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Review

The Roles of Plant-Derived Triptolide on Non-Small Cell Lung Cancer

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Over the past decade, natural compounds have been proven to be effective against many human diseases, including cancers. Triptolide (TPL), a diterpenoid triepoxide from the Chinese herb *Tripterygium wilfordii* Hook F, has exhibited attractive cytotoxic activity on several cancer cells. An increasing number of studies have emphasized the antitumor effects of TPL on non-small cell lung cancer (NSCLC). Here we mainly focused on the key molecular signaling pathways that lead to the inhibitory effects of TPL on human NSCLC, such as mitogen-activated protein kinases (MAPKs) modulation, inhibition of NF- B activation, suppression of miRNA expression, etc. In addition, the effect of TIG on immune response in cancer patients is summarized for improved immune modulation utilization. However, the clinical use of TPL is often limited by its severe toxicity and water insolubility. Future clinical trials and drug delivery strategies that will evaluate the security and validate the underlying tumor-killing properties of TPL in human NSCLC are also to be discussed.

Key words: Triptolide (TPL); Cancer cells; Molecular signaling pathways; Antitumor effects

INTRODUCTION

In recent years, more natural compounds obtained from plants have received considerable attention from the scientific community, owing to their increasing merit in the prevention and treatment of cancer[1,2]. Growing evidence indicates that multiple natural compounds, such as alkaloids, polyphenols, and flavonoids, are capable of fighting a variety of diseases, including cancer, and their many preparations have been used clinically[3]. For instance, Taxotere, a semisynthetic terpenoid antineoplastic agent, has recently demonstrated high efficacy in the treatment of a wide variety of solid tumors[4]. Irinotecan is a semisynthetic derivative of camptothecin used clinically for the treatment of adult metastatic colorectal cancer[5]. In addition to their nontoxic nature and fewer side effects compared to chemotherapeutic drugs, natural compounds are used in clinical practice due to advantages such as multitargeting properties, immediate availability, and low cost[6].

Since the turn of the century, research volume has been increasing in the prevention and treatment of cancer by traditional Chinese medicine. It has been reported that Danggui Buxue Tang induced autophagic death of colorectal cancer cells by upregulating Atg7 and regulating the mTOR/p70s6k signaling pathway[7]. A pseudonatural product inhibited cancer cell growth by selectively inhibiting glucose transporters GLUT-1 and GLUT-3[8]. Diosmetin, the aglycone of the lavonoid glycoside from medicinal herbs, enhanced the radiosensitivity of radioresistant non-small cell lung cancer (NSCLC) cells A549/IR[9]. Therefore, there is great potential for the development of new anticancer drugs extracted from Chinese medicine.

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Triptolide (TPL), a diterpenoid triepoxide, is the major active component of extracts derived from the Chinese herb thunder god vine (*Tripterygium wilfordii* Hook F), which possesses potent anticancer, anti-inflammatory, and immunosuppressive properties [10]. To date, many studies have reported that TPL inhibits multiple human solid tumors in vivo and in vitro[11,12], and revealed various anticancer mechanisms, such as inhibiting heat shock factor-1 (HSF-1)[13], suppression of DNA damage response[14,15], and regulating mRNA stability[16,17]. Taken together, these results suggest that TPL has a broad anticancer effect and can be used to treat NSCLC. In the present report, we review the activities and mechanisms of TPL and its prodrug Minnelide in inhibiting human NSCLC cells, providing ideas for further research.

CUMULATIVE ANTITUMOR EVIDENCE SUPPORTING TPL ACTIVITY AGAINST NSCLC

NSCLC is one of the malignant tumors with the highest rate of growth of morbidity and mortality and is the greatest threat to human health and life. At present, the clinical treatment of NSCLC includes chemotherapy, radiotherapy, surgical treatment, and traditional Chinese medicine treatment, which have achieved some clinical effects[18,19]. Recently, several studies have emphasized the antitumor effects of TPL on NSCLC cells (Table 1). These inhibitory effects of TPL, along with the unique clinical features, provide the possibility that TPL could act as a promising agent against NSCLC. To provide an exhaustive description of the rapid development in this field, the molecular mechanisms and potential functions of TPL in NSCLC will be discussed in the following sections (Fig. 1).

