Nano particle drug delivery system for Irinotecan in colorectal cancer

Balasubramanian J1,2*, Narayanan N2, Shahul hammed maraicar K1, Vijaya kumar N1, Azhagesh raj K1

1. Shield Health Care Pvt Ltd, Chennai-600095, Tamil Nadu, India
2. Periyar Maniammai University, Thanjavur-613403, Tamil Nadu, India

*Corresponding author: Balasubramanian, J, Shield Health Care Pvt Ltd, Chennai-600095, India, jvbalpharm@yahoo.co.in

Received 12 June; accepted 15 July; published online 01 August; printed 16 August 2012

ABSTRACT

Colorectal cancer is cancer that starts in either the colon or the rectum. Colon cancer and rectal cancer have many features in common. Colorectal cancer has long been considered as moderately resistant to chemotherapy, where the drug Irinotecan is used for colorectal cancer. Irinotecan is a water-soluble camptothecin analogue. The parent camptothecin was shown to have promising activity in an anti-cancer setting when it was discovered and there has been much interest and research into the various camptothecins in the years following, specifically with aim to increase the deliverable dose and to limit toxicities associated with use. This article reviews a number of approaches to formulate the camptothecins using NDDS approaches to allow for enhanced delivery, uptake and activity while potentially also reducing toxicity. CPT binds to the TOP1 nicked DNA complex and stabilizes it. This prevents re-ligation of the nicked strand to result in the formation of irreversible double stranded breaks.

Keywords: CPT-Camptothecin; TOP1- Topoisomerase 1; DNA- Deoxyribonucleic acid; NDDS -Nano particulate drug delivery systems.

Abbreviations: AUC - Area under curve; CED – Convection Enhanced Delivery; CPT - Camptothecin; DNA - Deoxyribonucleic acid; DSPC - Distearoylphosphatidylcholine; EPR - Enhanced Permeation And Retention; FAP - Familial Adenomatous Polyposis; FDA - Food and Drug Administration; HT 29 - Human Colon Carcinoma Cells; MPS - Mononuclear phagocyte system; NDDS - Nanoparticulate drug delivery systems; NP - Nanoparticles; SOS-sucrose octasulfate; TOP1-Topoisomerase.

1. INTRODUCTION

Cancer in the colorectal is the disease characterized by the development of malignant cells in the lining or epithelium of the first and longest portion of the large intestine. Malignant cells have lost normal control mechanisms governing growth. These cells may invade surrounding local tissue, or they may spread throughout the body and invade other organ systems. Colorectal cancer has long been considered as moderately resistant to chemotherapy. Previously 5-fluorouracil was the only proven treatment for this indication, but it has been slowly replaced by other drugs. It is hoped these newly the approved regimens will provide the building blocks for the combination chemotherapy of the future.

Irinotecan is a water-soluble camptothecin analogue. CPT is a quinoline alkaloid derived from the bark, wood and fruit of the Asian tree Camptotheca acuminata (Wall & Wani, 1995). Initial preclinical testing in mouse L1210 leukemia and rat Walker carcinosarcoma models showed promising results in terms of tumor inhibition (ME Wall, 1966). This was followed by early clinical trials carried out in mid 1970s that demonstrated partial success, but which were subsequently discontinued due to serious toxicity concerns. Research continued to provide information about the structure and biological activity of this molecule however it was not until the mid 1980s when the mechanism of action of CPT was fully understood and interest in use of camptothecin as a therapeutic was rekindled (Hsiang et al., 1985; Hsiang & Liu, 1988; Hsiang et al., 1989). In 1996 the FDA approved Irinotecan and topotecan for the treatment of colon, lung, breast and ovarian cancers (Saltz et al., 2000; Gore et al., 2001).

2. COLORECTAL CANCER

2.1. Symptoms

Blood in the stool and narrower stools are a change in bowel habits and general stomach discomfort. However, may not have symptoms at first, so screening is important. Everyone who is 50 or older should be screened for colorectal cancer. Colonoscopy is one method that your doctor can use to screen for colorectal cancer. Treatments for colorectal cancer include surgery, chemotherapy, radiation or a combination.

