Camptothecin

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Abstract As an alkaloid derived from *Camptotheca acuminata*, camptothecin exerted its anticancer activity by specifically targeted topoisomerase I. The intolerable toxicity and poor solubility and stability in vivo of camptothecin limited its clinical application, but the sequential approval of camptothecin derivatives has provided patients with a new selection for the treatment of cancer. Camptothecin is often used in combination with other drugs in clinical application. As one of the most important anticancer drugs derived from plants, camptothecin played an important role in the treatment of cancer with its unique anticancer mechanism and therapeutic effect.

Keywords Camptothecin · Alkaloid · Topotecan · Cancer

Origin: *Camptotheca acuminata* (Fig. 1)
Chemical name (Fig. 2)

4-Ethyl-4-hydroxy-1H-pyrano-[3′,4′:6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione

Molecular formula, $C_{20}H_{16}N_2O_4$; **MW**, 348.35; **CAS**, 7689-03-4

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Properties

Appearance: pale yellow needlelike crystal. *Solubility*: slightly soluble in ethanol and chloroform; poorly soluble in water; camptothecin fails to generate stable salt with acid, whereas it can produce sodium salt which is soluble in water by reacting with heated sodium hydroxide solution. *Melting point*: 264–267 °C.

Camptothecin derivatives (Fig. 3)

Dosage Forms

Camptothecin is recorded in the first edition of the national standards of chemical drugs. At present, several derivatives of camptothecin are used in clinical setting for treatment of malignant tumors, with the main dosage forms being hydroxylcamptothecine injection, irinotecan hydrochloride injection, and topotecan hydrochloride injection.

Indications

It is mainly used in digestive tract tumors and has a good effect on gastric cancer, rectal cancer, and colon cancer. Besides, it can improve the surgical resection of advanced gastric cancer and also has some therapeutic effect on bladder cancer and lung adenocarcinoma. Moreover, camptothecin can be used for treatment of psoriasis, warts, acute and chronic leukemia, and hepatosplenomegaly caused by schistosomiasis.

Literature

Camptothecin is an alkaloid derived from Xi Shu (*Camptotheca acuminata*), which belongs to Nyssaceae. The traditional Chinese medicine *Camptotheca acuminata* (Xi Shu) has been collected in the Compilation of Chinese Herbal Medicine, *Chinese Materia Medica*, and Great Dictionary of Chinese Medicine. *Camptotheca acuminata* (Xi Shu) is widely distributed in the basin of Yangtze river and the southwestern provinces. The main medicinal parts of *Camptotheca acuminata* (Xi Shu) are root bark and fruit, which get rid of heat and toxic materials and eliminate the disease.

History of R&D

In 1966, Wall M E et al. [1] from the United States isolated an alkaloid from *Camptotheca acuminata* and defined its chemical structure. The in vitro anticancer tests revealed the anticancer activity of the tryptophan-terpene alkaloid, which is known as camptothecin and received widely concern. At the beginning of the 1970s, the experimental treatment of human gastric cancer was carried out, and the symptoms of some patients were relieved. However, due to the toxicity and the intolerable side effects such as nausea and vomiting, as well as the reduction anticancer activity of its water-soluble sodium salt, the study of camptothecin has entered a low ebb stage.

The chemical composition of *Camptotheca acuminata* is very complex, but the main active ingredients are alkaloids. So far, various alkaloids like camptothecin, 10-hydroxycamptothecin, methoxy-camptothecin, and venoterpine have been isolated from *Camptotheca acuminata*. In addition, the camptothecin and methoxy-camptothecin have also been found in some other plants, such as Apocynaceae *Heynea Ervatamia*, Icacinaceae smelly *Nothapodytes obtusifolia*, and Rubiaceae *Ophiorrhiza japonica*.

The natural resources of *Camptotheca acuminata* are very limited, and the content of camptothecin is very low, which limited the extraction and application of camptothecin. In 1975, Corey et al. first opened the door for the chiral synthesis of camptothecin, but the reaction step was long and the yield rate was very low [2]. It was not until 1997 that Ciufolini et al. developed a new method for the synthesis of camptothecin by five steps, with a total yield rate up to 51%. The great breakthrough in the chemical synthesis of camptothecin has made its extensive application become a reality [3].

A study in the 1970s found that the synthesis of DNA and RNA in mammalian cells can be inhibited by camptothecin, whereas the removal of the alkaloid could restore the DNA and RNA synthesis function. It is speculated that camptothecin may exert a direct effect on the S phase of cell replication.

In 1985, Hsiang et al. found that CPT can directly inhibit topoisomerase I (topo I), which is an enzyme involved in DNA replication and transcription. Topoisomerase I was closely related to cell division, and blocking its enzyme activity can inhibit growth of cancer cell [4]. The anticancer mechanism of camptothecin by targeting topoisomerase I has created a new breakthrough point and led to a new upsurge in the study of camptothecin.