TPL MODULATION ON THE MAPK SIGNALING PATHWAYS

Mitogen-activated protein kinases (MAPKs) consist of three serine/threonine kinase cascades. These are important cell signaling pathways in vivo and play important roles in regulating cellular functional activities, especially in cancer cells, which offer prospective benefits for cancer therapy[20,21]. Four types of MAPK cascades have been found in mammalian cells: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), P38 MAPK, and ERK5.

Studies have shown that multidrug resistance cells can resist cell apoptosis induced by anticancer drugs through upregulation of survival signaling pathways, like p38 and MAPK, and preliminary observations have demonstrated that TPL can enhance apoptosis by regulating MAPK signaling pathways[22]. Indeed, Xie et al. performed an MTT assay and showed that SP600125, a JNK inhibitor, and U0126, an ERK inhibitor, significantly reinforced the inhibitory effects of TPL on human Taxol-resistant lung adenocarcinoma cell lines A549/Taxol[23]. Western blot results showed that TPL exerts its antiproliferative effect via downregulation of p-JNK and upregulation of p-ERK and p-P38. These findings suggest that the antiproliferative activity of TPL in multidrug resistance cancer cell lines is mainly related to the modulation of MAPKs and its downstream pathways. However, an opposite finding from Tai and colleagues showed that, functioning as inhibitor of MAPK phosphatase-1 (MKP-1), TPL pretreatment could reverse the antimetastatic effect of peroxisome proliferator-activated receptor- (PPAR) agonist in NSCLC NCI-H441GL cells[24]. These inconsistent findings might be due to the different cellular environment and phenotype, suggesting that the precise roles of TPL-mediated MAPK signaling pathway in cancer biology need to be carefully revised.

Apo2L/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which belongs to the tumor necrosis factor (TNF) superfamily and is closely connected with TNF- and FasL, induces apoptosis of various tumor cells[25]. However, many cancer cells develop resistance to Apo2L/TRAIL-induced apoptosis. An increase in TNF- -induced apoptosis by TPL has been suggested previously in A549, HT180, and MCF-7 cell lines[26], and Apo2L/TRAIL-induced apoptosis was enhanced when combined with chemotherapeutic drugs to treat NSCLC cells[27]. Studies have reported that combination treatment with TPL and Apo2L/TRAIL sensitized several cancer cells (A549, NCI-H358, Calu1, and SkLu) for Apo2L/TRAIL-induced apoptosis by phosphorylating ERK2 dually at Thr202 and Tyr204[27].

TPL SENSITIZES NSCLC CELLS BY INHIBITION OF NF-κB ACTIVATION

NF- B is involved in a wide variety of physiological processes in cells through a group of important transcriptional factors. The NF- B family consists of five members: p50, p52, RelA/p65, c-Rel, and RelB[28]. Lee et al. demonstrated that TPL almost blocked TNF-mediated induction of NF- B activation by impairing p65 transactivation in NSCLC cells A549[26], but further exploration is still required to determine how p65 transactivation is inhibited by TPL. Further studies from Zheng and colleagues group revealed that TPL effectively inhibited IKB phosphorylation and degradation, and then blocked TNF- -induced nuclear translocation of NF- B, leading to reduction of NSCLC incidence with no obvious side effects[29]. In addition, TRAIL activates NF- B via an interaction with TRAIL receptors. Lee et al. showed that TPL-sensitized TRAIL-induced apoptosis by anti-NF- B activity is achieved by another process in A549 and NCl-H1299 cells because TRAIL-induced apoptosis was enhanced when MG132 was added after TRAIL, but after the process was reversed this effect weakened[30].

