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REVIEW

Repurposing tranexamic acid as an anticancer drug: a systematic review and meta-analysis

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Abstract

Purpose Drug repurposing may be an efficient strategy for identifying new cancer treatments. Tranexamic acid (TXA), an antifibrinolytic agent that affects the plasminogen-plasmin pathway, may have potential anticancer effects by influencing tumor cell proliferation, angiogenesis, inflammation, immune response, and tissue remodeling—all crucial processes contributing to tumor progression and metastasis.

Objective Evaluate TXA's anticancer effects across in vitro, animal, and clinical studies to assess its potential as a repurposed cancer drug.

Methods The study was designed as a PRISMA-compliant systematic review and meta-analysis. The literature search was conducted in MEDLINE, EMBASE, Web of Science, and the Cochrane Library. In vitro, animal, and clinical studies investigating the anticancer effects of TXA or epsilon-aminocaproic acid (EACA) were included. Animal and clinical studies were critically appraised, and studies with a low risk of bias were included in the meta-analysis.

Results Of 4367 identified records, 38 articles were included, collectively reporting findings from 41 in vitro studies, 34 animal studies (n = 843 animals), and seven clinical studies (n = 91 patients). The meta-analysis included nine animal studies and showed a tumor growth reduction in animals treated with TXA compared to controls with a standardized mean difference of – 1.0 (95%CI – 1.5; – 0.4) (p = 0.0002). Equivalently, the majority of in vitro studies reported reduced proliferation, viability, and invasiveness in TXA-exposed tumor cell lines. The clinical studies were considerably susceptible to bias, rendering any conclusions futile.

Conclusions TXA shows promise as a repurposed cancer drug, revealing an overall reduction in tumor growth, viability, and invasiveness in animal and in vitro studies.

Keywords Tranexamic acid · Drug repurposing · Cancer therapy · Anticancer agents · Systematic review · Antifibrinolytics

Introduction

Repurposing drugs for cancer treatment is gaining increasing interest, particularly in targeting tumor-promoting inflammation: One of the hallmarks of cancer (Sousa et al. 2023; Hanahan 2022; Hanahan and Coussens 2012). The antifibrinolytic agent tranexamic acid (TXA) has been increasingly recognized for its anti-inflammatory effects, making it a potential candidate for repurposing as an anticancer agent (Okholm et al. 2022).

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Several properties make TXA a viable candidate for repurposing in cancer treatment. First, TXA modulates key pathways in cancer progression, particularly the plasminogen-plasmin system, influencing inflammation, angiogenesis, and tissue remodeling (Heissig et al. 2021; Amara et al. 2010). Second, TXA has a well-characterized safety profile, with extensive clinical use in surgical and trauma settings, facilitating its translation into cancer treatment (Ker et al. 2012; CRASH-2 trial collaborators 2010). Third, TXA is proven cost-effective in a number of conditions and widely available, addressing key barriers to cancer treatment, especially in resource-limited settings (Hubble et al. 2023; Ehresman et al. 2020; Howard et al. 2022; Williams et al. 2020).

TXA modulates the plasminogen-plasmin pathway by competitively blocking the lysine binding site on plasminogen, inhibiting conversion to the active form plasmin (Hoylaerts et al. 1981). Plasminogen, a proenzyme, is predominantly produced in the liver and constantly circulating (Hoylaerts et al. 1981). It can be converted into its active form plasmin by both tissue plasminogen activator and urokinase-type plasminogen activator (Raum et al. 1980; Hoylaerts et al. 1982; Bugge et al. 1996). The protease plasmin cleaves fibrin to dissolve blood clots (Macfarlane and Biggs 1948). In addition, emerging evidence suggests that this pathway impacts several processes hallmarks of cancer, such as tumor growth, angiogenesis, inflammation, immunomodulation, invasion, and metastases (Heissig et al. 2021, 2020; Baker and Strickland 2020; Sulniute et al. 2016).

This systematic review aims to critically evaluate TXA's potential anticancer effects, including in vitro, animal, and clinical studies, to assess its impact on cancer progression and its potential to be repurposed as an anticancer agent.

Methods

Protocol and registration

Before initiation, a protocol was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline (Page et al. 2021). The study was initially planned as a systematic scoping review and registered on the Open Science Framework.

Eligibility criteria

Inclusion and exclusion criteria were defined before the literature search and data extraction. Inclusion criteria: 1) Population or study subjects with cancer or cancerous cells. 2) Intervention with TXA or antifibrinolytics of lysine analog type excluding aprotinin. 3) Outcomes investigating anticancer effects. Studies were excluded if: 1) No original data.2)Study protocol. 3) Publication not retrievable in English or translatable. Duplicate data in multiple publications were included only once.

Information sources and search strategy

A comprehensive search was conducted in MEDLINE, EMBASE, Web of Science, and Cochrane Library. The latest search update was performed on June 14th, 2024. All results were imported into Endnote for duplicate removal and screened in Covidence. A broad search strategy was employed using controlled vocabulary and text word terms for the key concepts: *cancer* and *TXA*. No restrictions on publication date were applied. Citation searches were performed to identify additional relevant studies (Supplementary 1).