- Polyps - growths inside the colon and rectum that may become cancerous
- A diet that is high in fat
- A family history or personal history of colorectal cancer
- Ulcerative colitis or Crohn's disease

2.2. Pathophysiology

Colon cancer arises from mucosal columnar polyps. The critical parameter of polyps in terms of natural history, particularly malignant potential, is histology. The two most common histologic types are hyperplastic and adenomatous. Histologically, hyperplastic polyps contain an increased number of glandular cells with decreased cytoplasmic mucus, but lack nuclear hyperchromatism, stratification, or atypia (Tsi et al., 1995). Adenomatous nuclei are usually hyperchromatic, enlarged, cigar-shaped, and crowded together in a palisade pattern. Adenomas are classified as tubular or villous. Histologically, tubular adenomas are composed of branched tubules, whereas villous adenomas contain digitiform villi arranged in a frond. Tubulovillous adenomas contain both elements. Virtually all colon cancers arise from adenomas as demonstrated by multiple epidemiologic, clinical, and pathologic findings. First, about one third of operative specimens containing colon cancer contain one or more synchronous adenomas,
Colon cancer: Cancer of the colon is the disease characterized by the development of malignant cells in the lining or epithelium of the first and longest portion of the large intestine. Malignant cells have lost normal control mechanisms governing growth. These cells may invade surrounding local tissue, or they may spread throughout the body and invade other organ systems.

2.3. Staging colorectal cancer
If cancer is detected, it will be 'staged' a process of finding out how far cancer has spread. Tumor size may not correlate with the stage of cancer. Staging also enables your doctor to determine what type of treatment you will receive.

- Stage 0 - Cancer is only in the innermost lining of the colon or rectum
- Stage I - Cancer has not spread beyond the inner wall of the colon or rectum
- Stage II - Cancer has spread into the muscle layer of the colon or rectum
- Stage III - Cancer has spread to one or more lymph nodes in the area
- Stage IV - Cancer has spread to other parts of the body, such as the liver, lung, or bones. This stage does NOT depend on how deep the tumor has penetrated or if the disease has spread to the lymph nodes near the tumor (Fig. 1)

2.4. Pathology and histology
Colon cancers are classified as well-differentiated, moderately well differentiated, or poorly differentiated on the degree of preservation of normal glandular architecture and cytologic features. Progressively more poor differentiation is presumably a histologic marker of further underlying genetic mutations, but the mutations associated with poor differentiation are currently unknown. About 20% of cancers are poorly differentiated. They have a poor prognosis (Deans et al., 1994). About 15% of colon cancers are classified as mucinous or colloid because of prominent intracellular accumulation of mucin. These cancers are more aggressive (Kanazawa et al., 2002).

2.5. Epidemiology
Colon cancer is the second most common cause of mortality from cancer. The lifetime risk of colon cancer is about 1 in 17 (Jemal et al., 2004). Colon cancer incidence declined by about 2% per annum in America from 1985 through 1995, but has increased recently (Hawk et al., 2002). This probably reflects increased detection through screening programs (Cappell & Goldberg, 1992). If so, the incidence should begin to decline again in several years as the benefits of aggressive screening colonoscopy become manifest. Colon cancer has numerous environmental and demographic risk factors (Jemal et al., 2004). Environmental factors play a major etiologic role in colon cancer despite the importance of genetic mutations in colon cancer pathogenesis. Environmental factors presumably modulate the risk of the genetic mutations responsible for colon cancer, although the precise molecular mechanisms are currently unknown. The incidence of colon cancer exhibits a striking geographic variation: the age-adjusted incidence varies by up to 15-fold among different countries (Ziegler et al., 1986). Industrialized nations, except Japan, have the highest incidence, whereas South American countries and China have a relatively low incidence (Jemal et al., 2004). The wide variation in incidence is largely attributed to national differences in diet and other environmental factors (Tamura et al., 1996). In contrast to native Japanese, descendants of Japanese immigrants to America have, like other Americans, a high incidence of colon cancer attributed to dietary and other environmental adaptations. Indeed, the incidence of colon cancer has recently increased in native Japanese attributed to their adopting a Westernized diet and other environmental changes with industrialization (Tamura et al., 1996). The incidence of colon cancer attributed to dietary and other environmental changes with industrialization (Tamura et al., 1996). Native American Indians have a significantly lower risk. The incidence is slightly higher in American men than women (Gatof & Ahnen, 2003). The incidence of colon cancer rises sharply with age, beginning at age 50 years (Miller et al., 1983). This phenomenon is attributed to accumulation of chance somatic mutations with age.

