Intravenous Curcumin in Cancer Care

Healthcare Provider Resource

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Developed by:
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General information

Common name(s): Curcumin, turmeric

Proper names(s): *Curcuma longa*

Routes of administration:
Oral and intravenous (IV). This monograph will discuss only IV administration.

Reported uses in cancer care:
IV curcumin has been used by integrative cancer care practitioners with goals of improving survival and tumour response, enhancing the effect of cancer treatments, improving quality of life (QoL), and ameliorating cancer-treatment related adverse effects.

Summary

Curcumin is used to treat various health conditions, most commonly with oral formulations. When ingested, its clinical use is limited by poor bioavailability, solubility, rapid metabolism, and clearance. Intravenous (IV) administration has been suggested as a method to overcome some of these limitations. IV curcumin is used by some integrative cancer practitioners with goals of improving cancer outcomes and quality of life. Our search yielded 6 studies including one randomized controlled trial, three phase 1 studies of safety and pharmacokinetics (PK), and 2 case reports. One of the phase I studies was conducted in healthy adults but is included due to a paucity of data. There is insufficient data to establish efficacy, safety, dosage, and drug interactions for IV curcumin in cancer care at this time. Preliminary data suggests IV curcumin is likely safe when used at the studied doses and formulations. More high-quality research is warranted with standardization of curcumin formulations, doses, scheduling, and cancer patient population.

Background

Curcumin is one of the bioactive compounds of turmeric *(Curcuma longa)*, an herbaceous plant belonging to the Ginger family.[1,2] Curcumin represents about 3% of turmeric constituents. Most of the medicinal properties of turmeric are related to curcumin, mainly the anti-inflammatory and anticancer effects.[2-4]

Curcumin is investigated and used mainly in its oral form to treat various health conditions, including inflammatory conditions, liver diseases, metabolic and neurodegenerative disorders, and several types of cancer.[5] However, it's clinical use is limited by poor bioavailability, solubility rapid metabolism, and rapid clearance.[6,7]

Intravenous curcumin has been proposed as a method to overcome some of the limitations related to bioavailability. This monograph summarizes the available literature on the use of IV curcumin in cancer care.

Methods

Monographs are created by the Patterson Institute for Integrative Oncology Research and are updated approximately every two years, or when significant new literature is published. A comprehensive and structured literature search was completed in Medline and Cochrane Library for IV curcumin and cancer from inception to May 31, 2023. Eligibility criteria included English-language human studies in cancer reporting on efficacy, QoL, safety, or feasibility of using IV curcumin among cancer patients. Studies among healthy human populations were included if they commented on safety, PK, or pharmacodynamics (PD), and if there are limited studies among cancer populations. A scoping review was performed to identify missing papers

and background information. The papers were screened by two reviewers independently. Data was extracted into standardized spreadsheets, and studies summarized using descriptive statistics.

Pharmacokinetics

Pharmacokinetic distribution of curcumin is limited due to poor water solubility, low bioavailability, and subsequently low circulating levels.[8,9]

Various formulations of oral curcumin have been developed aiming to increase its bioavailability. These techniques include adding substances to curcumin such as lipids and piperine, manipulating adsorption and dispersion, and reducing particle size.[7] Examples include curcumin–piperine complexes, and nanoformulation curcumin including polymorphic nanoparticles, liposomes, cyclodextrin inclusions, incorporation into micelles, and curcumin phospholipid complexes.[10,11] The bioavailability of orally administered curcumin varies widely based on the formulation used. Amorphous, micellar and micronized oral formulations appear to provide the most significant absorption of free and bioactive curcumin with more than 100-400-fold enhanced absorption as compared to unformulated curcumin.[7,12,13] Despite the emergence of these enhanced-bioavailability formulas, the pharmacokinetics of oral curcumin remains a concern. By bypassing the digestive system IV curcumin may overcome some of these limitations.[9]

The pharmacokinetics of IV curcumin have been evaluated in three phase I studies, all of which used liposomal curcumin.[14-16] There were dose-dependent, and infusion-dependent increases in the plasma concentration of curcumin. The maximum concentration (Cmax) ranged from 42 – 2,575 ng/mL after IV administration with escalating doses up to 400 mg/m^2. The concentration increased rapidly in the first 15 minutes and remained stable throughout the infusion.[14,15] Increased plasma concentrations were also observed with increasing the rate of infusion.[15,16] The mean time to concentration maximum was 0.4 to 4.0 hours across a dose range of 100–400 mg/m^2 infused over 2-8 hours.[14,15]

