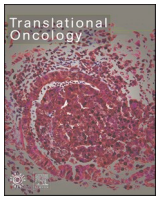
Translational Oncology 31 (2023) 101634

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon



Current clinical trials with non-coding RNA-based therapeutics in malignant diseases: A systematic review

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ARTICLE INFO

Keywords:
Cancer
Clinical trial
MicroRNA
Non-coding RNA
RNA interference
Malignant diseases

ABSTRACT

This systematic review aimed to shed light on the trend of current clinical trials of non-coding RNA (ncRNA)-based therapeutics for malignant diseases. We conducted a database search for published literature and ongoing clinical trials using PubMed, clinicaltrials.gov, and University Medical Information Network (UMIN) clinical trial registry. To ensure that our review was based on up-to-date clinical trials, we limited our search to literature published within the last five years (January 2017–September 2022). Furthermore, due to the "clinical" nature of our review, we focused only on studies involving human participants. Among ncRNAs, microRNAs have been extensively explored in observational studies of malignant diseases as potential diagnostic markers and prognostic predictors, as well as for their therapeutic monitoring and profiling capabilities. As therapeutic agents, microRNA or siRNA were estimated in interventional human clinical trials and showed promising outcomes; however, the number of trials was small. Evidence and ongoing clinical trials in which ncRNAs other than microRNA or siRNA have been evaluated for their potential as therapeutic agents are limited. Here, we summarized microRNA as a potential therapeutic agent in malignant diseases, but most of the current evidence suggests that it is useful as a potential biomarker. siRNA is also a promising ncRNA technique in cancer, however more data from clinical trials are warranted for clinical use.

Introduction

Non-coding RNA (ncRNA) are composed of several RNAs that do not encode proteins. ncRNAs are classified into two categories based on their length: small non-coding RNA (sncRNA) and long non-coding RNA (lncRNA) which are shorter or longer than 200 nucleotides, respectively. sncRNAs are further sub-classified into microRNAs (miRNAs), transfer RNAs (tRNAs), piwi-interacting RNAs (piRNAs), and small nucleolar RNAs (snoRNAs) [1,2]. Additionally, circular RNA (circRNA) is an ncRNA that is covalently closed, non-linear RNA produced by back-splicing [3–5]. circRNAs are further classified into exonic, exon-intron, or intronic circRNA [3,6,7]. circRNA interacts as a miRNA sponge and influences mRNA translation or stability [3,8,9].

Among ncRNA, miRNA is a short ncRNA of ~22 nucleotides [10] that silences target genes via mRNA degradation or translation repression [11]. Cancer environment can be modulated by the expression or suppression of miRNA. Therefore, miRNA can serve as therapeutic agent by inhibiting oncogenic miRNA activity or refilling tumor-suppressing miRNAs [12,13]. Numerous studies have explored the efficacy of miRNA as a diagnostic tool, prognostic indicator, or therapeutic monitoring marker, in addition to its role as a therapeutic agent.

Antisense RNA and small interfering RNA (siRNA) can also silence target genes through RNA degradation and repression [11]. Antisense RNA comprises 19–23 nucleotides complementary to mRNA and regulates target gene expression at the replication, transcription, or translation levels [14]. siRNA typically comprises 21–23 bases and has two overhanging phosphorylated bases at the 3′ end of each strand [15]. RNA interference is considered a natural defense system against the invasion of exogenous genes [16,17]. However, the clinical implications of interventional RNA interference techniques remain challenging.

This systematic review aimed to reveal the current trend of clinical trials in non-coding RNA-based therapeutic research in malignant diseases and to elucidate the status and issues of this promising therapeutic tool in cancer treatment.

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https://doi.org/10.1016/j.tranon.2023.101634
Received 9 October 2022; Received in revised form 1 December 2022; Accepted 25 January 2023