Table 1. The Targets and Mechanism of Triptolide (TPL) in Human Non-Small Cell Lung Cancer (NSCLC)

Target	Action	Outcome	Model Used	Reference(s)
MAPKs	p-JNK↓; p-ERK↑; p-P38↑	Apoptosis↑; proliferation↓;	A549; A549/Taxol	22, 23
	MKP-1↓	Reversing antimetastatic effect of PPAR agonist rosiglitazone	H441	24
	ERK2↑; caspase 3 and 8↑	Apo2L/TRAIL-induced apoptosis sensitization	A549; NCI-H358; Calu1; SkLu1	27
NF- B	p65 transactivation↓	TRAIL-induced apoptosis↑	A549	26
	IKB phosphorylation and degradation↓ NF- B nuclear translocation↓	Incidence↓	H460; H460; PC3; FEN1 E160D mice; LLC-grafted mice	29
	TRAIL-induced NF- B transcriptional activity↓	Sensitive to TRAIL-induced apoptosis↑	A549; NCl-H1299	30
	NF- B↓; NF- B-regulated drug-resistant gene expression↓	Reversal of the Taxol resistance	A549; A549/Taxol	51
HA-CD44/RHAMM	ERK↓; Akt↓; EGFR↓	Growth and survival↓	A549; H520; H1299; H1650; H1975; A549 xenograft in male nude mice	34
	Potential EGFR antagonist	Proliferation↓	Molecular dynamics simulation; H2347	35
miRNA	126 miRNAs↑; 101 miRNAs↓	Altering miRNA expression profile	H358	43
	miR-21↓; PTEN protein↑; caspase 3 and 9↑	Proliferation↓; apoptosis↑	PC-9	45, 46
FAK	p130Cas↓; Src↓; less metastatic colonization compared to control mice	Migration, invasion, and metastasis↓	H460; A549; H358; H358 xenograft in NOD SCID mice	43
PI3K/Akt	p-Akt↓; p-GSK-3β↑; Bax↑; caspases↑; Bcl-2↓	Proliferation↓; S-phase arrest	A549; A549/Taxol	23
	p-Akt↓	Cytotoxicity	H1299, H460	36
Tumor-related protein expression	Dysregulation of tumor-related protein	Apoptosis↑; G_2/M phase arrest	A549 (ITRAQ-based proteomics analysis)	52
Keap1/Nrf2	Nrf2 transcriptional activity↓	Chemoresistance to antitumor drugs↓	LLC; Nrf2-KD; 3LL and Nrf2-KD xenograft in C57BL/6 mice	53
Wnt	Epigenetic modifications to histone H3; WIF1	Growth↓	A549; H460; H358; H1299; E160D mice; A549 and H460 xenograft in NOD SCID mice	55
	WIF1 demethylation	Apoptosis↑; migration↓	A549; H460	57

MAPKs, mitogen-activated protein kinases; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; MKP-1, kinase phosphatase-1; Apo2L/TRAIL, Apo2L/tumor necrosis factor-related apoptosis-inducing ligand; Akt, protein kinase B; LLC, the Lewis lung cancer; EGFR, epidermal growth factor receptor, PTEN, phosphatase and tensin homolog; FAK, focal adhesion kinase; MMP14, matrix metalloproteinase 14, iTRAQ, isobaric tags for relative and absolute quantitation; Nrf2, nuclear factor erythroid 2-related factor 2; WIF1, Wnt inhibitory factor 1; ↑, activation/upregulation; ↓, suppression/downregulation.

