International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR |Volume 3 | Issue 1 | Jan-Mar- 2015
www.ijamscr.com

Review article ***Medical research***

Liver cancer: Recent developments in diagnosis and treatment

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ABSTRACT

Only cancers that start in the liver are called liver cancer (hepatocellular carcinoma). Liver cancer is the third leading cause of cancer death and the fifth most common solid tumor worldwide. Its incidence has increased dramatically in the past few years in all over the world. Despite advances in surgical and nonsurgical therapies in the treatment of liver cancer, a number of controversial issues regarding appropriate screening methods, diagnosis, staging, and management continue to evolve.[1] The aim of this review is to help the practicing Pharm D students, clinical pharmacist and physicians to identify high-risk patients, implement an appropriate screening strategy, order relevant tests to confirm the diagnosis, and formulate an appropriate management plan which include newer treatment options like virus therapy, nano knife, magnetic targeting, therasphere etc.

Keywords: Liver Cancer, Virus Therapy, Cancer Spotters, Magnetic Targeting, Nanoknife, Therasphere.

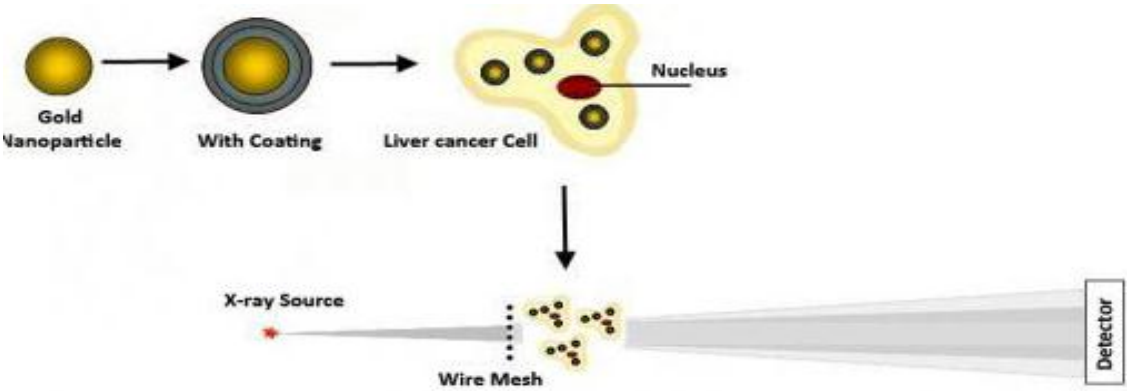
INTRODUCTION

Liver cancer or hepatic cancer (from the Greek hēpar, meaning liver) is a cancer that originates in the liver. Globally, as of 2010, liver cancer resulted in 754,000 deaths, up from 460,000 in 1990, making it the third leading cause of cancer death after lung and stomach. Of these deaths 340,000 were secondary to hepatitis B, 196,000 were secondary to hepatitis C, and 150,000 were secondary to alcohol. Primary liver cancer (hepatocellular carcinoma) tends to occur in livers damaged by birth defects, alcohol abuse, or chronic infection with diseases such as hepatitis B and C, hemochromatosis (a hereditary disease associated with too much iron in the liver), and cirrhosis. More than half of all people diagnosed with primary liver cancer have cirrhosis -- a scarring condition of the liver commonly caused by alcohol abuse. Hepatitis B and C and hemochromatosis can cause permanent damage and liver failure. Liver cancer may also be linked to obesity and fatty liver disease. Various cancer-causing substances are also associated with primary liver cancer, including certain herbicides and chemicals such as vinyl chloride and arsenic. Smoking, especially if you abuse alcohol as well, also increases risk. Aflatoxins, cancer-causing substances made by a type of plant mold, have also been implicated. Aflatoxins can contaminate wheat, peanuts, rice, corn, and soybeans. Other causes include the hormones and rogen and estrogen and a dye formerly used in medical tests called thorotrast. The main symptoms of liver cancer includes weight loss for no known reason swelling or pain in tummy, jaundice (yellow skin

and eyes), dark-coloured urine, pale-coloured stools (bowel motions), nausea, vomiting, loss of appetite, fever or sweating, feeling more tired than usual, pain in shoulder. Liver cancer often is challenging to diagnose. It usually has no symptoms in the early stages, and tumors often cannot be felt from outside the body. The usual diagnostic methods include blood tests, imaging techniques includes CT scan, angiogram, and biopsy. Treatment options are surgery (partial hepatectomy or liver transplant), tumor ablation, tumor embolization, and radiation therapy, and targeted therapy, chemotherapy using drugs like doxorubicin (Adriamycin), 5-fluorouracil, and cisplatin.