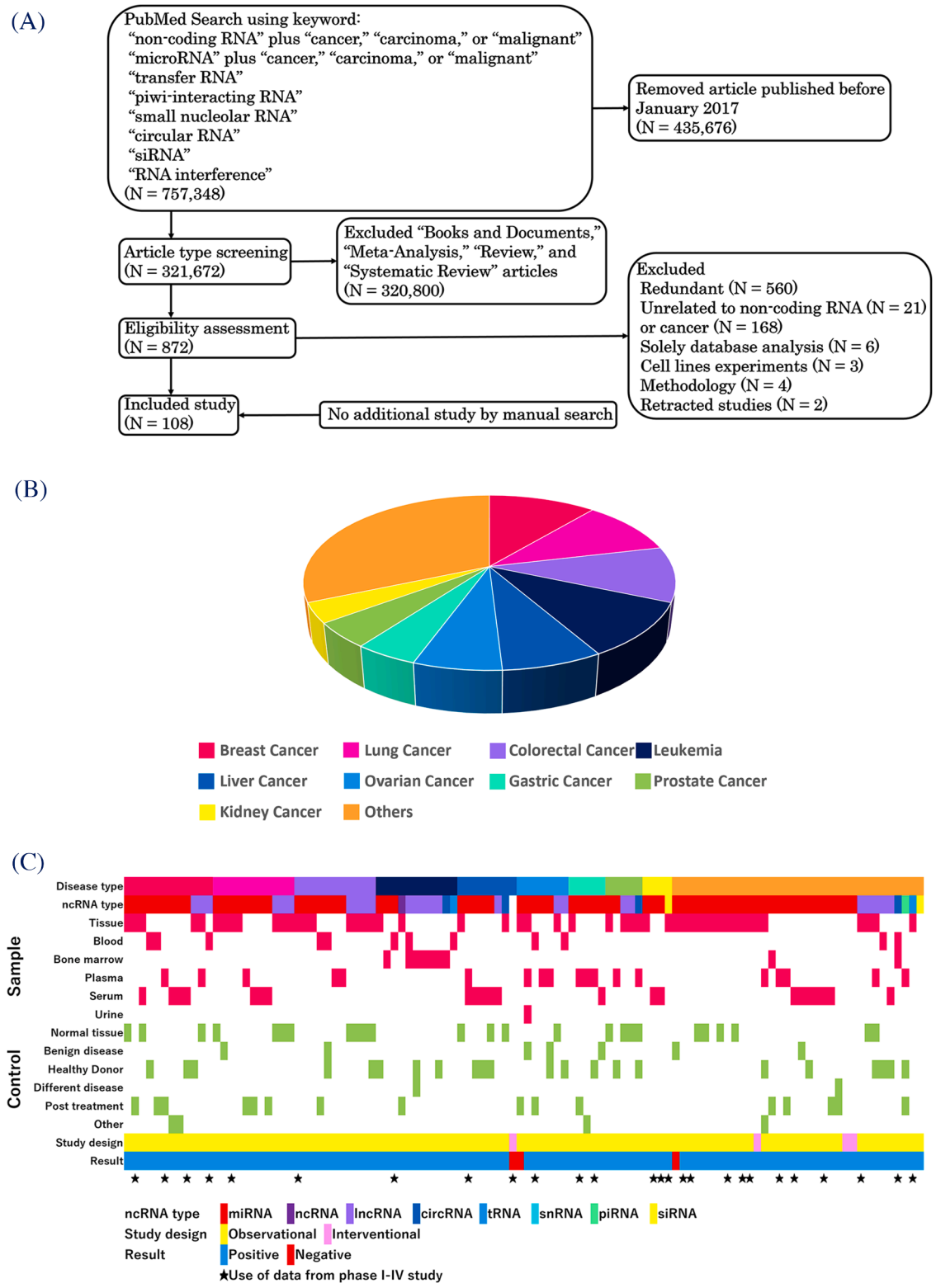

Fig. 1. Overview of the process followed for literature review and the major findings. (A) The consort diagram shows the method and results of the database literature search. This systematic review was performed via PubMed in reference to Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA). (B) The pie chart indicates the distribution of malignant diseases in 108 reviewed studies. Twelve publications focused mostly on breast cancer. Eleven articles reported cases of lung cancer, colorectal cancer, and leukemia. Kidney cancer was reported in four articles. (C) The bar diagram represents the characteristics of the 108 reviewed studies. Each study was characterized using six profiles [type of cancer, target ncRNA of study, sample type, character of control cohort, type of study (observational or interventional), and conclusion]. Features were visualized by colored rectangles. If a colored rectangle was not included in study information, it was because the study was performed with one cohort where the impact of ncRNA was evaluated as follows: patients were stratified by expression level of ncRNA, the relationship between ncRNA expression and the results was estimated using data from previous trial, or no control due to interventional study in which expression level of each case was not estimated.

Materials and methods

Search for published clinical trials employing non-coding RNA-based therapeutics

We conducted a database search using PubMed with reference to the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) [18].

The articles were searched using the following keywords: "non-coding RNA" or "microRNA" plus "cancer," "carcinoma," or "malignant." The terms "transfer RNA," "piwi-interacting RNA," "small nucleolar RNA," "circular RNA," "siRNA," or "RNA interference" were used without additional keyword in conducting a literature search in PubMed.

