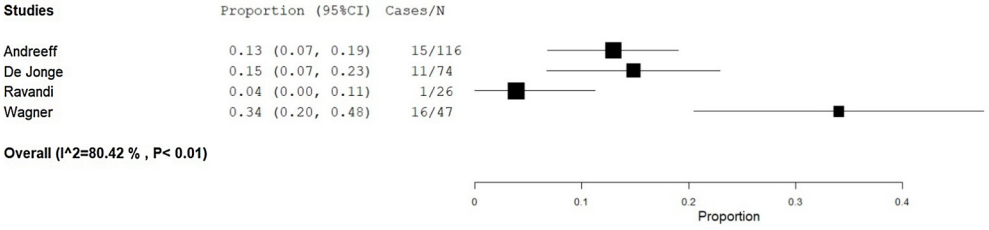

Fig. 2. Forest plot for a) nausea, b) vomiting, c) diarrhea and d) treatment related thrombocytopenia, across 4 full text studies.

how toxicities were reported, thus limiting meaningful comparisons between various agents. Our work therefore highlights the need for more complete and standardized reporting of toxicities in studies on antineoplastic agents and the greater use of reporting guidelines to help maximize research impact and utilization. Our findings echo previous reports that have identified inconsistent and incomplete reporting of adverse events in oncology randomized controlled trials to be a common phenomenon [31–33].

Despite these limitations, data from over 1000 patients included in our analysis shows that reported toxicities of MDM2 inhibitors are similar to those experienced by patients receiving conventional leukemia treatment. In acute myeloid leukemia, in particular, the conventional backbone of therapy includes intensive chemotherapy known as induction with cytarabine- and anthracycline-based chemotherapy, as well as allogeneic stem cell transplant for eligible candidates [34]. According to a 2016 meta-analysis of cytarabine in induction treatment for adult AML patients, common toxicities observed with cytarabine-based treatment include hematologic toxicities, and infections [35]. Non-hematologic side effects of cytarabine including neurotoxicity are well known but were poorly reported; mortality was not reported. With respect to anthracyclines, in a 2018 systematic review comparing daunorubicin and idarubicin in adult AML patients, common toxicities observed included febrile neutropenia (77.4% for idarubicin, and 77.3% for daunorubicin), and cardiotoxicity (1.8% for idarubicin, and 1.1% for daunorubicin) [36]. Estimates for 60-day induction-related mortality vary between 12 and 24% in the first 60 days depending on factors such as age, comorbid status and treatment location [37,38]. The side effect and toxicity profile of MDM2 inhibitors in leukemia treatment therefore appears to be either comparable to or less than those associated with conventional chemotherapy for acute leukemia and is therefore not likely to be a limiting factor for its use in combination with conventional chemotherapy. Rather, the indications for combination treatment with MDM2 inhibitors would likely depend on demonstration of improved efficacy.

A recent study from our institution demonstrated in a xenograft mouse model of patient-derived chemotherapy-resistant AML, that treatment with MDM2 inhibitors rendered leukemic cells chemo-sensitive through restoration of the p53-MDM2 axis. Given the synergistic anti-leukemic effect demonstrated in these *in vivo* studies, and favourable toxicity profile reported here, development of further studies of MDM2 inhibitors in AML represent an intriguing possibility.

An important area for further study is the presence of MDM2 splice variants in cancer cells, and the implications of these splice variants on treatment of malignancies with MDM2 inhibitors. A 2014 review on p53 and MDM2 in cancers reported the presence of at least 72 splice variants of MDM2 associated with oncogenesis [39]. These variants are found in a variety of hematologic malignancies (such as leukemia, Hodgkin's lymphoma, Burkitt's lymphoma) and non-hematologic malignancies (including breast, lung and colorectal cancers, soft tissue sarcomas, osteosarcomas, and ovarian and bladder cancers). The majority of MDM2 splice variants retain both the N-terminal and C-terminal components, allowing MDM2 to exhibit its E3 ubiquitin ligase function against p53 [39].

With respect to MDM2 inhibitors, the majority of currently identified molecules (including RG7112 [40], RG7388 [41], DS-3032b [42], NVP-CGM097 [43], SAR405838 [44], and AMG-232 [45]) target the MDM2-p53 binding within the MDM2 hydrophobic cleft. There have been no studies to date examining the implications of splice variants affecting this domain of MDM2 on the efficacy of various MDM2 inhibitors. Additional studies are therefore needed to investigate whether splice variants within MDM2 in cancer cells can impact the mechanism of action of MDM2 inhibitor molecules, and the implications on treatment outcomes for both hematologic and non-hematologic malignancies.

4.1. Conclusions

MDM2 antagonists have been studied in a variety of solid organ and hematologic malignancies. The most commonly reported toxicities were cytopenias, metabolic disturbances, gastrointestinal toxicities and fatigue, making them well suited for further study in combination with traditional chemotherapeutic agents.

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Author contributions

Lebei Pi and Jasjit Rooprai carried out data collection, data analysis and manuscript preparation.

Grace Christou carried out conceptual study design, data analysis strategy design, content verification and major manuscript editing.

Mitchell Sabloff helped design the literature search strategy and contributed to critical manuscript editing and content verification.

David Allan, Jill Fulcher and William Stanford all contributed to critical manuscript editing and content verification.

Risa Shorr designed the literature search strategy and carried out literature search.

Harold Atkins, Christopher Bredeson, Caryn Ito, and Tim Ramsay contributed to manuscript editing.

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