RECENT DEVELOPMENTS IN DIAGNOSIS

Gold nanoparticles help earlier diagnosis of liver cancer -cancer spotter



A new diagnostic technique that can spot tumor-like masses as small as 5 millimeters in the liver. Gold nanoparticles with a polyelectrolyte coating can make smaller tumors more visible through X-ray scatter imaging, enabling earlier diagnosis of liver cancer. The gold nanoparticles of 10 and 50 nanometers in diameter are used and ringed them with a pair of 1-nanometer polyelectrolyte coatings. The coating gave the nanoparticles a charge, which increased the chances that they would be engulfed by the cancerous hepatic cells. Once engulfed, X-ray scatter imaging is used to detect the gold nanoparticles within the malignant cells. In lab tests, the nontoxic gold nanoparticles made up just 0.0006 percent of the cell's volume, yet the nanoparticles had enough critical mass to be detected by the X-ray scatter imaging device.

Glypican-3 targeting using multifunctional nanoparticles in liver cancer

Imaging is important in accurately detecting, staging, and treating liver cancer, one of the most prevalent and lethal malignancies. GPC3 is a heparan sulfate proteoglycan essential in regulating embryonal cell growth, as evidenced by its mutation causing the Simpson-Golabi-Behmel overgrowth syndrome [2]. While its expression is absent in normal adult tissues, GPC3 is significantly over-expressed in up to 80% of human HCC's [3,4,5]. Attached to the cell membrane via a glycosyl phosphatidylinositol anchor, GPC3 is readily accessible for antibody-mediated targeting and binding [3, 6]. Moreover, GPC3 has been shown to promote HCC growth by stimulating the canonical Wnt signaling pathway, exhibiting potential as an important therapeutic target [6,7]. These auspicious attributes make GPC3 an ideal biomarker for HCC targeting. This novel NP construct has a number of advantages in its design and application. First, the target ligand GPC3 is a proteoglycan expressed on the cell surface of most HCCs, potentially making it widely applicable to most HCC patients. In contrast, normal adult human cells and tissues, and even dysplastic nodules found in cirrhotic livers that often account for indeterminate lesions encountered on conventional CT or MR imaging, lack GPC3 expression, making GPC3 a potentially powerful tool to discriminate between these benign entities and HCC[8]. Secondly, the characteristics of the NP construct are optimal for targeted delivery to the cells of interest, and an ideal target-specific imaging contrast agent. The NP construct also has the unique advantage of dual modality imaging; targeted MR imaging which

can be used for pretreatment staging/planning, and targeted NIRF imaging which can be used in the operating theater to ensure adequate surgical margins during tumor resection. It also offers the potential utilization as a Nano carrier for HCC-targeted therapeutics, delivering drugs and other payloads. For all of these reasons, this GPC3 targeted NP system may potentially improve the diagnosis of indeterminate liver lesions, which in turn will enhance the accuracy of staging and surgical risk stratification of the HCC patient.[9]

RECENT DEVELOPMENTS IN TREATMENT

Targeting glucose metabolism: A new class of agents against liver cancer - 3-bromopyruvate (3-brpa)

3-Bromopyruvate (3-BrPA) is a halogenated analog of pyruvic acid, with significant antitumor effects and lower toxicity profile. These metabolic blockers mainly target the glycolysis process. Glycolysis plays a main role in several biosynthetic processes that facilitate uninterrupted tumor growth and is an indispensable "metabolic event" critical for the sustained growth and invasion of tumors. Cancer cells preferred glycolysis because that the cancer cells are able to generate ATP through glycolysis at a much faster rate than oxidative phosphorylation to meet the energy demands of aggressive malignant growth. Increased glucose metabolism via glycolysis provides cancer cells with essential substrates for rapid proliferation, ribose for nucleic acid synthesis (producing molecules like NADPH), and pyruvate for cell membrane assembly. Targeting glycolysis for the treatment of cancer should, therefore, be a promising novel therapeutic strategy. The addition of the halogen bromine to the monocarboxylic acid, pyruvate, results in alkylating properties of the compound. As a result, 3-BrPA will bind to its target by forming an irreversible chemical bond. In vitro testing against human HCC cells demonstrated that 3-BrPA inhibits glycolysis and blocks ATP production, causing apoptosis in a dose-dependent manner. Further investigation with radio labeled 3-BrPA identified the glycolytic enzyme, GAPDH, as the primary intracellular target of this agent. The binding of 3-BrPA to GAPDH caused inhibition of the enzyme activity and, therefore, glycolytic ATP production leading to apoptotic cell death. Unlike other alkylating agents, 3-BrPA demonstrated tremendous specificity in molecular targeting, enforcing its ant tumorigenic effects by promoting energy depletion, disruption of redox balance, and induction of intracellular stress in a concurrent fashion. Therefore, it appears that 3-BrPA is an extremely promising agent because of its tumor selectivity and ability to promote a multipronged antitumor effect. [10]

Nanoknife- irreversible electroporation (ire)

NanoKnife is a minimally invasive cancer treatment that uses a targeted approach to treating hard-to-reach tumors at the cellular level. It relies on the body's natural healing ability to replace cancer cells once they are destroyed, so it leaves almost no scarring. NanoKnife offers an effective treatment option for small tumors –usually less than five centimeters – which are considered inoperable or where radiation treatment is not advised. It can be used for both primary tumors or for tumors that have spread from cancer in other parts of the body. It works by applying electrical energy directly into tumors. This opens the cell walls of the tumor; the cancer cells die; and healthy tissue remains unharmed. NanoKnife serves as an alternative to thermal ablation which kills cells with extreme heat or cold.