3. Nanoparticulate drug delivery systems of camptothecins
3.1. Preclinical studies

Camptothecin was discovered and there has been much interest and research into the various camptothecins analogue. The parent camptothecin was shown to have promising activity in an anti-cancer.
IRINOTECAN CHEMISTRY

Irinotecan hydrochloride is (4S)-11-diethyl-4-hydroxy-9-(4-piperidino) 1-carboxyloxy)-1H-pyran-3'-4',6'-7',8'-7,6'-6-[6-(4,11-dioxa, 3,14(4H,12H) diode hydrochloride, a water-soluble analog of camptothecin with high antitumor activity. It is a pale yellow to yellow crystalline powder, with the empirical formula C_{36}H_{50}N_{10}O_{2}·HCl·3H_{2}O and a molecular weight of 677.19.

7-Ethyl-10-hydroxy-camptothecin (SN-38), a metabolite of Irinotecan x HCl, is poorly soluble in aqueous solutions and practically insoluble in most physiologically compatible and pharmaceutically acceptable solvents. Formulation of SN-38 in concentrated pharmaceutical delivery systems for parenteral administration is thus very difficult. Due to their biocompatibility and low toxicity, liposomes were considered for the delivery of SN-38. In this study, pegylated liposomes with containing SN-38 were prepared and their characteristics, such as particle size, encapsulation efficiency, in vitro drug release and bio distribution, were investigated. The particle size of liposomes was in the range of 150-200 nm. The encapsulation efficiency and in vitro release rate of pegylated liposomes was higher than those of non-pegylated liposomes. As expected, the distribution of pegylated liposomes in body organs such as liver, kidney, spleen and lung was considerably lower than that of non-pegylated liposomes. Also, their blood concentration was at least 50% higher than that of non-pegylated liposomes.

3.2. Irinotecan

The numerous pre-clinical as well as early clinical studies, pharmaceutical nanotechnology has emerged as a very promising platform in the field of drug delivery. The success of NDDS has been reflected in the regulatory approval of number of nanopharmaceuticals in the last decade. Lipid based carriers and biopharmaceutical polymers have emerged as two of the more promising options following impressive achievements liposomal and micellar formulations. The potential of liposomal carriers to improve the therapeutic activity of anticancer drugs has become increasingly established.

The effective delivery of drugs to the target tumor site, nanoparticles should remain in the circulation for extended time without getting eliminated by either renal or hepatic mechanisms. EPR based targeting relies on exploiting the leaky vasculature present at the tumor site (Fig.2). Neovascularization developed around tumor masses typically has defective vascular architecture with large gaps in normally tightly packed endothelial cell junctions and is accompanied with impaired lymphatic clearance. Thus macromolecules in the circulation with particle diameter below 600 nm can be selectively extravasated to the tumor interstitial spaces through this leaky tumor vasculature. The absence of an active lymphatic network prevents clearance of extravasated macromolecules from tumor interstitium. However, for the EPR effect to take place the size of macromolecules should also be large enough to bypass renal clearance (Li et al., 1993). The size of macromolecules also plays an important role in extending the circulation time and avoiding rapid clearance by macrophages and cells of MPS as the size of sinusoids in the spleen and kuffer cells in liver varies between 150-200 nm. Small molecule drugs can thus be optimized for extended circulation and tumor delivery by virtue of encapsulation or conjugation in custom designed nanoparticles that are approximately 100 nm in size. While this method of passive targeting is effective, issues of specificity and intracellular drug delivery still exist. Active targeting by incorporating ligands or antibodies specific to antigens or growth factors overexpressed by tumor cells either directly on the surface of the drug molecules or nanoparticles carrier is currently being pursued to get around these issues with varying degree of success (Drummond et al., 1999). Irinotecan is currently used clinically in the treatment of colorectal and lung cancers. It is an active pro-drug that undergoes carbonylase mediated conversion to the more active SN-38 metabolite. Both Irinotecan and SN-38 are sensitive to the hydrolytic conversion of the lactone form to inactive carboxy methylate as that of other CPTs. Several liposomal formulations of Irinotecan have been prepared with varying degree of success and are being evaluated preclinically or clinically (Messerer et al., 2004). This formulation showed greater than 95% Irinotecan loading efficiency at a D/L of 0.2. When evaluated pharmaceutically, Irinophore showed 8-fold increase in 1/2, a 100-fold increase in Cmax, a 1,000-fold increase in AUC and a 1,000-fold decrease in clearance of the active lactone form of Irinotecan (Ramsay et al., 2006). The efficacy of Irinophore has been evaluated in multiple different xenograft tumor models following single-dose treatment, three doses administered at 4-day intervals, or three doses administered at 7-day intervals (Ramsay et al., 2006). Delay in the time required for tumors to reach four times their original size was used as a marker of activity. Irinophore showed significantly greater delay in tumor progression than free Irinotecan at equivalent dose of 40 mg/kg in all five models tested with most striking values observed in HT-29 and Capan-1 models (Drummond et al., 2006). These liposomes achieved loading efficiency of >800 g Irinotecan per mole of phospholipid and high drug retention ability as observed from in vivo drug release 1/2 of 56.8 h. Further pharmacokinetic analysis following i.v. administration of polyphosphate or SOS in Sprague-Dawley rats showed impressive results with plasma t1/2 of 7 and 11 h, respectively and AUC increases of 200 and 300-fold respectively over that of free Irinotecan. The authors have utilized the CED technique to overcome blood brain barrier limitations to drug delivery to successfully increase levels of formulated irinotecan and doxorubicin delivered to rat brain tissue and further, demonstrated a significant survival advantage in rats bearing orthotopic brain tumor xenografts (Krauze et al., 2007). In recognition of the majority of cancer therapy relying on combinations of two or more drugs, particularly when considering regimens containing Irinotecan, Celator Pharmaceuticals has developed a single liposomal formulation with both Irinotecan and flouxuridine encapsulated within the same DSPC/DSPG/Cholesterol based vesicles at levels designed to optimize a synergistic ratio as defined in vitro (Tardi et al., 2007). This formulation has progressed through Phase I testing and was found to be well tolerated, with the desired plasma drug ratio of 1:1 being maintained for up to 24 hours post administration (Balist et al., 2009).