Selection, data collecting process, and data items

The study selection and data collection processes were performed by one reviewer screening title and abstract, two reviewers full-text screening, and two reviewers independently extracting data. Discrepancies were settled with dialogue. The data items were predefined as:

- Study information: Author and year.
- Methods: Design, population, sample size, intervention, and comparison.
- Outcomes: In vitro *studies*: Viability, proliferation, migration, and invasiveness. *Animal studies*: Tumor growth, metastatic burden, and survival. *Clinical studies*: Tumor growth, clinical response to treatments evaluated by symptoms and examination, and adverse events.

Critical appraisal assessment

Studies exclusively reporting in vitro results were excluded from the quality assessment, as critical appraisal tools are not applicable (Tran et al. 2021). Two reviewers independently appraised the included studies using the appropriate assessment tool for quasi-experimental studies (Barker et al. 2024), case reports (Moola et al. 2020), and case series (Munn et al. 2019). If multiple methods were used, each study was evaluated separately.

Synthesis methods and certainty assessment

A qualitative synthesis was conducted, summarizing study design, methodology, and key findings across all included studies. Tumor models with low risk of bias, as determined by the critical appraisal, were included in the meta-analysis. The meta-analysis was performed

using R (version 4.3.2). Standardized mean differences (SMDs) of tumor growth outcomes were used as effect measures. If available, primary tumor or metastasis growth data were extracted; otherwise, tumor count was used. The mean, sample size, and standard deviation were collected. When standard deviation was not reported, it was estimated from figures and/or derived from standard errors (Supplementary 3). The meta-analysis employed Hedges' G to correct for small sample bias. Due to significant conceptual heterogeneity, a random-effects model was applied. Statistical heterogeneity was assessed using I2. Since ≤ 10 studies were included, publication bias assessment was not applicable. Sensitivity analyses were not conducted, as the level of heterogeneity rendered them irrelevant. Statistical significance was set at $p < 0.05$.

Results

Study selection and characteristics

The PRISMA flow diagram displays the study selection process, including records identified (n = 4367) (Fig. 1). This review included 38 articles, many of which reported several experiments. Collectively, the number of included studies among the three categories is: 41 in vitro studies (Law et al. 2022; Esmaeili et al. 2020; Wu et al. 2019; Kaphle et al. 2019; Suojanen et al. 2009; Wang et al. 1996; Kariko et al. 1993; Kikuchi et al. 1987, 1986a, 1986b; Ogawa et al. 1982; Iwakawa and Tanaka 1982; Sekiya et al. 1980), 34 animal studies (n = 843) (Law et al. 2022; Kikuchi et al. 1986a; Ogawa et al. 1982; Iwakawa and Tanaka 1982; Hiramoto and Yamate 2022; Hiramoto et al. 2019; Yamamoto et al.