Curcumin is rapidly metabolized to tetrahydrocurcumin (THC) and hexahydrocurcumin by reductase enzymes.[17,18] Following the infusion there is a rapid decrease of curcumin and its metabolites within 60 minutes. The half-life of curcumin varies, but is consistently reported as less than one hour.[14-16] A shorter duration of clearance was detected in cancer patients compared to healthy individuals.[16]

In summary, IV curcumin is rapidly absorbed and metabolized, and has a short elimination half-life. Increasing the dose and infusion rate increases the maximum concentration obtainable. Only the liposomal form has been well studied for its pharmacokinetic profile, and whether this data can be extrapolated to other forms is unclear.

Mechanism of Action

Curcumin has pleotropic effects which may be beneficial as a supportive cancer treatment. In addition to anti-inflammatory effects, curcumin targets several signaling pathways leading to immune modulation, counteracting drug resistance, anti-angiogenic, cytotoxic, anti-proliferative, and pro-apoptotic effects.[2] Curcumin has minimal harmful effects against normal cells,[19-21] and has demonstrated stimulatory and protective effects on normal stem cells.[22-26]

Most data on the mechanism of action of curcumin in cancer management is derived from preclinical data.

Immune modulation and anti-inflammatory effects

Chronic inflammation can produce genetic instability, which can serve as one of the first signals for the initiation of cancer.[27,28] Curcumin acts on various inflammatory molecules and pathways, inhibiting their actions. Curcumin binds directly to reactive oxygen species (ROS) and may lead to suppressing the growth and metastasis of some types of cancer.[29] Curcumin also has an inhibitory action on the NF-κB-dependent pathway,[30,31] can downregulate the expression of pro-inflammatory cytokines through binding of nuclear proteins,[32] and can downregulate the expression of the transcription factor AP-1 and of (COX2).[33,34]

In addition, curcumin has been found to modulate the cellular response of B and T lymphocytes, macrophages, and natural killer cells,[35] and also effect both the expression and action of immune cytokines.[2]

Anti-angiogenic effects

Angiogenesis is among the factors that can lead to maintaining cell survival, cell spread, and chemoresistance of a tumour and contributes to the initiation and survival of cancer cells through induction of the NF-κB pathway.[36] Curcumin, through inactivation of the NF-κB pathway, may lead to downregulating cancer-related genes and curtailing angiogenesis.[37,38]

Counteracting drug resistance

Curcumin may decrease drug resistance to various chemotherapy agents by reducing the expression of proteins related to drug resistance.[39] This has been demonstrated in preclinic studies using different chemotherapy-resistant cell lines including breast, colon, cervical, prostate, and lung cancer cells, and various chemotherapy agents including paclitaxel, docetaxel, cisplatin, oxaliplatin, and 5-fluorouracil.[40-42]

Cytotoxic, anti-proliferative, and apoptotic effects

Curcumin may suppress the proliferation of cancer cells by interrupting the cell cycle through inhibiting the Wnt/β-catenin pathway and increasing the levels of p53, p21, and p27.[43] Curcumin could also promote apoptosis by enhancing the expression of apoptotic proteins (Bax, Cleaved-caspase-3, etc.), and inhibiting the expression of anti-apoptotic proteins (Bcl-2).[43] Further, curcumin has been shown to induce cytotoxic effects on different cancer cell lines.[44,45]

Protection of normal cells

Curcumin has differential effects on cancer cells compared to healthy cells. In healthy cells it has a protective effect, even stimulating proliferation.[46] Curcumin may concentrate in cancer cells more so than in normal cells.[47,48]

Clinical Evidence Related to Effectiveness

Six studies were identified for the use of IV curcumin. Five studies were conducted among cancer patients,[15,16,49-51] and one study in healthy adults.[14] These six studies comprised one randomised controlled study,[49] three phase 1 studies,[14-16] and 2 case reports.[50,51] Two of the phase I studies[14,16] and one of the case reports[51] did not report on any efficacy outcomes, and thus are not discussed in this section but are discussed elsewhere in the monograph. Overall, there is insufficient data to determine the efficacy of IV curcumin use among cancer patients and more high-quality research is warranted.