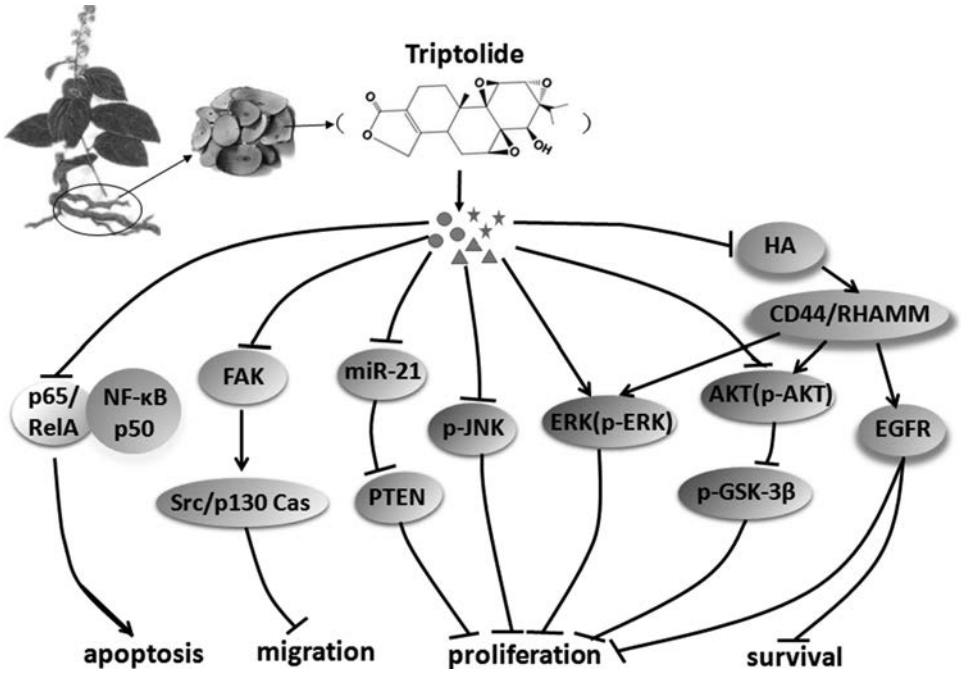

Figure 1. Overview of the natural compound triptolide (TPL) on aberrant molecular signaling pathways for non-small cell lung cancer (NSCLC) research and therapy. TPL exerts its anticancer effects by inhibiting proliferation, suppressing survival, and inducing apoptosis of NSCLC cells via modulating several key signaling pathways, including MAPK, NF- B, and FAK.

However, the exact mechanism is still to be elucidated. Based on a report that downstream effectors of NF- B activation and members of the inhibitor-of-apoptosis (IAP) family were required to suppress TNF-induced apoptosis[31], the team above assumed that TPL deactivated c-IAP1 and c-IAP2 by TRAIL. Although they failed to prove this speculation in A549 and NCI-H1299 cell lines, they found differences in NF- B activation induced by TRAIL and TNF potency, which might explain this finding.

TPL SUPPRESSES NSCLC CELL GROWTH BY TARGETING HA-CD44/RHAMM SIGNALING

Hyaluronan (HA) is a nonsulfated linear glycosaminoglycan polymer comprised of D-glucuronic acid and *N*-acetyl-D-glucosamine. In tumor tissues, markedly elevated levels of HA can be observed, leading to increased development and progression of cancer cells[7]. In cancer cells, the receptor for hyaluronic acid-mediated motility (RHAMM) and clusters of differentiation 44 (CD44), a transmembrane glycoprotein and expressing as multiple isoforms in many cells, are the best characterized cell surface receptors for HA. CD44 promotes cancer cell movement and is often used as a marker for cancer stem cells in human tumors. Studies indicated that HA-CD44 binding leads to the interaction of CD44 and its signaling receptors like epidermal growth factor receptor (EGFR), which affects various downstream signaling pathways, the PI3k/Akt and MAPK pathways in particular[32].