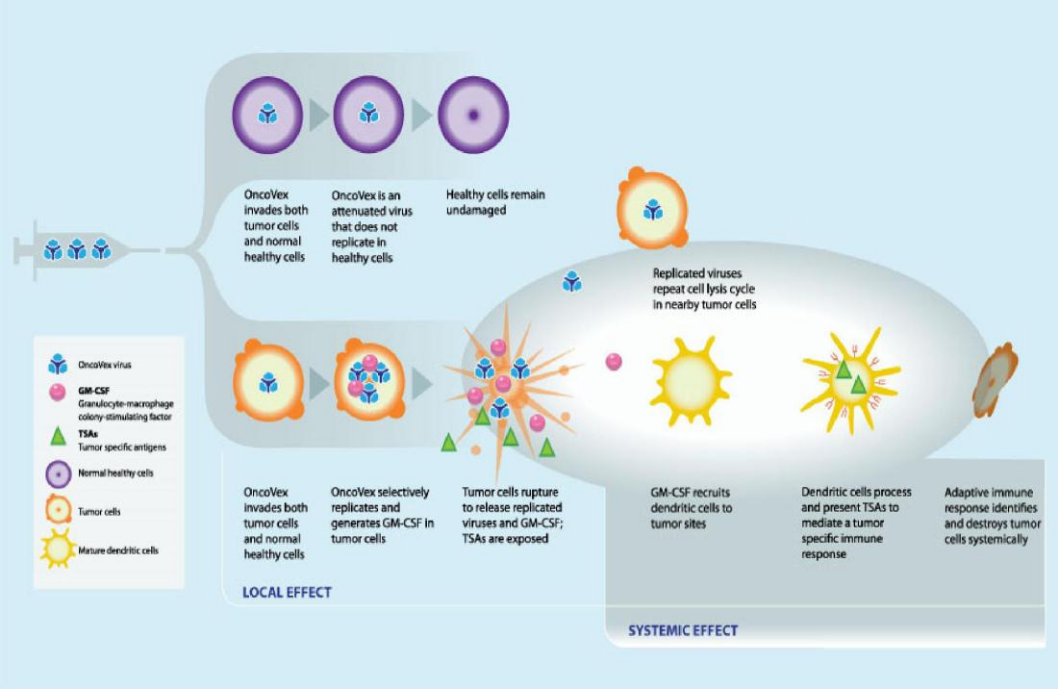
Benefits of NanoKnife include;

- A minimally invasive alternative to major surgery
- Can be performed in conjunction with surgical resection to treat margins
- Shorter hospital stay
- Does not preclude other therapies
- Offers effective option to patients with surgical contraindications

Limitations are;

- Not beneficial for large tumors, greater than 4 cm
- Not appropriate for all tumor types