Our search limited to literature published within the last five years (January 2017–September 2022) to ensure up-to-data clinical trials. Each search excluded "Books and Documents," "Meta-Analysis," "Review," and "Systematic Review" by selecting the filtering option for "Clinical Trial" and "Randomized Controlled Trial" articles. In addition, because of the "clinical" nature of our review, we only focused and included studies involving human participants. Studies performed exclusively on animals or cell lines were excluded. Additionally, studies that were only conducted through public database analysis were excluded from the review. A flowchart of our review process is shown in Fig. 1A. We utilized additional keywords "cancer," "carcinoma," or "malignant" in using term "non-coding RNA" or "microRNA" due to large number of articles generated without additional keywords in "non-coding RNA" or "microRNA" keyword searching. After using the additional keywords, more than 300,000 candidate articles remain. Before screening commenced, in the "Eligibility assessment" phase, we excluded all duplicate articles. This process differs from the original PRISMA process.

Search for ongoing clinical trials involving non-coding RNA-based therapeutics

Registered clinical trials were searched using the keywords "non-coding RNA," "microRNA," "transfer RNA," "piwi-interacting RNA," "small nucleolar RNA," "circular RNA," "siRNA," or "RNA interference" via clinicaltrials.gov [19] and University Hospital Medical Information Network (UMIN) [20]. In addition, manual PubMed searches for unregistered clinical studies were conducted.

Although antisense RNA is therapeutic non-coding RNA, antisense DNA and RNA are collectively referred to as antisense oligonucleotides and cannot always be clearly distinguished. Therefore, antisense trials were excluded from this review.

Results

Published non-interventional clinical trials employing non-coding RNA-based therapeutics for malignant diseases

The consort diagram for researching the literature and illustrating the findings are shown in Fig. 1. We selected 108 articles after excluding inadequate article.

Twelve publications focused primarily on breast cancer. Eleven articles reported cases of lung cancer, colorectal cancer, and leukemia (Fig. 1B). Over 95% of them focused on ncRNAs as observational tools. miRNAs were used in 72 (66.7%) of reviewed articles. ncRNAs were extracted from tissue, blood, bone marrow, plasma, and serum in 49 (45.4%), 12 (11.1%), 9 (8.3%), 19 (17.6), and 22 (20.3%) articled, respectively. The expression of ncRNAs in cancer was compared to that in normal tissue, benign, and healthy donor samples in 25 (21.3%), 7 (6.5%), and 22 (20.4%) articles, respectively. Some diseases compared the ncRNA expression levels with those of other diseases or pre- and post-treatment in same cohort. ncRNAs have been utilized as diagnostic markers, therapeutic monitors, or profilers to distinguish tumors from benign regions. Few studies conducted interventional therapies using ncRNA. Only four studies used ncRNA as an interventional therapeutic agent. Of the studies selected, 105 concluded that ncRNA was a promising tool, whereas the other three did not report positive conclusions. Twenty-six studies were performed using phase I-IV clinical trial data. Most of them were secondary analyses of clinical trials (Fig. 1C).

Published interventional clinical trials involving non-coding RNA-based therapeutics for malignant diseases

As mentioned above, there are interventional clinical trials based on ncRNA technology for the treatment of malignant diseases in humans. There were six investigations involving miRNA and RNA interference (three studies each). Zandwijk et al. confirmed the safety of the mimic miRNA agent in malignant pleural mesothelioma [21]. Phase I research employing MRX34 (a liposomal miR-34a) was conducted by Hong et al. [22] in 85 patients with advanced solid tumors after phase I safety confirmation [23]. Although the trial was terminated early because of serious adverse events including patient fatalities, they showed the reproducibility of the therapeutic benefit of ncRNA-based therapeutics. Partial response in three patients and disease stability in sixteen patients were confirmed.

Ishihara et al. conducted a clinical trial using siRNA to treat solid tumors with significant therapeutic results [24]. Dika et al. conducted a phase I trial using TKM-080301 (agent targeting Polo-like kinase I via small interfering RNA) in 43 advanced hepatocellular carcinoma patients [25]. They found that TKM-080301 has a manageable level of toxicity but could not prove its efficacy as a single agent. Kumthekar et al. reported a well-designed RNAi-based technological study of recurrent glioblastoma [26]. They also demonstrated the proof-of-concept of the ncRNA treatment technology.

These recent clinical trials in humans are outlined in Table 1.

