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A Review on Comprehensive Therapy of Ascites Cancer

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Abstract

Ascites cancer is a condition in which there is a fluid accumulation in the peritoneal cavity due to diseases like liver disease, heart failure, renal disease and malignancy. Approximately 50% of all cirrhotic patients develop ascites cancer every year. The average survival after development of malignant ascites is only about 5 months. The most common symptoms of Ascites are recent weight gain, increased abdominal girth and dyspnoea. The development of ascites leads to significant symptoms and poor quality of life for the cancer patient. There are many potential causes of ascites in cancer patients, including peritoneal carcinomatosis, portal vein thrombosis, elevated portal venous pressure, congestive heart failure, nephrotic syndrome and peritoneal infections. The first line treatment of ascites includes education regarding dietary sodium restriction and oral diuretics. A guideline on the management of symptomatic malignant ascites by abdominal paracentesis, diuretics and peritoneovenous shunting, based on the review of this literature is presented. This review is intended to add clarity and valuable treatments to the current procedures for the management of malignant ascites and furthermore discusses new promising approaches.

Keywords: *Peritoneal cancer, carcinoma, diuretics, portal vein thrombosis*

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INTRODUCTION

Ascites cancer is the pathological accumulation of free fluid in the peritoneal cavity. This free fluid causes the belly to become swollen and distended. The fluid accumulates due to some conditions directly involving the peritoneum e.g. infection, malignancy and also the other diseases from the peritoneum i.e. liver disease, heart failure and hypoproteinaemia. Tumours causing carcinomatosis are more commonly referred to as secondary peritoneal surface malignancies which include ovarian, colorectal, pancreatic and uterine, the extra-abdominal tumours originating from lymphoma, lungs, breast and a small number of unknown primary tumours. The development of ascites leads to significant symptoms and poor quality of life for the cancer patient [1]. The most prevalent symptoms are: increased abdominal swelling, shortness of breath, decreased appetite, sense of work, abdominal pain, indigestion, weight gain, fatigue, constipation, nausea, ankle swelling. Ascites can be different from obesity due to symptoms of this disease because the onset of symptoms in ascites is fast. The main cause of ascites cancer is cirrhosis; approximately 85% of all cases of ascites are caused by cirrhosis of the liver. Other common causes of ascites are portal hypertension, edema, blood pressure and heart failure. This type of ascites is typically an action of advanced cancers for the organs that are present in the abdominal cavity, such as colon cancer, ovarian cancer, pancreatic cancer, breast cancer, stomach cancer, lymphoma and lung cancer. 10% of all ascites are caused by malignancy. Epithelial malignancies, particularly ovarian, endometrial, breast, colon, gastric, and pancreatic carcinomas are the factors which cause 80% of malignant ascites. The left 20% are due to malignancies of unknown origin.

The pathophysiology of malignant ascites is multifactorial but it mainly originates from an imbalance between fluid, secretion and absorption by peritoneum. Due to this imbalance of fluid, there is the occurrence of alterations in vascular permeability, release of inflammatory cytokines and decreased lymphatic drainage. Tests of liver enzymes, coagulation, basic metabolic profile and routine complete blood count should be