Previous studies have demonstrated that HA and its receptors CD44 and RHAMM are at elevated levels in NSCLC patients, and this increased expression can influence its poor prognosis and metastasis to some extent[33]. Song et al. separately inoculated A549-expressing cells and liposomal TPL 4 weeks apart into the lung of male nude rats via intranasal instillation and observed growth suppression of orthotopically xenografted NSCLC cells[34]. This study also demonstrated that the antiproliferative activity of TPL is associated with the inhibition of HA-CD44/RHAMM signaling axis in NSCLC, inhibiting the level of downstream effector EGFR, Akt, and ERK. Moreover, using molecular docking analysis, Zhao et al. also identified TPL as a potential EGFR antagonist and its antiproliferative potency similar to the well-known EGFR-targeted drugs[35]. In addition, TPL exerts obvious cytotoxicity in NSCLC cells by docking into the activation pocket of Akt-1 protein structure and then downregulating Akt phosphorylation in NSCLC cell lines H1299 and H460[36]. These results are consistent with previous reports[32,37], which demonstrated that the phosphorylation of EGFR and Akt increased when the interaction of HA and RHAMM was blocked by the EGFR signaling inhibitors. These results indicated that HA-RHAMM signaling promotes cell survival via EGFR in a mouse model of

islet cell tumorigenesis[38]. Studies also indicated that apart from being a ligand of CD44 and RHAMM, HA also acts as HA synthase 2 (HAS2) siRNA to downregulate CD44 and RHAMM expression in NSCLC cells[34]. Although this phenomenon is also observed in other tumors, the mechanisms by which CD44 and RHAMM regulate each other are unclear and require further study.

TPL REDUCES NSCLC CELL GROWTH BY TARGETING miRNAs

MicroRNAs (miRNAs) are a type of noncoding small RNAs approximately 20–25 nucleotide in length with regulatory functions, and they usually deregulate gene expression during the onset and progression of cancer[39,40]. Based on the findings that TPL can regulate miRNA expression by binding to xeroderma pigmentosum type B, a subunit of the human transcription factor II[41], or by inducing proteasome degradation of RNA polymerase II[42], Reno et al. demonstrated 126 miRNAs that were upregulated and 101 miRNAs that were downregulated after TPL treatment in NSCLC cells H358 and determined the top molecular and cellular functions regulated by these genes with the use of ingenuity pathway analysis, which showed that TPL alters miRNA expression profile in NSCLC cells[43].

miR-21 is one of the earliest miRNA molecules, of which there are now over 700 identified types. The expression of miR-21 is increased in NSCLC. Yang et al. indicated that miR-21 downregulation results in the inhibition of proliferation and migration of NSCLC A549 cells by inducing programmed cell death[44]. Li et al. showed that TPL decreased miR-21 expression in NSCLC cells PC-9[45]. Phosphatase and tensin homolog (PTEN) is a cancer-suppressor gene that is involved in cancer progression. Previous studies have reported the association between PTEN and NSCLC[46]. Li et al. further demonstrated that in PC-9 cells, TPL inhibited miR-21 expression but increased the level of PTEN protein expression further to promoting cell apoptosis[45]. They also found that the effect of TPL on the expression of PTEN protein and cell viability was inhibited when upregulating the expression of miR-21. In a word, TPL influenced NSCLC cell proliferation and apoptosis through PTEN by downregulating miR-21.

TPL DECREASES FAK PROTEIN EXPRESSION AND IMPAIRS DOWNSTREAM SIGNALING

The anticancer effects of TPL described in this article are mostly achieved by regulating the proliferation and apoptosis of cancer cells. In fact, the TPL anticancer mechanism is also involved in cellular movement. Cell migration, a collection of physiological processes, is also a common form of exercise in living cells. Metastasis of cancer cells depends on abnormal activity of the mechanisms of cell migration. Likewise, it is required for cancer cell metastasis to invade and degrade the surrounding tissues and surrounding the extracellular matrix of the basement membrane[47]. Studies demonstrated that TPL treatment decreased metastatic colonization of the lungs and reduced metastatic lesions in the liver, thus suppressing NSCLC cell migration, invasion, and metastasis in vivo. Tail vein injections of H358 cells in NOD SCID mice before intraperitoneal injection of TPL also showed a significantly reduced growth of NSCLC[43].