3.3. PEG-SN38

SN38 is the active metabolite of the widely used cancer drug Irinotecan. Although unmodified SN38 is 1,000 times more potent than Irinotecan, it has not been converted into a viable drug candidate because it is insoluble. Using new PEylation technology, the PEG-SN38 is developed, which results in a compound with excellent pharmaceutical properties as shown in animal models: increased solubility, higher exposure, and longer half-life than unmodified SN38. Preclinical data presented at the 18th annual, European Organization for Research and Treatment of Cancer-National Cancer Institute-American Association for Cancer Research, meeting showed that these features led to greater efficacy over camptothecins derivative in breast, colorectal and pancreatic cancer models.

3.3.1. Antitumor properties of Irinotecan-containing nanoparticles prepared using poly (DL-lactic acid) and poly (ethylene glycol)-block-poly (propylene glycol)-block-poly (ethylene glycol)
3.3.1. Pharmacokinetic of irinotecan

This article reviews the clinical pharmacokinetics of a water-soluble analogue of camptothecin, irinotecan [CPT-11 or 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carboxyloxy-camptothecin]. Irinotecan, and its more potent metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin), interfere with mammalian DNA topoisomerase I and cancer cell death appears to result from DNA strand breaks caused by the formation of cleavable complexes. The main clinical adverse effects of Irinotecan therapy are neutropenia and diarrhoea. Irinotecan has shown activity in leukaemia, lymphoma, and the following cancer sites: colorectum, lung, ovary, cervix, pancreas, stomach and breast. Following the intravenous administration of Irinotecan at 100 to 350 mg/m², mean maximum Irinotecan plasma concentrations are within the 1 to 10 mg/L range. Plasma concentration can be modelled using a 2- or 3-compartment model with a mean terminal half-life ranging from 5 to 27 hours. The volume of distribution at steady-state (Vss) ranges from 136 to 255 L/m², and the total body clearance is 8 to 21 L/h/m². Irinotecan is 65% bound to plasma proteins.

The areas under the plasma concentration-time curve (AUC) of both Irinotecan and SN-38 were increase proportionally to the administered dose, although interpatient variability is important. SN-38 levels achieved in humans are about 100-fold lower than corresponding Irinotecan concentrations, but these concentrations are potentially important as SN-38 is 100- to 1000-fold more cytotoxic than the parent compound. SN-38 is 95% bound to plasma proteins. Maximum concentrations of SN-38 are reached about 1 hour after the beginning of a short intravenous infusion. SN-38 plasma decay follows closely that of the parent compound with an apparent terminal half-life ranging from 6 to 30 hours. In human plasma at equilibrium, the Irinotecan lactone form accounts for 25 to 30% of the total and SN-38 lactone for 50 to 64%. Irinotecan is extensively metabolised in the liver. The bipiperidino-carboxyloxy group of Irinotecan is first removed by hydrolysis to yield the corresponding carboxylic acid and SN-38 by carboxysterase. SN-38 can be converted into SN-38 glucuronide by hepatic UDP-glucuronyltransferase. Another recently identified metabolite is 7-ethyl-10-[4-N-(3-aminopentanoyl)-1-piperidino]-carboxyloxy-camptothecin (APC). This metabolite is a weak inhibitor of KB cell growth and a poor inducer of topoisomerase I DNA-cleavable complexes (100-fold less potent than SN-38).