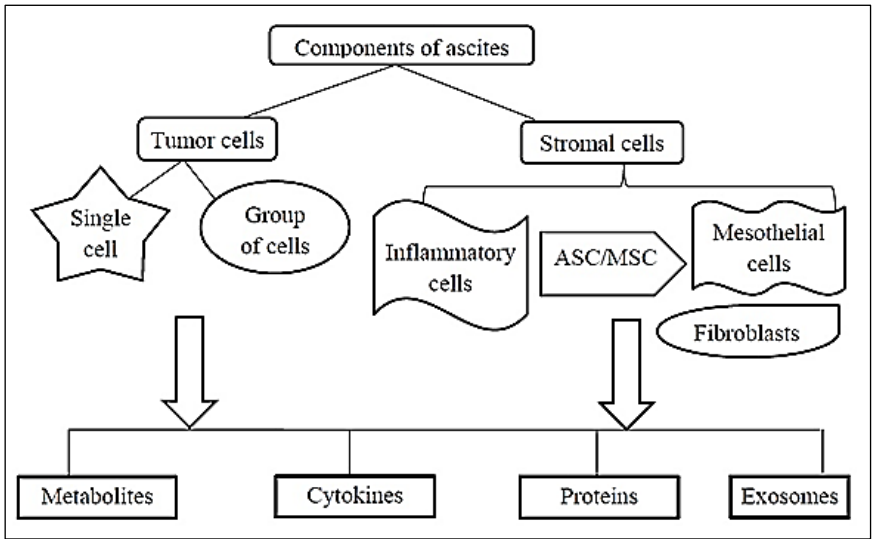

Fig. 1: *Development of Ascite Cancer.*

performed for the diagnosis of ascites. Use of diuretics, shunts, baclofen, vaptans and bed rest are the beneficial treatments of ascites cancer [2].

Ascites is composed of both tumour cells and stromal cells, tumour cells are present either as single cells or as spheroid shape cells, including fibroblasts, mesothelial cells, and adipose tissue derived stromal cells (ASC/MSC), endothelial cells, adipocytes and inflammatory cells. These cellular components communicate with each other through acellular factors, such as cytokines, proteins, metabolites and exosomes (Figure 1).

PHARMACOLOGICAL APPROACH

Treatment of Ascites Cancer with the Use of First Line Treatment Drugs

Diuretics

Diuretics are often used in the management of malignant ascites, even though their use is highly controversial. As dietary salt restriction is the basic approach in the treatment, and aldosterone is the hormone that tends to increase salt retention, so the medicine that counterbalances aldosterone should be used. Spironolactone is the drug of choice as it blocks the aldosterone receptor in the collecting tubule. This choice has been affirmed in a randomized controlled trial. The dose of diuretics for ascites should be once daily. Oral Spironolactone and furosemide are given as a single morning dose in the normal diuretic regimen, starting with 100 mg of the spironolactone and 40 mg of furosemide [3].

Paracentesis

In case of severe ascites, therapeutic paracentesis may be required. Review of the literature demonstrates that temporary relief of symptoms related to the build-up of fluid in about 90% of patients is managed by paracentesis. It is a simple, safe and effective method of inserting a 14-gauge needle with a 16-gauge catheter into the free peritoneal cavity, draining up to 9 l at a time with concurrent intravenous fluids running to prevent hypotension due to rapid vascular space depletion. In this disease the major concern is that how much and how fast fluid can be removed. So, the paracentesis can result in rapid symptom control in 90% of patients [4].

Intraperitoneal Immuno-Stimulants

Corynebacterium parvum has been administered intraperitoneally to treat ascites. In some cases, surgically confirmed tumour regression has been noted. Its mechanism of action is unclear. Patients who responded to treatment clearly show the increased natural-killer activity and antibody-dependent cell-mediated cytotoxicity of peritoneal lymphocytes.

Second Line Treatment with the Use of Shunts

Peritoneovenous Shunt

It is initially developed for use in cancer with refractory ascites due to liver cirrhosis. The peritoneovenous shunts subsequently became popular in the management of malignant ascites. Shunts function as a connection

between the peritoneal cavity and large venous vessels, such as the vena cava, allowing escape of the peritoneal fluid back into the circulation. Two types of shunts are available for the treatment of ascites, i.e. Leveen and the Denver shunt. Both shunts can direct back severe fluid into the vena cava through a one-way valve. Higher pressures to increased flow are achievable with the Leveen shunt. Both types of shunts were designed to prevent repeated paracentesis and prevent protein loss that can occur with repeated paracentesis. Shunts can prevent symptoms in 70% of patients [5].