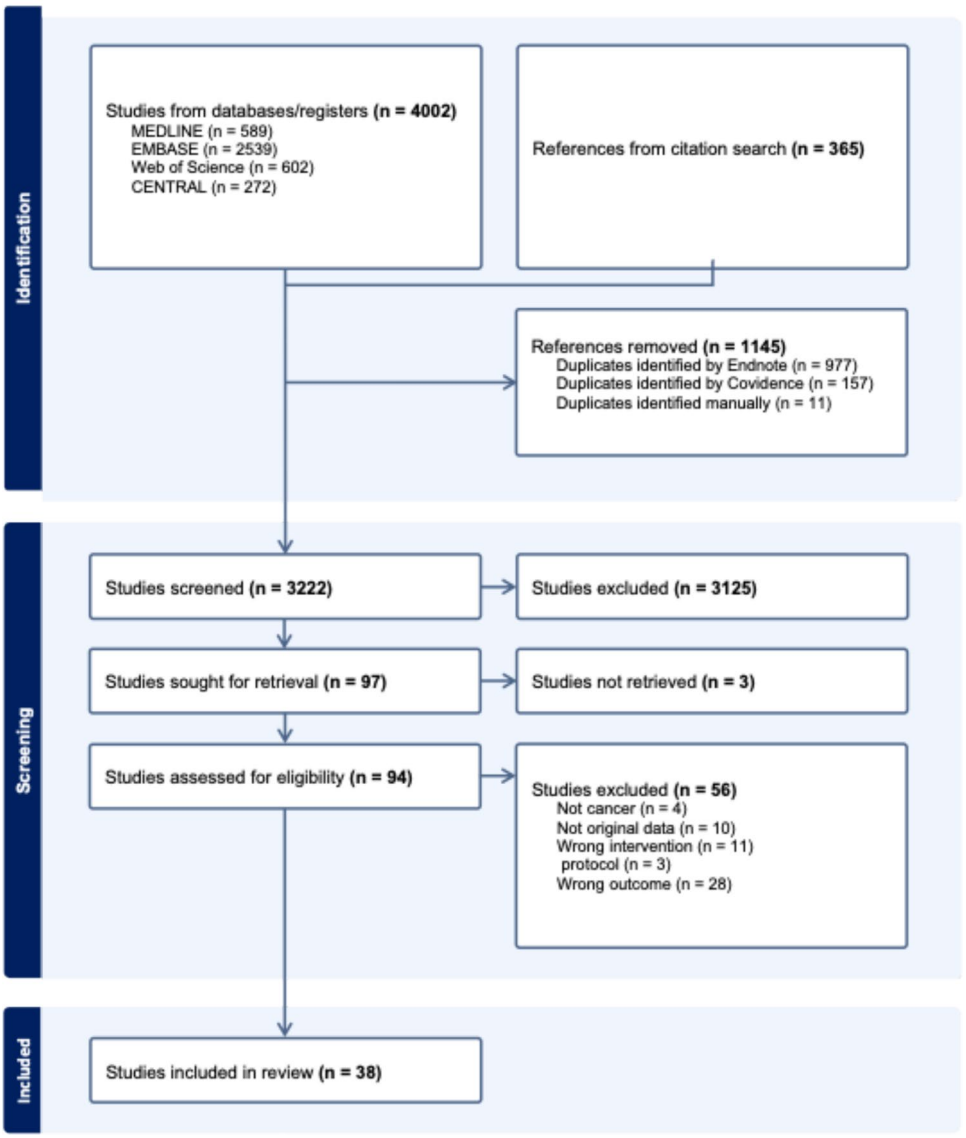

Fig. 1 PRISMA diagram: All records were identified through a literature search and citation search. The exclusion process is depicted until the final inclusion of studies

2017; Garona et al. 2014; Kirstein et al. 2008; Horiguchi 2000; Wanaka et al. 1996; Shinkfield et al. 1992; Sawaya et al. 1986; Shibata 1986; Conforti et al. 1984; Tanaka et al. 1982; Sundbeck et al. 1981, 1981a; Kodama and Tanaka 1981; Astedt and Trope 1980; Peterson and Risberg 1976; Boeryd et al. 1974; Hisazumi and Fukushima 1973), and seven clinical studies (n = 91) (Kikuchi et al. 1986b; Sigurdsson et al. 1983; Soma et al. 1980; Fosså et al. 1978; Rutqvist et al. 1977; Petrelli et al. 1986; Bramsen 1978). A comprehensive overview of all included studies is provided in Supplementary 2.

Historical outline of studies investigating TXA's anticancer effects

Research in this field began to gain interest in the 1970s and peaked in the 1980s. Notably, clinical studies were primarily conducted during the 1970s and 1980s, while the number of animal studies and in vitro experiments increased through the 2010s and 2020s (Fig. 2). The most investigated tumors, tumor models, and tumor cell lines listed by frequency are *gynecological*, *breast, sarcoma*, *melanoma, lung*, *urological*, *nonmelanoma skin*, *head and neck, gastrointestinal cancer*, *central nervous system (CNS), hematological*, and *adenocarcinoma.*

Critical appraisal

The critical appraisals of all animal and clinical studies are provided in Supplementary 3. The animal studies demonstrated an overall risk of bias due to the lack of repeated measures, control groups that were either untreated or not placebo-controlled, and inadequate reporting on follow-up, results, or statistical analyses. However, nine animal tumor models with sufficient validity were included in the meta-analysis (Table 1) (Law et al. 2022; Kikuchi et al. 1986a; Ogawa et al. 1982; Hiramoto et al. 2019; Yamamoto et al. 2017; Horiguchi 2000; Boeryd et al. 1974).

According to the appraisal, all clinical studies were significantly susceptible to bias. None of the clinical studies were designed as randomized controlled trials or cohort studies with both an intervention and control group. Additionally, inclusion and exclusion criteria were not predefined, and the studies did not report consecutive inclusion or had pre-determined outcomes.