Numerous SN-38 metabolites have been detected in bile and urine. The mean 24-hour Irinotecan urinary excretion represents 17 to 25% of the administered dose. Recovery of SN-38 and its glucuronide in urine is low and represents 1 to 3% of the Irinotecan dose. Cumulative biliary excretion of Irinotecan is only 2% for SN-38 glucuronide and about 1% for SN-38. The pharmacokinetics of Irinotecan and SN-38 are not influenced by prior exposure to the parent drug. The AUC of Irinotecan and SN-38 correlate significantly with leuko-neutropenia and sometimes with the intensity of diarrhoea. Certain hepatic function parameters have been correlated negatively with Irinotecan total body clearance. It was noted that most tumour responses were observed at the highest doses administered in phase I trials, which indicates a dose-response relationship with this drug. In the future, these pharmacokinetic-pharmacodynamic relationships will undoubtedly prove useful in minimising the toxicity and maximise the likelihood of tumour response.

3.3.4. Pharmacogenetics of irinotecan

At the present time, pharmacogenetic investigation of Irinotecan (CPT-11, Camptosar) therapy is mainly focused on the clinical relevance of genetic variation in the UDP-glucuronosyltransferase (UGT1A1) gene. The glucuronidation of the potent topoisomerase I inhibitor SN-38 is a major inactivation pathway of Irinotecan metabolism. UGT1A1 genotypes associated with Gilbert’s syndrome (a mild intermittent hyperbilirubinemia) are characterized by reduced glucuronidation of SN-38. Such UGT1A1 genetic variants have different distribution across individuals of different ethnicity. The (T)₃₄₅ TA₆ polymorphism of the promoter is more frequent in Caucasians as compared to Asians, in whom missense polymorphisms in the exons are more common. Two recent pharmacogenetic trials (one performed in the United States and the other in Japan) investigated the clinical significance of UGT1A1 gene mutations for both the pharmacokinetics of Irinotecan metabolites and the toxicity profile. The results of these association studies showed that preliminary genotyping of the (T)₃₄₅ TA₆ polymorphism might predict the occurrence of toxicity in genetically predisposed patients.

3.3.5. Nanoparticle drug delivery system for intravenous delivery of TOP-1 inhibitors

Camptothecin-based drugs, because of their poor solubility and labile lactone ring, pose challenges for drug delivery. The purpose of this research was to develop a nanoparticle delivery system for camptotheca alkaloids. Initial investigations SN-38 was selected as the candidate camptotheca alkaloid for further development. Nanoparticles comprising SN-38, phospholipids and polyethylene glycol were developed and studied in vitro and in vivo. The SN-38 formulations were stable in human serum albumin and high lactone concentrations were observed even after 3 h. In vivo studies in nude mice showed prolonged half-life of the active (lactone form) drug in whole blood and increased efficacy compared to Camptosar in a mouse xenograft tumor model.

3.3.6. Toxicity

Irinotecan is a camptothecin analog used as an anticancer drug. Severe, potentially life-threatening toxicities can occur from Irinotecan treatment. Although multiple genes may play a role in Irinotecan activity, the majority of evidence to date suggests that variation in expression of UGT1A1 caused by a common promoter polymorphism (UGT1A1) is strongly associated with toxicity; however, this link is dose dependent. Variations in other pharmacokinetic genes, particularly the transporter ABCC2, also contribute to Irinotecan toxicity. In addition, recent studies have shown that pharmacodynamic genes such as TDP1 and XRCC1 can also play a role in both toxicity and response.
3.3.7. Pharmacogenetics of Irinotecan disposition