Ongoing clinical trials involving non-coding RNA-based therapeutics for malignant diseases

We used the terms "non-coding RNA," "microRNA," "transfer RNA," "piwi-interacting RNA," "small nucleolar RNA," "circular RNA," "siRNA," or "RNA interference" to search the databases clinicaltrials.gov and UMIN for ongoing clinical trials. A total of 64 trials on malignant diseases were found (fifty-five trials in clinicaltrials.gov and nine trials in UMIN). Most of these studies (51/64, 79.7%) were observational studies using miRNAs as diagnostic, prognostic, and monitoring tools. Seven studies were observational studies they used ncRNAs other than miRNAs. Five studies were interventional, and one study explored the utility of miRNAs as therapeutic agents. The details of these seven plus five trials are summarized in Table 2.

The remaining four ongoing interventional studies were siRNA-based trials. Three phase I trials aimed at determining the optimal dose and adverse effects of the agent, and one phase II trial evaluated the therapeutic efficacy in pancreatic adenocarcinoma. No unregistered trials were found by manual keyword searches in the database.

Discussion

Numerous efforts have been made to use ncRNAs in clinical applications, including cancer therapy. Previous clinical trials before 2016 [27] or ncRNA experiences in vivo have been summarized in the literature [28].

In clinical settings, advancement in cancer genetic treatments have facilitated targeted therapies for specific mutations, rearrangements, or amplifications [29,30]. An intriguing feature of therapeutic strategies based on ncRNA technology is that they can target disorders in a gene-specific manner even if targetable enzyme activation is not identified. It is advantage compared to tyrosine kinase inhibitor treatment.

Table 1
Interventional clinical trials involving non-coding RNA-based therapeutics published between January 2017 and September 2022.

Author [Reference]	Study design	Agent	Patients (N)	Results	Conclusion
Zandwijk [21]	phase I	TargomiRs (minicells loaded with miR-16-based mimic microRNA and targeting EGFR)	Malignant pleural mesothelioma with EGFR expression, 26	PR in 1 and SD in 15	Acceptable safety profile and early signs of activity
Beg [23]	phase I	MRX34 (a miR-34a mimic, encapsulated in a liposomal nanoparticle)	Advanced solid tumor, 47	PR in 1 and SD in 4	Acceptable safety and evidence of antitumor activity
Hong [22]	phase I	MRX34 (a liposomal miR-34a)	Advanced solid tumor, 85	PR in 3 and SD in 16	Positive proof-of-concept *
Ishihara [24]	phase I	TBI-1301 (NY-ESO-1-specific T-cell receptor enabling siRNA)	Solid tumor with NY-ESO-1 expression, 6	Maximum tumor size change: >30% reduction in 3 and stable between −20% and +20% in 3	Significant response in tumors with high NY-ESO-1
Dika [25]	phase I, II	TKM-080301 (agent targeting Polo-like kinase I through siRNA)	Advanced hepatocellular carcinoma, 43	SD in 18 subjects by RECIST, PR in 8 subjects in Choi criteria	Insufficient as monotherapy agent
Kumthekar [26]	phase 0	Brain-penetrant RNAi-based SNAs	Recurrent glioblastoma (GBM), 8	SNAs uptake in glioma cells and reduction in tumor-associated protein	SNA nanoconjugates are brain-penetrant approach for GBM

* : early terminated. Abbreviations: RECIST; response evaluation criteria in solid tumors, PR, partial response; RNAi, RNA interference; SD, stable disease; siRNA, small interfering RNA; SNAs, spherical nucleic acids.

Table 2
Ongoing observational clinical trials using non-coding RNA (excluding microRNA and interventional clinical trials).

Ongoing observational clinical trials using non-coding RNA, excluding microRNAs

NCT number	Study design regarding ncRNA	Type of ncRNA	Type of malignancy, (Number of total participants)	Aim
NCT04946266	Observational	lncRNA: MFI2-AS1	Kidney cancer, 260	Estimate the diagnostic biomarkers
NCT05088811	Observational	lncRNA: WRAP53, UCA-1	Hepatocellular carcinoma, 80	Estimate the diagnostic biomarkers
NCT05141383	Observational	lncRNA	Prostate cancer, 118*	Establish the diagnostic and prognostic biomarker
NCT04584996	Observational	circRNA	Pancreatic cancer, Biliary tract cancer, 186*	Estimate the diagnostic and prognostic role
UMIN000044430	Observational	small RNA	Pancreatic cancer, Biliary tract cancer, 100	Evaluate small RNAs associated with diagnostic, recurrence, and therapeutic effects
UMIN000042276	Observational	small RNA	Head and neck cancer, 475	Evaluate small RNAs associated with diagnostic, recurrence, and therapeutic effects
NCT04636788	Observational	small RNA	Pancreas adenocarcinoma, 102*	Evaluate the role of diagnostic marker and prognostic predictor