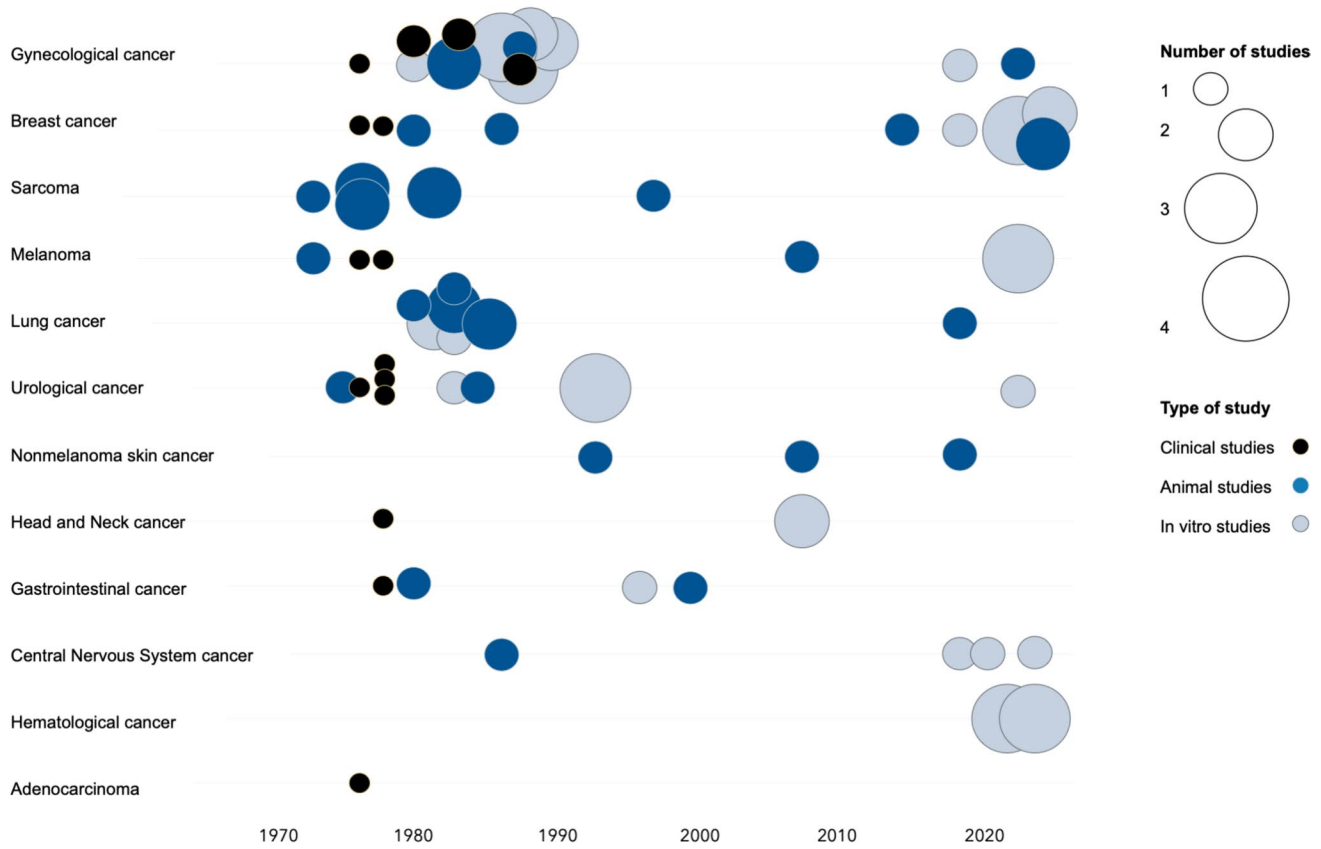

Fig. 2 Bubble chart: Historical overview of conducted studies investigating TXA's anticancer effects

Table 1 Animal tumor models included in the meta-analysis

Author	Year	Population	Intervention	Comparison, sample size	Outcomes
Law (2022)	2022	NOD-SCID-gamma (NSG) mice inoculated with 012/ LVM2/LR10 breast tumor cell line	TXA P.O. 375 mg/kg 1 × daily for 12 days Control: Peanut oil	TXA treatment group (n = 5) Control group (n = 5)	TXA treatment group: Reduced tumor volume 9.3 mm3 vs. 81.7 mm3 (p = 0.035)
Hiramoto (2019)	2019	Hairless, male, specificpathogen-free mice with 7,12-Dimethylbenz(a)anthrac ene (DMBA) and UVAinduced non-melanoma skin cancer	TXA P.O. 750 mg kg- 1 3 × weekly for 15 weeks Control: Distilled water	TXA + DMBA + UVA treatment group (n = 5) DMBA + UVA control group (n = 5)	TXA treatment groups: Reduced area per tumor 7.5 mm2 vs. 17.5 mm2 (p < 0.05)
Yamamoto (2017)	2017	Male KSN/slc mice implanted S.C. with lung carcinoma SBC- 3 A cells	TXA I.P. 30 mg 1 × daily for 10 days Control: NR	TXA treatment group (n = 4) Control group (n = 4)	TXA treatment group: Tumor growth reduced 30% (p < 0.05)
Horiguchi (2000)	2000	Female Syrian Goldso hamsters with nnitrosobis(2 hydroxypropyl)amine-induced pancreatic ducts carcinoma	TXA P.O. 0.1% 1 × daily 50 days after induction until euthanasia on day 88 Control: Untreated	TXA treatment group (n = 18) Control group (n = 17)	TXA treatment group: Mortality: 2 vs. 3 animals died (ns) Decreased no. of carcinoma lesions 0.27 ± 0.57 vs. 0.88 ± 0.78 (p < 0.05)
Kikuchi (1986a, b)	1986	Nude female BALB/c mice inoculated S.C. with TXA-exposed or non-TXA-exposed ovarian tumor (HR) cell line	TXA 10 mg/ml culture for 2 h prior to inoculation Control: Untreated	TXA-exposed-cell tumor group (n = 10) Unexposed-cell tumor control group (n = 10)	TXA treatment group: Decreased tumor volume at day 43 2.57 ± 1.39 cm3 vs. 4.96 ± 1.56 cm3 (p < 0.01)
Ogawa (1982)	1982	Female, nude mice (BALB/cAnu/ nuJCL) inoculated S.C. with lung squamous carcinoma (QG- 56) cells	TXA P.O. 1% Control: Untreated	TXA treatment group (n = 11) Control group (n = 10)	TXA treatment group: Reduced tumor weight (± se) 1.23 ± 0.10 g vs. 0.81 ± 0.11 g (p < 0.01)
		Female, nude mice (BALB/cAnu/ nuJCL) inoculated S.C. with lung adenocarcinoma (PC- 1 2) cells	TXA P.O. 1% Control: Untreated	TXA treatment group (n = 11) Control group (n = 10)	TXA treatment group: Reduced tumor weight (± se) 1.30 ± 0.16 g vs. 0.81 ± 0.11 g (p < 0.05)
		Female, nude mice (BALB/cAnu/ nuJCL) inoculated S.C. with ovarian carcinoma (OC- 1) cells	TXA P.O. 1% Control: Untreated	TXA treatment group (n = 11) Control group (n = 10)	TXA treatment group: Reduced tumor weight (± se) 2.03 ± 0.26 g vs. 1.21 ± 0.18 g (p < 0.01)
Boeryd (1974)	1974	C57BL/6 J mice inoculated I.V. with melanoma (B16) cells	TXA I.P. 12 mg single dose 30 min before inoculation Control: Saline 0.2 ml	TXA treatment group (n = 30) Control group (n = 32)	TXA treatment group: Increased total volume of lung metastases 34 10^{-3} cm^3 vs. 13 10^{-3} cm^3 (p < 0.05)