The only RCT was a placebo-controlled, double-blind study with 150 advanced and metastatic breast cancer patients.[49] Patients received paclitaxel (80 mg/m^2) with either curcumin 300 mg (CUC-1® , a micellar nanoformulation of curcumin) or placebo, once weekly for 12 weeks. Objective response rate (ORR) was the primary outcome. Secondary outcomes included time to tumour treatment failure, time to tumour progression (TTP), progression-free survival (PFS), quality of life, and safety.

At four and 12 weeks post-intervention in the intention to treat analysis, the ORR (complete + partial response) in the curcumin group was higher than in the placebo group (4 weeks: 50.7% vs. 33.3%, $p < 0.01$; 12 weeks: 29% vs. 20%, $P = 0.091$). In a per-protocol analysis the difference was more pronounced (4 weeks: 61% vs. 38%, $P = 0.004$, 12 weeks: 44.9% vs. 27.8%, $p = 0.034$ for curcumin and placebo groups respectively). The median PFS in the curcumin group was non-significantly longer than in the control group (27.0 weeks vs. 24.6 weeks, $P = 0.35$). Compared to placebo, the curcumin group had lower rates of fatigue (3 vs. 10 patients $P = 0.05$) and better performance status based on Karnofsky Performance Status ($P = 0.046$). However, no significant difference was observed between groups regarding other patient reported QOL scores and Eastern Cooperative Oncology Group (ECOG) scores. Eighty-one patients (54.0%) reported treatment-emergent adverse events (TEAEs), with no difference between the curcumin and placebo arms (54% and 56% respectively)**.** Further discussion of the safety and tolerability outcomes are outlined in the safety section. The authors reported that curcumin in combination with paclitaxel was superior to the paclitaxel-placebo combination concerning physical performance after 12 weeks of treatment and ORR at a short-term follow-up in patients with advanced and metastatic breast cancer.

In a phase I study, 32 patients with metastatic tumours who were not candidates for further anti-tumour treatment received a weekly IV infusion of liposomal curcumin for 8 weeks in dose escalation from 100 mg/m^2 over 8 hours to 300 mg/m^2 over 6 hours.[15] The primary outcomes were tolerability and safety of escalating doses of liposomal curcumin, and secondary outcomes included anti-tumour activity and curcumin's PKs. Only eight patients (25.0%) received all eight planned infusions. The most common reasons for stopping the treatment were disease progression and deterioration of general medical condition. Objective tumour responses were not detected; however, significant tumour marker responses and transient clinical benefit were observed in two patients. No dose limiting toxicities were observed.

One case report involved a 50-year-old male patient who had recurrent metastatic (in the lung) adenoid cystic carcinoma of the submandibular salivary gland post resection, radiotherapy, and first line chemotherapy.[50] The patient received IV curcumin (water soluble 225 mg/m^2 twice weekly for six months plus oral bioavailable curcumin (Arantal®) 2 × 84 mg/day and imatinib 400 mg/day (both continued after the IV curcumin). The aim was to target c-kit overexpression with imatinib and inhibit NF-kB overexpression through the addition of curcumin. After six months of treatment, PET/CT scan indicated significant anatomical reduction and metabolic regression of the tumour masses. At 24 months, near complete anatomic and complete metabolic response was reported. IV curcumin and the bio-optimized oral were well tolerated, with no toxicities or adverse reactions reported. However, due to the activity of imatinib against c-kit–positive tumors, the contributions from adding curcumin to the efficacy of this patient’s treatment regimen is unknown.

Adverse Events and Side Effects

In general, based on the limited clinical data available, IV curcumin has been well tolerated. It should be noted that different curcumin formulations could have different safety and tolerability profiles.