Hydroxycamptothecin, as a camptothecin derivative with a hydroxyl group on the tenth carbon atom, is widely used for the treatment of various cancers. In 1969, researchers from Shanghai Institute of Materia Medica found that hydroxycamptothecin possessed potent anticancer activity and low toxicity. And this finding promoted the production and clinical application of hydroxycamptothecin, but its usage was interrupted for technology and quality [5]. In the 1980s, hydroxycamptothecin

was reproduced for clinical application with an improvement in producing technology, and hydroxycamptothecin got its approval number in 1986 for clinical usage in China. In the 1990s, the US Food and Drug Administration approved the clinical application of topotecan and irinotecan, which played a significant role in the prevention and treatment of cancers [6].

Pharmacology

The pharmacology of camptothecin was mainly manifested as antitumor activity. Camptothecin specifically targeted topoisomerase I and exerted anticancer activity by inhibiting the synthesis of DNA. Camptothecin mainly influenced the S phase of cell cycle and was considered as a specific inhibitor agent of cell cycle. The results of animal experiments showed that camptothecin had some inhibitory effects on leukemia, Yoshida sarcoma, and Ehrlich ascites carcinoma.

Previous clinical trials showed that camptothecin and its analogs have therapeutic effects on bladder cancer, brain cancer, breast cancer, cervical cancer, colon cancer, neural stromal tumor, lymphoreticulosis, lung cancer, leukemia, lymphoma, melanoma, ovarian cancer, pancreatic cancer, pediatric cancer, prostate cancer, and liver cancer [7].

Injection of camptothecin (2.5 mg/ml, 5–10 mg/day) with a treatment course of 140 mg achieved effective rate of 44.8% and 38.3% for gastric cancer and colon cancer, respectively. Hydroxycamptothecin can be used for the prevention and treatment of gastric, liver, head, and neck cancer and leukemia, and the effective rate is 44% [6]. In addition, the dimethyl sulfoxide solution of camptothecin was also successfully used for treatment of psoriasis.

Clinical Application

Because of the toxicity and side effects of camptothecin, the currently used agents in clinical applications are camptothecin derivatives like topotecan, irinotecan, and hydroxycamptothecin. Topotecan, a water-soluble camptothecin derivative developed by SmithKline Beecham, was approved by FDA in 1996 for the treatment of ovarian cancer. As another water-soluble camptothecin derivative approved by FDA in 1996, irinotecan was mainly used in the treatment of advanced colorectal cancer. In addition, it was also shown to have obvious inhibitory effect on small cell lung cancer and leukemia [8]. Hydroxycamptothecin possesses a broad-spectrum antitumor activity and was clinically used for intravesical therapy of bladder cancer. In addition, it has remarkable curative effect on colon cancer, breast cancer, gastric cancer, and leukemia.

Discussion

With an increasing morbidity and mortality, cancer becomes one of the most serious diseases threatening human health. Camptothecin has been shown to exert anticancer effect by targeting topoisomerase I, thus providing a new thinking for cancer therapy. The intolerable toxicity and poor solubility and stability in vivo of camptothecin limited its clinical application, but the sequential approval of camptothecin derivatives has provided patients with a new selection for the treatment of cancer. There is no obvious cross drug resistance between camptothecin and other most commonly used anticancer drugs. Camptothecin is often used in combination with other drugs in clinical application. As one of the most important anticancer drugs derived from plants, camptothecin played an important role in the treatment of cancer with its unique anticancer mechanism and therapeutic effect.

Fig. 1 *Camptotheca acuminata*

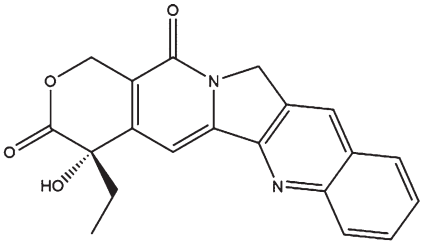

Fig. 2 Chemical structure of camptothecin

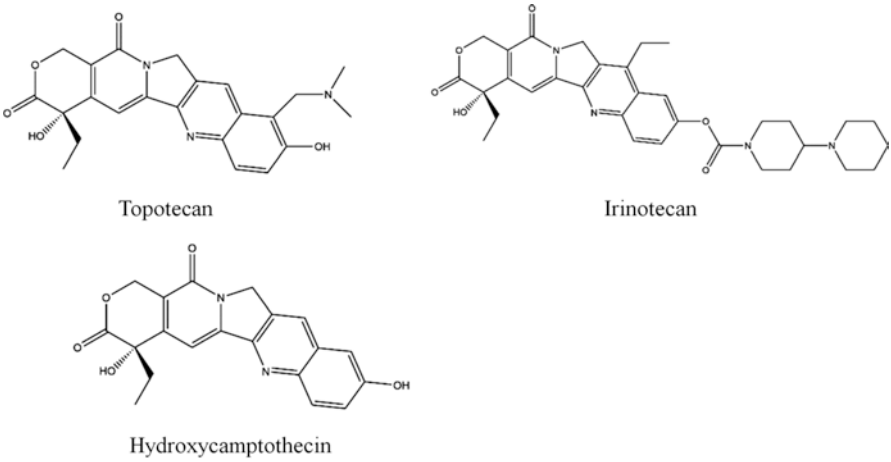

Fig. 3 Chemical structure of camptothecin derivatives

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