Ongoing interventional clinical trials using microRNA or siRNAs

NCT number	Study design	Agent	Patients, (N)	Aim	Remarks
NCT04675996	Interventional (Phase I/Ib)	INT-1B3, a lipid nanoparticle formulated miRNA (miR-193a-3p) mimic agent	Advanced solid tumors, 80	Evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy	
NCT04995536	Interventional (Phase I)	CpG-STAT3 siRNA CAS3/SS3	Recurrent lymphoma, 18	Identify the optimal dose and side effects	Combination with radiation therapy
NCT01591356	Interventional (Phase I)	EphA2-targeting DOPC-encapsulated siRNA	Advanced malignant solid neoplasm, 76	Identify the optimal dose and side effects	
NCT03608631	Interventional (Phase I)	Mesenchymal Stromal Cells-derived Exosomes with KRAS G12D siRNA	Pancreatic cancer harboring KRAS G12D mutation, 28	Identify the optimal dose and side effects	
NCT01676259	Interventional (Phase II)	siG12D-LODER	Pancreatic ductal adenocarcinoma, 80	Overall response rate at 6 months	Combination with chemotherapy

* Including benign and/or healthy donor controls.

miRNAs are promising therapeutic agents because they can target several genes simultaneously [11]; however, few studies have evaluated them as treatment agents. Most published or ongoing trials have focused on the usefulness of diagnostic, prognostic, and/or monitoring tools. Although almost every study reached a satisfactory conclusion, we must keep in mind that it is partially due to bias that positive results are easier to submit or publish, and recent comprehensive analyses might acquire positive, statistically significant outcomes even if the result is not biologically true. Albeit, clinical trial data are regularly employed for miRNA studies and positive results have been reported, as a number of ongoing studies suggest, miRNA is useful and will make progress as a biomarker rather than a therapeutic agent.

Therapeutically, siRNAs may be preferable to miRNAs because they can provide more targeted silencing. Recently, the FDA licensed three siRNA-based drugs (patisiran, givosiran, and lumasiran) to treat non-cancerous diseases following positive phase III clinical studies with minimal to moderate side effects [31–35]. This is a big step in the development of siRNA-based drugs, and progress in cancer therapy drugs is expected due to this innovation. Although some clinical trials showed promising results on siRNA studies, there is still much work to be done before they will be used to treat malignant human diseases. There are no data based on a large number of cases or long-term follow-up. It is unknown whether siRNA treatment can be a novel treatment option in cancer, where several treatments have been established and new strategies are in progress certainly. Hong et al. demonstrated the therapeutic efficacy of miR-34a in advanced solid tumors [22]. Although the therapeutic effect was confirmed in a preceding study [23], the study was terminated early because of serious adverse events.

The authors analyzed the consequences and side effects of immune-related mechanisms. Off-target immune activation is also known to occur with siRNAs [36]. Numerous RNA modifications have been proposed to overcome off-target events and improve siRNA drug delivery system [11,37]. Progress in RNA modification is necessary for ncRNA-based therapies.

Apart from miRNAs or siRNAs, researchers are conducting exhaustive searches for promising novel therapeutics among other ncRNAs. Some studies have reported the utility of circRNA [38,39]. The concept was first proposed in 1976 [40], however, extensive research only began in 2012 with the development of high-throughput sequencing and analysis technologies [3,41]. Immune-checkpoint inhibitors (ICIs) have revolutionized cancer treatment in clinical settings. It is notable that the efficacy of snoRNA transcriptomic profiles in predicting OS was suggested in a recent phase III ICI therapy clinical trials [42]. More studies using various types of ncRNAs and estimating the treatment efficiency and safety in humans are warranted for clinical therapeutic use.

Conclusion

We investigated current clinical trials with ncRNA-based therapeutics, limiting our review to literature published between January 2017 and September 2022, and registered ongoing clinical trials. Most studies have primarily focused on siRNAs and miRNAs. Almost all miRNA-related previous studies and ongoing trials are observational. In addition, there is a dearth of interventional research regarding the use of siRNA in cancer treatment.

Nevertheless, non-coding RNA-based therapeutic strategies have an advantage over conventional anti-cancer treatments because of their potential for target gene silencing. More studies on ncRNAs, advancements in analysis technology or modification of therapeutic RNA agents, and human clinical trials will contribute to the development of effective ncRNA-based therapeutics for malignant diseases.

Funding

None.

Declaration of Competing Interest

None.

Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing

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