Four identified studies reported on safety and adverse events: one RCT,[49] two phase I studies,[14,15] and one case report.[51] In all studies other than the case report, IV curcumin was well tolerated with reported adverse events generally being mild and resolving without complication. The adverse events listed are all from the phase I studies.[14,15] The RCT of curcumin in breast cancer patients receiving paclitaxel found no significant difference in any adverse event between groups.[49]

The most commonly reported adverse events from the two phase I studies included fever and chills, anemia, red blood cell abnormalities (primarily echinocytes, however one case of grade 3 hemolysis was reported), dizziness/headache, nasopharyngitis/rhinitis, various laboratory abnormalities including increased AST, mean cell volume, blood lactic acid, and EKG deviations and QT prolongation.[14,15] Other less frequently reported adverse effects included gastrointestinal effects, fatigue, chest discomfort, epistaxis, decreased platelet count, cough, hypertrichosis, and infusion-related reactions.

Three serious adverse events were reported including one case each of hemolysis (grade 3), hyponatremia (in patient with pre-existing hyponatremia), and facial edema (grade 2 but required treatment).[15]

Unpublished data from a clinician with experience using IV curcumin in cancer populations reported the following side effects with the use of IV curcumin emulsion: nausea and vomiting, transient "manic"/euphoric symptoms (during/up to 2-4 hours post IV), peripheral heat and hand/foot itching in higher doses (duration 1-2 days), skin rash and redness, dizziness, and diarrhea.[52]

One case study reported on a woman with metastasized endometrial sarcoma who received frequent infusions of curcumin.[51] The outlet connection of the catheter was clogged with a yellow substance, and the patient repeatedly presented with occlusion of the catheter port. This occlusion was assumed to be related to the curcumin infusion. No information was provided on the type, frequency and dose of the curcumin infusion used.

Interactions with cancer treatments and other medications

Chemotherapy, radiation, and endocrine therapy:

Data on the interaction potential of IV curcumin with standard cancer treatments is limited. Therefore, studies using oral curcumin have also been included to help inform this section.

Taxane chemotherapy: One clinical trial administered IV curcumin with paclitaxel and reported no significant difference between the curcumin and placebo groups regarding toxicities or response rates;[49] therefore, a negative interaction is unlikely. Oral curcumin has been combined without evidence of a negative interaction with docetaxel in metastatic breast, [53] and metastatic castration-resistant prostate cancer.[54] Additionally, in vitro, a synergistic effect on docetaxel with the use of curcumin has been detected.[55]

Other chemotherapy agents: Oral curcumin has been combined with gemcitabine in advanced and

metastatic pancreatic cancer,[56-58] and FOLFOX chemotherapy in metastatic colorectal cancer.[59,60] In vitro studies demonstrated that vinblastine-induced tumour cell death might be inhibited by curcumin,[61] and doxorubicin-induced apoptosis of breast cancer cell lines could be inhibited by curcumin.[62] Animal studies revealed that dietary curcumin inhibits cyclophosphamide-induced tumour regression,[62] and camptothecin-induced apoptosis of breast cancer cells.[62] These interactions could be through curcumin's interference with cytochrome P450 enzymes.[62-64] However, research is conflicting and the clinical relevance of these findings not certain.

Radiation: Multiple studies have investigated the concomitant use of oral curcumin with radiation therapy for mitigation of radiation induced side effects such as dermatitis,[65-67] and mucositis.[68-70] However, none of these studies reported on radiation efficacy outcomes, thus a negative interaction cannot be ruled out. Ample preclinical data has suggested that curcumin has radiosensitizing effects.[71-77]

Endocrine therapy: Among breast cancer patients,, the use of oral curcumin significantly reduces the PK parameters of tamoxifen and its metabolite endoxifen, which may decrease the efficacy of tamoxifen. This effect was more pronounced in patients who were extensive CYP2D6 metabolizers compared to intermediate.[78]

Other medications:

Anticoagulants and antiplatelet medications: There is concern that curcumin may interact with anticoagulant and antiplatelet medications through pharmacokinetic or pharmacodynamic pathways; however, the evidence on this is mixed. For example, oral curcumin may affect the PKs of warfarin and clopidogrel but there is no evidence concerning an impact on the coagulation rate and platelet aggregation.[79] Similarly oral curcumin supplementation for 10 days resulted in no significant differences in bleeding time in patients on acetylsalicylic acid, ticlopidine or clopidogrel at standard dosages. Additionally, there was no difference in INR in patients taking warfarin or dabigatran after the initiation of curcumin.[80] In contrast, curcumin and its derivatives have antithrombotic and anti-coagulant activities through prolongation of aPTT and PT and inhibition of thrombin and FXa activities in the preclinical setting.[81] One case report of increased international normalized ratio (INR) has been reported in a patient who began taking turmeric while he was on warfarin with stable INR.[82] Caution is warranted when combining curcumin with anticoagulant and antiplatelet medications.