Animal studies included in the meta-analysis listed by year: Overview of author, year, population, intervention, comparison, sample size, and outcomes. Findings are reported as mean ± sd unless otherwise specified. *P.O.* Per OS, *I.V.* Intravenous, *I.P.* Intraperitoneal, *TXA* tranexamic acid, *NR* Not reported, *SE* Standard error, *No.* Number. A complete overview of all included studies in the review is provided in Supplementary 2

TXA's effect on cancer cell lines in vitro

An overview of all included in vitro studies can be found in Supplementary 2.

Viability

Of 21 cell lines, TXA reduced the viability in 17 cell lines, including three melanoma cell lines, five breast cancer cell lines, six hematologic cancer cell lines, one prostate cancer cell line, and two CNS cancer cell lines (Law et al. 2022; Esmaeili et al. 2020). However, TXA did not affect the viability of two lung cancer cell lines and two squamous carcinoma cell lines (Suojanen et al. 2009; Ogawa et al. 1982).

Proliferation

The cell proliferation rate was investigated in 14 cell lines, of which TXA decreased the rate in 11 cell lines. TXA inhibited nine gynecological cancer cell lines (Kikuchi et al. 1987, 1986a; Sekiya et al. 1980), this effect was reproduced in two of the cell lines in a separate study (Kikuchi et al. 1986b). TXA did not affect the proliferation rate in three cell lines: one lung cancer, one urological cancer, and one gynecological cancer cell line (Kikuchi et al. 1986a; Iwakawa and Tanaka 1982).

Migration

Six cell lines were investigated, and the cell migration rate was decreased in two, unaffected in two, and inhibited only under specific culture conditions in two cell lines. TXA decreased migration rate in one breast cancer cell line and one squamous carcinoma cell line (Wu et al. 2019; Suojanen et al. 2009). The cell migration rate was unaffected by TXA in one gynecological cancer cell line and one squamous carcinoma cell line (Wu et al. 2019; Suojanen et al. 2009). Two CNS cancer cell lines were unaffected by TXA when cultured by standard practice (Esmaeili et al. 2020; Kaphle et al. 2019). However, when cultured in collagen-hydrogel or cultured with endothelial cells, the migration rate decreased (Esmaeili et al. 2020; Kaphle et al. 2019).

Invasiveness

TXA reduced invasiveness in all six of the investigated cell lines (Suojanen et al. 2009; Wang et al. 1996; Kariko et al. 1993). Three urological cancer cell lines, one gastrointestinal cancer cell line, and two squamous carcinoma cell lines (Suojanen et al. 2009; Wang et al. 1996; Kariko et al. 1993).

The effects of TXA on tumor progression and metastases in animals

Findings from included animal studies reported in results are from the nine highly appraised animal models (Law et al. 2022; Kikuchi et al. 1986a; Ogawa et al. 1982; Hiramoto et al. 2019; Yamamoto et al. 2017; Horiguchi 2000; Boeryd et al. 1974). Relevant findings from all included animal studies are provided in Supplementary 2.

Tumor growth

TXA reduced growth in all seven studies investigating primary tumors (Law et al. 2022; Kikuchi et al. 1986a; Ogawa et al. 1982; Hiramoto et al. 2019; Yamamoto et al. 2017), three lung, two ovarian, one breast, and one nonmelanoma skin cancer model. Similarly, TXA reduced the number of tumors in a pancreatic duct carcinoma model (Horiguchi 2000) and the non-melanoma skin cancer model (Hiramoto et al. 2019).

Metastatic tumor growth

One study investigated the effects of TXA and EACA on metastatic tumor growth in a melanoma and a sarcoma model (Boeryd et al. 1974). TXA increased the number and volume of lung metastases, while EACA did not change the number but increased lung metastases volume in the melanoma model. However, TXA did not affect metastatic growth extrapulmonary, pulmonary, or in the liver in the sarcoma model (Boeryd et al. 1974). The sarcoma model was excluded from the meta-analysis due to insufficient reporting (Boeryd et al. 1974).