Focal adhesion kinase (FAK) is an important member of integrin-mediated signal transduction, which plays an important role in tumor cell invasion and is one of the factors that affect cell migration[48]. Reno et al. also found that the activation and expression of FAK were decreased after TPL treatment, which leads to impairment of downstream signaling, including the phosphorylation level of p130Cas and Src[43]. A result showed that PYK2, an ortholog of FAK, could make up for the inhibitory effects of FAK losses. Furthermore, an increase in PYK2 activity can be observed after treatment with FAK inhibitors[49]. Further research is needed to more fully understand this mechanism in the future.

TPL INHIBITS NSCLC BY THE REGULATION OF OTHER MECHANISMS

Previous studies have shown that TPL enhances cell apoptosis and cell cycle arrest activities and contributes to its antitumor effect through the modulation PI3K/Akt and JAK/STAT, which subsequently modulates Bcl-2 family expression[22,50]. On the basis of these studies, the antiproliferative activity exerted by TPL on A549/Taxol cells was due to the modulation of MAPK pathways[23] or inhibition of NF- B-regulated drug-resistant genes[51], thereby improving the Taxol sensitivity and clinical outcomes. Li et al. used an ITRAQ-based proteomics analysis to investigate TPL antitumor activity on NSCLC A549 lung adenocarcinoma cells, revealing that the antitumor effect is achieved by regulating tumor-related protein expression and that TPL blocked A549 cells at the G_2/M phase, promoting cell apoptosis[52].

In addition to the mechanisms described above, there are probably many other TPL anticancer mechanisms that have yet to be discovered. Moreover, for all anticancer mechanisms of TPL, further research and validation of clinical trials are needed. Recent studies indicated that nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated oxidative stress response pathway is associated with tumor cell resistance to chemotherapy. Zhu et al. found that TPL could make NSCLC cells more sensitive toward chemotherapeutics in vitro and in vivo by effectively inhibiting Nrf2 transcriptional activity[53].

In the last decade, it has become clear that epigenetic changes in genome play key roles in promoting every stage of tumorigenesis and cancer progression[54]. This knowledge has triggered pharmacologists to look

for "epigenetic drugs" that could be developed into new cancer therapies. TPL administration could decrease the methylation status of H3 lysine residues in A549 and H460 NSCLC cell lines along with the xenograft model. These downregulated epigenetic changes in H3 promoted the expression of Wnt inhibitory factors, leading to cell growth depression[55]. TPL derivative MRx102 exerts potent antitumor effects by significantly inhibiting the Wnt pathway in NSCLC patient tumors[56]. In addition, using methylation-specific PCR assays, Mao and colleagues found that TPL treatment could directly demethylate Wnt inhibitory factor 1 (WIF1), subsequently inducing apoptosis and inhibiting migration of NSCLC cells A549 and H460[57]. These studies establish that TPL could serve as a prospective novel epigenetic agent in NSCLC and is a prospective novel NSCLC therapeutic.