One study explored interactions of IV curcumin with 44 commonly used medications which have the potential to interact with hepatic uptake transporters.[16] The only notable effect was that three medications targeting the renin–angiotensin system (Lisinopril, Ramipril, and Valsartan), elevated plasma levels of curcumin in three cancer patients who received IV curcumin. However, there was no data on the effect of curcumin on these medications.

Based on preclinical data, curcumin may reduce efficacy of ciprofloxacin and cotrimoxazole.[83,84] Curcumin increased the plasma levels of tacrolimus an (immunosuppressant) in a murine model.[85]A case report noted acute nephrotoxicity related to tacrolimus in a patient with a history of liver transplantation following concurrent use of high amounts of turmeric.[86]

In addition, in vitro studies revealed that curcumin increases concentrations of verapamil.[87] Curcumin's cytotoxic effects have been shown to be increased in the presence of acetaminophen,[87] aspirin or ibuprofen.[88] However, the clinical effects of these interactions

are not known.

Impact on cytochrome P450 system

Curcumin may alter some cytochrome P450 enzymes.[89] Curcumin may inhibit CYP 1A2 [64] and CYP 2D6 ,[90] and induce CYP 2A6 enzymes.[64] Curcumin is not likely to impact CYP3A4 or CYP 2C9 in a clinically meaningful way based on several human studies.[90-94] Therefore caution should be exercised when using curcumin with CYP 2D6, CYP 1A2, or CYP 2A6 metabolized medications.

Cautions and Contraindications.

Caution should be applied when administering IV curcumin with patients receiving anticoagulant and anti-platelet medications.[95] As noted, an in vivo study demonstrated that oral curcumin may affect the PKs of warfarin and clopidogrel but without impacting the coagulation rate and platelet aggregation.[79] Similarly, caution should be applied with the use of IV curcumin in patients with gall bladder disease as this might increase gall bladder contractions.[52,96]

Two deaths have been reported from the administration of IV curcumin with polyethylene glycol (PEG) 40 castor oil. However, upon investigation it was determined that the deaths were not related to the curcumin itself.[97] The deaths were found to be related to non-pharmaceutical grade components and uncontrolled ingredients which caused acute hypersensitivity reactions.[49,98]

Dosing, frequency, and length of treatment

For liposomal curcumin, the doses reported in studies ranged between 100-300 mg/m^2 over 2 to 8 hours.[14-16] This equates to a dose of 170-510 mg for an average adult with a 1.7 m^2 surface area. One study recommended the dose for future anticancer research be 300 mg/m^2 delivered over 6 hours.[15] In this study, patients were pre-medicated with 50 mg of diphenhydramine before each treatment. Another study using a curcuminoid formulation in polyoxyl castor oil in a micellar nonoformulation applied a dosage of 300 mg IV once weekly.[49]

Unpublished data from an integrative cancer practitioner based on clinical experience recommends starting with a test dose for reaction/allergy of 5 – 10 mg / kg of IV curcumin emulsion formulation then escalating to a maximum of 30-40 mg/kg.[52] Similarly, data presented at the 2022 Oncology Association of Naturopathic Physicians (OncANP) conference reported administration of IV curcumin at doses ranging from 1.2 mg/kg - 40 mg/kg in patients with advanced cancer.[99] The authors suggested that higher doses (20-40 mg/kg) may be more effective.

At least one practitioner recommends that patients consume a fiber supplement for bile sequestration before, during, and on the evening of the infusion to counteract the aggressive choleretic effects that might happen with the start of the infusion.[52]

Disclaimer

This monograph provides a summary of available evidence and neither advocates for nor against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Prior to using a new therapy or product, always consult a licensed health care provider. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a qualified health care provider.