Meta-analysis of TXA's effect in animal cancer studies

The meta-analysis included nine animal studies (n = 208) and showed an overall protective effect of TXA against tumor growth with a combined standardized mean difference of − 1.0 (95% CI − 1.5; − 0.4) and with significant heterogeneity of $I^2 = 73.4\%$ and $p = 0.0002$ (Fig. 3) (Law et al. 2022; Kikuchi et al. 1986a; Ogawa et al. 1982; Hiramoto et al. 2019; Yamamoto et al. 2017; Horiguchi 2000; Boeryd et al. 1974).

The effects of TXA in patients with cancer

The included clinical studies encompass 91 patients with different cancers; ovarian (n = 40) (Kikuchi et al. 1986b;

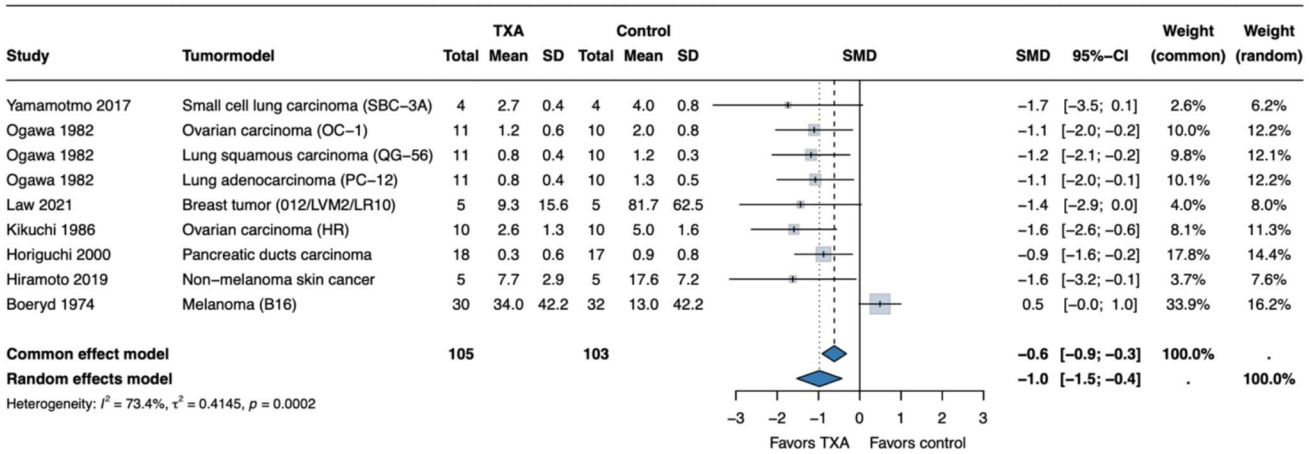

Fig. 3 Forrest plot: Meta-analysis of the anticancer effects of TXA compared to control. SMD = Standardized mean difference

Sigurdsson et al. 1983; Soma et al. 1980; Rutqvist et al. 1977), colon (n = 25) (Fosså et al. 1978; Petrelli et al. 1986), breast (n = 11) (Fosså et al. 1978; Rutqvist et al. 1977), urological (n = 3) (Fosså et al. 1978), choroidal melanoma (n = 4) (Bramsen 1978), melanoma (n = 3) (Fosså et al. 1978; Rutqvist et al. 1977), sarcoma (n = 1) (Rutqvist et al. 1977), adenocarcinoma of unknown origin (n = 1) (Rutqvist et al. 1977) and sublingual (n = 1) (Fosså et al. 1978). All included patients had recurrent or advanced disease except in one study (Bramsen 1978). TXA was applied as palliative treatment as most of the patients in the study had recurrent or advanced disease resistant to chemotherapy or other cytostatic treatment. However, the study with patients with choroidal melanomas applied TXA as a neoadjuvant treatment in three patients before resection and as a ameliorative treatment in one patient, who avoided resection by enucleation altogether (Bramsen 1978).

No conclusions on the effects of TXA in patients with cancer can be made from the included studies due to bias susceptibility. Despite that, some interesting findings may contribute to understanding the effects of TXA and are therefore worth highlighting. Ascitic fluid regression was observed in > 50% of patients with advanced ovarian cancer treated with TXA (Kikuchi et al. 1986b). A separate study with equivalent findings performed an exploratory laparotomy showing fibrin-encased tumor mass (Soma et al. 1980). Similarly, the three patients with choroidal melanomas treated with TXA before enucleation also showed fibrin-rich deposits surrounding the tumors on histopathological examination (Bramsen 1978). Regarding adverse events, two studies with 39 patients reported 16 events with gastrointestinal side effects and one thromboembolic event (Petrelli et al. 1986). Detailed descriptions of the studies are provided in Supplementary 2.

Discussion

To investigate the potential of repurposing TXA as an anticancer agent, we reviewed existing literature assessing its impact on cancer outcomes across in vitro, animal, and clinical studies. In total, 38 articles were included: 41 in vitro studies, 34 animal studies (n = 843), and seven clinical studies (n = 91). Nine critically appraised animal studies demonstrating acceptable internal validity were included in the meta-analysis. The analyses assessed TXA's combined effect on tumor growth, revealing an overall reduction in tumor growth in TXA-treated groups compared to controls.