THE EFFECT OF TPL WATER-SOLUBLE PRODRUG MINNELIDE ON NSCLC CELLS

TPL is a diterpenoid triepoxide from the Chinese herb *T. wilfordii*, possessing anticancer, antifertility, anti-inflammatory, and immunosuppressive properties. However, it cannot be well used in the clinic due to its hydrophobic nature. Therefore, Chugh and colleagues synthetized a water-soluble TPL prodrug called Minnelide[58], and the findings demonstrated that Minnelide could target pancreatic cancer cells and inhibit the function of HSP70 that help tumor growth, thereby blocking the necessary factors for growing and disintegrating pancreatic cancer cells[58]. Subsequent studies further explored the antipancreatic cancer mechanism of Minnelide. One study showed that Minnelide effectively depleted the stromal architecture in pancreatic cancer by inhibiting collagen stabilization and HA synthesis, which eventually resulted in improved vascular function, promoted drug delivery, and enhanced survival of treated KPC ($KRas^{G12D}$; $Trp53^{R172H}Pdx\text{-}1^{Cre}$) mice[59]. In an orthotopic murine model of pancreatic cancer, another study showed combined therapy of low doses of Minnelide and oxaliplatin were superior to either drug alone in the inhibition of tumor growth[60]. In addition, there are studies that show that Minnelide effectively reduced not only the bulk tumor but also $CD133^+$ stem cell population in the KPC mouse model of pancreatic cancer[61], and subsequent studies further confirmed that tumors derived from $CD133^+$ cells in pancreatic ductal adenocarcinoma cell lines responded to Minnelide[62]. Several phase I clinical trials have been completed, and phase II clinical trials are currently ongoing, with promising initial responses (Table 2).

These reports provided promising evidence for studying Minnelide in NSCLC treatment. Most patients diagnosed with NSCLC are already in advanced stages of disease. Hence, chemotherapy becomes a crucial treatment strategy when compared with surgery. Rousalova et al. investigated the therapeutic effect of Minnelide on a murine model of human NSCLC tumors and demonstrated that Minnelide inhibits tumor growth in NSCLC cells and xenograft mouse models[63]. Recent studies have also provided evidence that Minnelide significantly reduced the expression of genes associated with prosurvival and antiapoptosis in NSCLC tumors[64]. Although the precise mechanism of how Minnelide kills NSCLC cells remains ambiguous, Minnelide has been evaluated as a potent chemopreventive drug against pancreatic cancer[65], osteosarcoma[66], prostate cancer[67], and gastric cancer[68] in current preclinical studies. The in vitro and in vivo antitumor

Table 2. Clinical Trials of TLP and its Derivatives in Anticancer Research

Studies	Ref. 79	NCT01927965*	NCT03129139*	NCT03117920*
Type	Phase I (completed)	Phase I (completed)	Phase I (recruiting)	Phase II（recruiting）
Targeted enrolment	20	45	54	35
Tumor type	Advanced solid tumors	Advanced gastrointestinal tumors	Advanced cancer, gastric cancer, breast cancer, pancreatic cancer, prostate cancer metastatic, colorectal cancer, solid tumor, solid carcinoma, solid carcinoma of stomach, cancer of stomach	Pancreatic cancer
Interventions	Drug: F60008	Drug: Minnelide™ 001	Drug: Minnelide™ capsules	Drug: Minnelide
Major findings/ purpose	F60008 cannot be considered the optimal derivative of triptolide	Determined the maximum tolerated dose (MTD), the dose-limiting toxicities (DLT), and the recommended dose for future phase 2 protocol	Research on safety, pharmacokinetics, and pharmacodynamics	To investigate whether it can slow tumor growth in patients with unresponsive pancreatic cancer
Year of registration	–	2013	2017	2017

*Further information can be found at http://clinicaltrials.gov

properties of TPL described above provide favorable evidence for the therapeutic potential of Minnelide as an anticancer drug for NSCLC.

IMMUNE MODULATION BY TPL IN CANCER RESEARCH

Nowadays, due to its low toxicity and inducing the lifelong immune response, immune therapy is changing the current treatment pattern for NSCLC patients, especially with the novel drug development that could modulate immune checkpoint pathways[69]. TPL has multiple promising pharmacological activities including anti-inflammatory, immune modulation, and antiproliferative activity[70]. In an array study, TPL administration has been proven to regulate the expression of 22.5% of 195 immune signaling genes by inhibiting TNF- -induced NF- B activation in RAW 264.7 mouse macrophage cells[71]. Recently, TPL could be used to target senescent malignant cells that escape immunosurveillance by restraining the cytoprotective Nrf2 pathway further to enhance the radiochemotherapy sensitivity in human cancers[72]. In the presence of lipopolysaccharide (LPS), TPL significantly promoted T- and B-cell proliferation and increased macrophage phagocytosis, inducing apoptosis and autophagic cell death of murine leukemia cells WEHI-3 in vivo[73]. Liang et al. found that TPL could promote the reactive immune responses in human breast cancer cells by downregulating programmed death-1 ligand 1 (PD-L1), an important modulator for tumor immune evasion[74]. Though there is no direct evidence, further research should be focused on the detailed immune modulation of TPL in NSCLC patients, which might provide a new understanding of the strategy to improve anti-NSCLC therapeutic effect.