Irinotecan (CPT-11) is a widely used anticancer drug, especially for the treatment of colorectal cancer. Irinotecan is considered an inactive prodrug that requires activation to the active metabolite SN-38. Patients treated with Irinotecan occasionally experience severe neutropenia and delayed diarrhea, and the occurrence of these adverse reactions is unpredictable and still largely unexplained. Various studies have demonstrated a relationship between SN-38 pharmacokinetics and the experienced toxicity. In recent years, polymorphisms in UDP-glucuronosyltransferase (UGT) 1A1, an enzyme involved in SN-38 glucuronidation, has been linked to interindividual pharmacokinetic variability and Irinotecan toxicity. In addition, variants in other genes encoding drug-metabolizing enzymes or transporters that are involved in the disposition of Irinotecan may play a crucial role in the pharmacokinetic and pharmacodynamic profile of Irinotecan. In this review, we provide an update on the pharmacogenetics of Irinotecan.

3.3.8. Insights, challenges, and future directions in irinogenetics

Irinotecan is widely used in the treatment of metastatic colorectal cancer and extensive small-cell lung cancer. Its use is limited by severe toxicities such as neutropenia and delayed-type diarrhea. Irinotecan is converted to its active metabolite SN-38. SN-38 is further metabolized to SN-38G by various hepatic and extrahepatic UGT1A isozymes, mainly UGT1A1. Impaired glucuronidation activity of the UGT1A1 enzyme has been linked with elevated levels of SN-38, leading to toxicities. UGT1A1 involves an extra TA repeat in the UGT1A1 promoter region and is the variant most frequently contributing to interpatient variability in Irinotecan pharmacokinetics and toxicities. This information led to the revision of the Irinotecan label by the US Food and Drug Administration. Recently, UGT1A1 seems to contribute to the risk of toxicity of Irinotecan in Asian patients. The pharmacogenetics of Irinotecan (irinogenetics) is one of few promising examples of the application of pharmacogenetics to individualized drug therapy. This review summarizes ongoing studies and unanswered questions on irinogenetics.

4. CONCLUSION

Nanoparticulate drug delivery systems are being actively researched and applied to the use of Irinotecan in oncology therapy. While liposomal systems are certainly more advanced in general terms, with several formulations marketed for various indications, including cancer, research in micellar and other polymer based formulations is rapidly advancing and it is likely that one or more of these formulations will progress successfully through clinical testing in the near future. This paper has provided an overview of research on Irinotecan in nanoparticulate drug delivery system with the help of various polymers as a carrier molecule in targeting the colorectal cancer cells, there by bioavailability of the drug can be improved well. Making the formulation as a nano particle drug delivery system can improve the therapeutic efficacy, reducing the ADR, improving the stability of formulation. It is concluded that NP’s are called as smart bombs in colorectal cancer therapy. These types of formulations enable the delivery of higher amounts of drugs to target tissues by virtue of the pharmacokinetic properties of the carrier and may also reduce toxicity to non-target tissues.

SUMMARY OF RESEARCH

1. This paper has provided an overview of research of Nanoparticulate drug delivery systems on Irinotecan, in the treatment of colorectal cancer cells.
2. These types of formulations enable the delivery of higher amounts of drugs to target tissues by virtue of the pharmacokinetic properties of the carrier and may also reduce toxicity to non-target tissues.

FUTURE ISSUES

1. Can we develop a simple, safe, and effective preventive measure for colorectal cancer.
2. In future can we develop more bio availability and bioequivalence studies?
3. Can we improve the drug metabolism and pharmacokinetics (DMPK) studies?

DISCLOSURE STATEMENT

No financial support for research.

ACKNOWLEDGMENTS

I express my heartfelt thanks to Mr Mahadavan, Dhamodar singh in Shield Health Care Pvt Ltd, Chennai-600095, India

REFERENCES

Chabot (1997). This article reviews the clinical pharmacokinetics of a water-soluble analogue of camptothecin, irinotecan (CPT-11 or 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin), interferes with mammalian DNA topoisomerase I and cancer cell death appears to result from DNA strand breaks caused by the formation of cleavable complexes. The main clinical adverse effects of irinotecan therapy are neutropenia and diarrhoea. Irinotecan has shown activity in leukaemia, lymphoma and the following cancer sites: colorectum, lung, ovary, censix, pancreas, stomach and breast.


Heald RJ, Bussey HJR. Clinical experiences at St. Mark’s Hospital with multiple synchronous cancers of the colon and rectum. Dis. Colon Rectum., 1975, 18, 6-10.


Balasubramanian et al.
Nanoparticle drug delivery system for irinotecan in colorectal cancer.
www.discovery.org.in/ds.htm