Tumor progression involves a series of interconnected pathways, yet few of the included studies explored the mechanisms underlying TXA's effects (Law et al. 2022; Kaphle et al. 2019; Suojanen et al. 2009; Hiramoto and Yamate 2022; Hiramoto et al. 2019; Yamamoto et al. 2017). TXA is well-known to affect the plasminogen-plasmin pathway (Takada and Takada 1989), a key cancer-related pathway influencing multiple hallmarks of cancer (Hanahan 2022; Hanahan and Weinberg 2011). Recent reviews by Heissig et al. have highlighted this pathway's role in proliferative signaling, growth suppression, angiogenesis, tumor-promoting inflammation, and immune evasion (Heissig et al. 2021).

Sustaining proliferative signals and evading growth suppression are key hallmarks of cancer (Hanahan 2022). Regardless, the summarized evidence from the in vitro studies shows that TXA reduces viability and proliferation, suggesting some interference with proliferative signaling in tumor cells, although the mechanism of action is unclear and may involve both direct and indirect effects of exposure to TXA (Law et al. 2022; Esmaeili et al. 2020; Suojanen et al. 2009; Kikuchi et al. 1987, 1986a, 1986b; Ogawa et al. 1982; Iwakawa and Tanaka 1982; Sekiya et al. 1980).

Angiogenesis is critical for tumor growth in solid tumors, supplying oxygen and nutrients to rapidly proliferating cancer cells (Hanahan 2022). TXA has been shown to inhibit angiogenesis in vitro by directly targeting VEGF receptors (Zhu et al. 2020). Supporting evidence of TXA's anti-angiogenic effects includes reduced tumor hemoglobin content and suppressed growth via galanin inhibition (Yamamoto et al. 2017). Additionally, TXA reduced vascular connections between tumors and surrounding tissue, slowing tumor growth rates in rodent models (Sundbeck et al. 1981). Further investigations using the Xenon clearance technique found that while short-term TXA administration did not alter local tumor blood flow, prolonged treatment shifted intratumoral blood flow toward lower values, diminishing tumor blood supply (Sundbeck et al. 1981b).

Inflammation and immune cell infiltration are central to cancer progression (Hanahan and Coussens 2012). TXA reduced endometrial cancer growth, while decreasing proinflammatory cytokines, including TNF-α, and increasing tumor-associated macrophage count (Hiramoto and Yamate 2022). These findings suggest that TXA may drive the inflammatory response and the macrophage function towards anti-tumor activity, perhaps through altering TNF-α levels (Hiramoto and Yamate 2022; Carswell et al. 1975; Kratochvill et al. 2015). The effects on immune cell function are demonstrated in mice with traumatic brain injury (Draxler et al. 2019a). TXA increased migration and proliferation of dendritic cells, antigen-presenting cells, and T cells in local lymph nodes (Draxler et al. 2019a). In surgical patients, TXA decreased pro-inflammatory cytokines, although it is unclear if a decrease in cytokines is associated with altered immune cell function (Ma and Wu 2025; Zhang et al. 2020). However, TXA is reported to upregulate immune-enhancing and downregulate immunosuppressive cellular and noncellular markers, while reducing surgical infection rates in patients (Draxler et al. 2019b). Further investigations are required to fully disclose TXA's effect on inflammation and immunomodulation, in addition to the extended effects on cancer.

Metastases are the primary cause of cancer mortality (Dillekås et al. 2019). The tumor-infiltrating immune cell proteolytic activity and extracellular matrix degradation vastly contribute to the metastatic potential (Hanahan and Coussens 2012; Heissig et al. 2016). TXA's ability to interfere with proteolytic activity and extracellular matrix degradation is crucial to its potential anti-metastatic effects. This potential is somewhat supported by in vitro studies, reporting conflicting findings regarding migration rate but reduced invasiveness in tumor cell lines exposed to TXA (Esmaeili et al. 2020; Wu et al. 2019; Kaphle et al. 2019; Suojanen et al. 2009; Wang et al. 1996; Kariko et al. 1993). Tumor-encapsulating fibrin deposit is a suggested effect of TXA and observed in both animal and clinical studies, likely influencing metastatic potential (Ogawa et al. 1982; Tanaka et al. 1982; Soma et al. 1980; Bramsen 1978; Lanir N, Ciano PS, Van de Water L, McDonagh J, Dvorak AM, Dvorak HF 1988). Fibrin deposits and tumor encapsulation may prevent local and systemic release of micrometastases, which could be imperative in surgical oncology, where tumor cells can be identified 9/10 times in surgical field blood and on postoperative phlebotomy in 1/4 of patients (Hansen et al. 1995). However, one included study investigated perioperative tumor cell shedding by collecting venous blood from an operatively treated tumor (Peterson and Risberg 1976), which was injected into recipient animals treated with TXA before intervention and found no difference in tumor incidence or weight compared to control (Peterson and Risberg 1976). A nonsurgical lung tumor model describes tumor-associated microthrombi as more frequent in animals treated with TXA, while the number of metastatic foci was significantly lower compared to controls (Tanaka et al. 1982). Thrombosis may also facilitate tumor seeding and protect primary tumors and micro-metastases from immune elimination (Evans et al. 2017; Nieswandt et al. 1999; Palumbo et al. 2005; Sahni and Francis 2000; Brown et al. 1993). Endorsing this hypothesis, one study found that EACA increases melanoma lung metastases, arguing that tumor-associated microthrombi facilitate metastases (Kirstein et al. 2008).