CLINICAL PERSPECTIVE OF TPL

The extensive pharmacological effects of TPL are particularly prominent and widespread in its anticancer activities. Up to now, based on the attractive preclinical pharmacokinetics data[75], several clinical trials about TPL administration for cancer patients are still in progress at present[76] (Table 2). Preclinic study showed that a water-soluble derivative of TPL, PG490-88, could act in synergy with DNA-damaging chemotherapeutic agents, acting as a potential chemosensitizer for the treatment of patients with solid tumors[76]. Wu et al. performed an open clinical study of 103 patients with psoriasis vulgaris who received TPL tablet, and obtained an exciting therapeutic effect with little adverse reactions, apart from slight white blood cell (WBC) decrease in a few patients[77]. Another prospective and controlled study demonstrated the favorable short-term disease remission of TPL in children with severe Henoch–Schonlein purpura nephritis[78]. However, a recent phase I and pharmacological study indicated that intravenous injection of F60008, a semisynthetic derivate of TPL, results in some severe adverse reactions in patients with advanced solid tumors, like lethal immune cell death[79]. Thus, further knowledge should provide more opportunities to evaluate the detailed influence of TPL in cancer patients, and might enable us to improve prognosis and ameliorate side effects. If clinical tests show safety and tolerability, TPL may be approved for a much greater range of applications.

Even though TPL administration could effectively kill cancer cells in vitro and in vivo, their biological effects are easily influenced by many factors, such as the delivery strategy. Studies have shown that development of drug delivery systems (DDSs) can greatly increase the therapeutic effect of TPL, paving the way for TPL toward clinical applications. Recently, a novel intravenous TPL-loaded delivery system, TP-loaded lipid emulsion (TP-LE), has been developed by Li and colleagues. The pharmacokinetic study showed that utility of TP-LE conferred improvements in biodistribution and therapeutic efficacy in pancreatic cancer cells, with reduced toxicity to the normal tissues[80]. Lin et al. developed an anti-carbonic anhydrase IX (CA IX) antibody and CPP33 dual-ligand-modified TPL-loaded liposomes (dl-TPL-lips), and demonstrated that dl-TPL-lip use significantly enhanced tumor cell penetration of TPL and improved TPL anti-NSCLC effect specifically in NSCLC cells A549-Red-FLuc, without apparent systemic toxicity[81]. CA IX-TPL-Lips ameliorated the cellular uptake efficiency, then restrained cell growth of NSCLC A549 cells in vitro and in vivo[82]. Therefore, with the development of improved DDSs, the cytotoxicity effects of TPL in cancer cells could be enhanced, with minimum side effects. Although the development of TPL as drug is still in its infancy, this agent may become economical and practical anticancer therapies in the near future.

CONCLUSION

NSCLC has become one of the most serious diseases that threaten human health, and TPL has shown great potential in the treatment of human NSCLC. Some TPL derivatives are undergoing clinical trials for the treatment of cancer and have broad application prospects. There is a preliminary understanding of the mechanism of the anti-NSCLC activity of TPL, but its exact mechanism of action has not yet been fully elucidated, and further studies are needed, especially in vivo. In conclusion, with TPL cancer prevention and anticancer mechanisms continuing to be studied and recognized in depth, TPL is extremely promising as a new drug in the clinical treatment of NSCLC.

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