Table 1: Clinical trials of IV curcumin for cancer

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Saghatelyan 2020 [49]	RCT	150 patients (75 in each group) with advanced and metastatic breast cancer	Curcumin (CUC-1®) 300 mg IV once weekly for 12 consecutive weeks) + paclitaxel	Placebo (riboflavin) + paclitaxel once weekly for 12 consecutive weeks).	ORR, TTTF, TTP, PFS, QoL, and safety.	The ORR in the curcumin group was higher than that of the placebo group at 4 weeks of follow-up (51% vs. 33%, P < 0.01) and at 12 weeks of follow-up (29% vs. 20%, P = 0.091) in the ITT analysis. The median PFS in the curcumin group (27.0 weeks) was 2.4 weeks longer than in the placebo group (24.6 weeks), P = 0.35, HR: 1.278). Longer median TTP was also detected in favor of the curcumin group (27.0 weeks vs 24.6 weeks, P = 0.30, HR: 1.319). Fatigue was reported at a lower rate in the curcumin group vs. placebo (3 vs. 10 patients, respectively; OR =3.7, P = 0.05). The overall physical performance reported was higher with curcumin vs. placebo. The percentage of TEAEs was 54% in curcumin group vs 65% in the placebo group with no p value reported
Bolger 2019 [16]	Phase 1 PK study	Cancer patients (Not defined) and healthy individuals	Lipocurc™ IV liposomal curcumin (Polymun Scientific (Klosterneu burg, Austria) of 37.5 and 50 mg/m2 /h in cancer patients and at 120 and 160 mg/m2 /h in healthy individuals	NA	To compare plasma levels of curcumin and THC at different infusion rates between cancer patients and healthy individuals. Correlation analysis to determine the impact of co-medication on infusion rate normalized plasma levels of curcumin and THC in cancer patients.	The PK of curcumin infusion patients was impacted by either co-medications, health status (cancer vs. healthy), or both. Increased infusion rate from 37.5 to 50 mg/m^2 /hour in cancer patient and in healthy individuals from 120 to 160 mg/m^2 /hour, led to increased plasma levels of curcumin which was more evident in cancer patients compared to healthy individuals. The mean ± SD of the C max (ng/mL) for healthy adults varied between 1446± 382 and 2574 ± 453 vs. 1027± 199 and 1428±552 for cancer patients. The mean ± SD of t1/2 (h) was varied between 1.30 ±0.50 and 1.83± 0.87 for healthy vs 0.26 ± 0.06 and 0.36± 0.17 for cancer patients.

						Compared to healthy participants, cancer patients had higher plasma levels of curcumin, and shorter elimination phase and half-life. Of 44 co-medications studied, three medications targeting the renin–angiotensin system, Lisinopril, Ramipril, and Valsartan, elevated plasma levels of curcumin and THC in three cancer patients who received IV curcumin.
Greil 2018 [15]	Phase I study,	32 patients with metastatic tumors not eligible for further anti-tumour treatment	A weekly IV infusion of liposomal; Lipocurc™ curcumin for 8 weeks in dose escalation from 100 mg/m^2 over 8 hours to 300 mg/m^2 over 6 hours.	NA	Safety, tolerability, anti-tumour activity and curcumin PK were secondary outcomes	No dose-limiting toxicity was observed in 26 patients at doses between 100 and 300 mg/m^2 over 8 h. Of the six patients who received 300 mg/m^2 over 6 h, one patient developed hemolysis, and three other patients experienced hemoglobin decreases >2 g/dL without signs of hemolysis. Two of the 40 serious AEs detected were related to IV curcumin: facial edema, and anemia. Echinocytes were observed in one patient. Four Grade 3 AEs were detected: anemia in two patients, hemolysis in one patient, and hyponatremia in one patient. An anti-tumour effect was not detected. PK analyses revealed stable curcumin plasma concentrations during infusion, followed by rapid declines to undetectable levels after the infusion.

Abbreviations: AEs = adverse events, C max = maximum concentration, h = hour, HR = hazard ratio, ITT = intention to treat, IV = intravenous, ORR = objective response rate, NA = not applicable, PK = pharmacokinetics, PFS = progression-free survival, QoL = quality of life, RCT = randomized clinical trial, SD = standard deviation, t1/2 = terminal elimination half-life, TEAE = treatment emergent adverse event, THC = tetrahydrocurcumin , TTTF = time to tumour treatment failure, TTP = time to tumour progression.

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