Thus, a key consideration for repurposing TXA in a cancer setting is its safety profile regarding tumor growth, metastasis, and adverse events in clinical practice. No clinical cohort or randomized studies have been conducted to investigate cancer risk in patients treated with TXA. According to our assessment, the evidence from case series and reports is vastly susceptible to bias, and the summarized evidence should be considered anecdotal rather than definitive (Kikuchi et al. 1986b; Sigurdsson et al. 1983; Soma et al. 1980; Fosså et al. 1978; Rutqvist et al. 1977; Petrelli et al. 1986). Therefore, it would be incoherent to draw any conclusions regarding the efficacy of TXA as an anticancer agent. In addition, the evidence is limited to advanced stages of cancer. Regardless, TXA may potentially improve ascites production in patients with advanced ovarian cancer (Kikuchi et al. 1986b; Soma et al. 1980).

Between two clinical studies, gastrointestinal symptoms were the most reported adverse event, while one thromboembolic event was reported, acknowledging that the patient group under investigation is already at an increased risk of thromboembolic events due to chemotherapy, large tumor burden, and systemic disease (Fosså et al. 1978; Petrelli et al. 1986) Cancer-associated thrombosis significantly contributes to morbidity and mortality in cancer patients (Mahajan et al. 2022), and thromboembolic adverse events are a common concern for patients treated with TXA. However, TXA treatment is not associated with an increased

risk of thromboembolic events, according to a meta-analysis of 125.550 patients (Taeuber et al. 2021). Nor yet can an association between TXA treatment and thromboembolic risk be observed in patients undergoing cancer surgery according to retrospective investigations and a meta-analysis (Zhang et al. 2020; Longo et al. 2018; Wright et al. 2020; Varady et al. 2021; Kulkarni et al. 2023). Seizures are an established side effect of systemic treatment with high-dose TXA, which limits its utility in patients particularly susceptible to seizures (Lin and Xiaoyi 2016). Currently, two prospective clinical trials are recruiting patients. A sub-study of the larger TRIGS trial examines recurrence after gastrointestinal cancer surgery (NCT04192435) (TRIGS trial 2025) and the PRIME trial investigating recurrence after melanoma surgery (NCT05899465) (Kristjansen et al. 2024). Hopefully, these studies will contribute to knowledge of safety and efficacy in patients with cancer.

In summarizing the evidence, we show that there has been and still is interest in investigating the effects of TXA treatment on cancer-related outcomes in various types of cancer. A systematic approach should be taken to ensure successful TXA repurposing in cancer treatment. Thus, potential cancer disease candidates should be screened to validate plasmin-plasminogen-related disease mechanisms, e.g., by utilizing gene expression profiling (Dave et al. 2024). The following step may involve validating the hypothesis using real-world data analysis (Tan et al. 2023). In designing clinical trials, considerations regarding the therapeutic purpose should be established to determine whether the treatment intends to be curative, adjuvant, neoadjuvant, palliative, prophylactic, or have other intended purposes. Indeed, dosages, route of administration, frequency, duration, and timing are also to be considered. Finally, clinical testing should ensure safety, efficacy, and superiority to successfully establish TXA as an anticancer agent.

Limitations

This systematic review provides an elaborate overview of existing literature investigating TXA's anticancer effect but faces several limitations. The included studies exhibit substantial heterogeneity in methodologies, tumor models, and outcome measures. In vitro studies were not critically appraised, limiting the reliability of findings. Critical assessment of animal and clinical studies revealed an insufficient quality to draw reliable conclusions. Animal studies were generally exploratory; further protocolled studies with sample size calculations are required to produce unbiased results. The validity of the conducted meta-analysis is challenged by significant conceptual and statistical heterogeneity of the included studies. The conceptual heterogeneity is significant, as the included animal tumor studies span serval tumor types, which may have different oncogenic driver mutations. Moreover, the utilized outcome measure, standardized mean difference, ultimately prevents direct extrapolation to specific tumor studies. Clinical studies were published before establishing current scientific and ethical guidelines, such as The International Council for Harmonisation guideline on Good Clinical Practice, and do not measure up to current standards (Vijayananthan and Nawawi 2008). In addition, only case reports and series were published, making evidence anecdotal.

Conclusion

The summarized evidence from in vitro, animal, and clinical studies combined with a quantitative analysis of quality animal models suggest TXA to be a promising anticancer candidate. The results must be interpreted cautiously and cannot be directly applied. Nevertheless, the current evidence strongly legitimizes further research investigating TXA's anticancer effects. Further research should identify applicable cancer types as treatment targets, validate efficacy and safety through existing data, investigate the effects in protocolized clinical cohorts or randomized trials, and further explore underlying mechanisms of actions.

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Declarations

Competing interests The authors declare no competing interests.

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