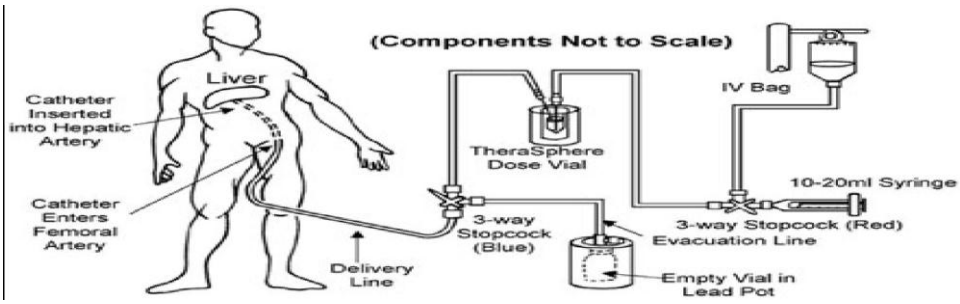
Virus therapy



An oncotic virus (OV) is a virus having the capacity to specifically infect and lyse cancer cells, while leaving normal cells unharmed. Here, certain viral genes act as tumour destructive agent, and the viral capsid as a nano-sized nucleic acid delivery vehicle. The anticancer activities of OVs are derived from multimodal cancer killing mechanisms. The first is the direct oncolysis of cancer cells by the virus, which is, in most cases a mixture of apoptosis, necrosis, pyroptosis and autophagic cell death, often with one as predominant for a particular OV. The second is apoptotic and necrotic death of uninfected cells induced by anti-angiogenesis and antivasculature of the OVs as shown in animals and humans [11-13]. The last is cytotoxicity to cancer and stromal cells by activated innate and tumor-specific immune cells [14-16]. OVs provide a number of potential advantages as cancer vaccines over conventional therapies. First, OVs are tumor-selective, thus in situ cancer vaccines, providing higher cancer specificity and better safety margin. Second, immunogenic/inflammatory types of cell death, including recently characterized "immunogenic cell death" (ICD) of cancer and stromal cells induced by OVs provides a natural repertoire of tumor-associated antigens (TAAs) in conjunction with danger signals [damage-associated molecular pattern (DAMP) and OV-derived pathogen-associated molecular pattern (PAMP) molecules, and inflammatory cytokines] [17-19], to elicit antitumor immunity. Virus used currently in research includes adenovirus, herpes virus, vaccine virus, reovirus etc.

Therasphere

TheraSphere is a liver cancer treatment that uses millions of small beads. Each glass bead has radioactive Yttrium-90 inside. The surgeon will inject TheraSphere into the main artery of your liver through a small tube (catheter). The tiny radioactive glass beads are delivered directly into the liver tumor through the blood vessels. The radiation destroys the tumor cells from within the tumor, with little injury to the healthy liver tissue. The Yttrium-90 in TheraSphere turns into Zirconium-90. Zirconium-90 is harmless in the small amounts that stay in the body. This means that most of the radioactivity of Yttrium-90 is gone in about 10-12 days following treatment.



Magnetic chemotherapy

Multifunctional doxorubicin loaded super paramagnetic iron oxide Nanoparticles for chemotherapy and magnetic resonance imaging

Conventional chemotherapeutic compounds are distributed nonspecifically all over the body, thus indiscriminately affecting both normal healthy cells as well as rapidly proliferating cancer cells. For this reason, for the desired therapeutic dose to reach the tumor, side effects occur in most cases due to high toxicity levels. The lack of targeting specificity of conventional chemotherapeutic agents makes magnetic nanoparticles (MNPs) attractive drug Nano carriers. Multifunctional doxorubicin loaded super paramagnetic iron oxide nanoparticles is a new drug delivery system with enhanced efficacy and minimized adverse effects. This novel polymeric nanoparticles, (YCC-DOX) composed of poly (ethylene oxide)-trimellitic anhydride chloridefolate (PEO-TMA-FA), doxorubicin (DOX) and super paramagnetic iron oxide (Fe_3O_4) and folate. YCC-DOX showed the anticancer efficacy and specifically targeted folate receptor (FR)-expressing tumors, thereby increasing the bioavailability and efficacy of DOX. Furthermore, YCC-DOX showed higher MRI sensitivity comparable to a conventional MRI contrast agent (Resovist®), even in its lower iron content. In the immune histo chemical analysis, YCC-DOX group showed the lower expression of CD34 and Ki-67, markers of angiogenesis and cell proliferation, respectively, while apoptotic cells were significantly rich in the YCC-DOX group in terminal deoxy nucleotidyl transferase dUTP nick end labeling (TUNEL) assay. These results indicate that YCC-DOX is a promising candidate for treating liver cancer and monitoring the progress of the cancer using MRI.[20]

FUTURE DIRECTIONS FOR PREVENTION OF LIVER CANCER

Liver cancer is preventable if the primary risk factors such as chronic hepatitis B and C infections can be eliminated. By taking some steps we can prevent liver cancer. These are; 1) prevention of new HBV infections, including thorough HBV vaccination programs, especially in high risk areas, 2) prevention of new HCV infections, 3) identification of HCV-infected persons in order to control HCV-related chronic liver disease, using antiviral treatment to prevent progression of chronic liver disease (rather than relying on early detection of liver cancer), and counseling of both infected and uninfected persons, as well as providing referral for medical evaluation and treatment, 4) surveillance and research to evaluate the effectiveness of preventive activities.[21]

CONCLUSION

The incidence of liver cancer is increasing in the present world. Although HBV, HCV and alcohol use constitute the most important risk factors for the development of live cancer, diabetes and obesity may contribute to increased carcinogenicity. Primary care physicians taking care of patients with chronic viral hepatitis and cirrhosis will need to have a heightened awareness of liver cancer, because the translation of bench research into clinical practice will lead to newer diagnostic tests, better therapeutic options, and improved survival of these patients. Finally, an important frontier in the battle against liver cancer will be the application of effective preventive strategies aimed at decreasing the risk of transmission of HBV and HCV, and the development of safe and effective medications for the treatment of chronic HBV and HCV.

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