Transjugular Intrahepatic Portosystemic Shunt

The transjugular intrahepatic porto-systemic shunt (TIPS) is a technique performed by interventional radiologists that creates a side-to-side shunt that effectively relieves portal hypertension. For patients with cirrhosis and refractory ascites that have relatively good hepatic and renal function, TIPS is considered the treatment of choice. In two cases of the malignant portal and hepatic vein occlusion, TIPS improved ascites and quality of life [6].

Angiography

In addition, to lymph-angiography with or without embolization is another useful technique which has been described for the review in the treatment of postoperative ascites cancer when conservative therapy fails [7].

Treatment with the Use of New Approaches to Malignant Ascites

Hyperthermic Intraperitoneal Chemotherapy

Peritoneal cavity is one of the most important causes of malignant ascites, so that the specific treatment may yield better survival results. The systemic chemotherapy is less effective and more toxic in paritoneal cavity due to poor blood supply [8]. Intra peritoneal chemotherapy as well as hyperthermic intra peritoneal chemotherapy (HIPEC) is proven to have enhanced cytotoxicity. The objective of cytoreductive surgery in combination with HIPEC is to remove all macroscopic tumours after abdominal exploration leaving only microscopic residual disease for improved tumour tissue penetration with HIPEC. This combination has been shown to improve survival in appropriately selected patients and is mainly applied to patients with metastatic colorectal cancer.

Octreotide

It is a somatostatin analog which is given for the management of malignant bowel obstruction and it acts as an antisecretory agent in case of lymphatic leakage due to abdominal ascites and was found to successfully reduce ascites.

Intraperitoneal Monoclonal Antibodies

Intraperitoneal monoclonal antibodies are the tri-functional antibodies; they have a much higher capacity for tumour kill than previous monoclonal antibody lines. Preclinical models have shown that the improved effectiveness of these antibodies lies in the ability to trigger an immune response by interacting with EpCAM and the cluster of differentiation to treat ascites cancer. Example is Catumaxomab, which is a tri-functional bispecific antibody that binds to tumour cells expressing human epithelial cell adhesion antibody, bevacizumab supports the hypothesis that targeting VEGF may have the potential to prevent local fluid accumulation. Therefore, the i.p. application of bevacizumab is currently being investigated in a randomised Phase II trial [9].

Metalloproteinase Inhibitors

Recent studies on humans have been conducted with metalloproteinase inhibitors such as batimastat. In a phase I study, 22 patients with malignant ascites had batimastat injected into the peritoneal cavity after paracentesis. No reaccumulation of ascites occurred, after that, single dose in five patients out of the 23, and these five patients survived for up to 112 days. Seven other patients died without re-accumulation during this follow-up period. The major adverse effects in the first 24 h were nausea and vomiting [10].

Treatment with the Use of Immunologic Therapies

Interferons

The new therapeutic responses have been noted in patients with resistant ascites when recombinant α-interferon or β-interferon was used intraperitoneally. Augmentation of natural

killer activity restricted to the peritoneal cavity was noted in most cases. Fever in the first 24 h, leukopenia, and non-specific 'flu like' symptoms were documented [11].

Tumour Necrosis Factor-α

It has to be an effective palliative treatment for malignant ascites. In the present study of 29 patients with refractory malignant ascites, 22 patients have responded to intraperitoneal TNF-α administration. The response is found to be predominating in patients with non-bulky distribution of tumours in the abdomen. Adverse effects such as chills, nausea, fever, fatigue, and vomiting were reported.

Treatment with Herbal Drugs

A number of plants are used for the treatment of ascites cancer which are given below in Table 1 [12].

Treatment of Ascites with Intracavitary Radio-colloids

Radiocolloids have been used for many years. The most useful example is radio-phosphorus (^{32}P), with a response rate of up to 58% reported.

^{32}P is a β-emitter with a maximum tissue penetration and a half-life of 14.3 days. There is a low level of total body irradiation, as a result of systemic absorption of the small amount of soluble^{32}P released. The colloidal solutions of ^{63}Zn and ^{19}Au have also been administered. These incurred higher complication rate and their use was largely discontinued in favour of ^{32}P [13].

NON-PHARMACOLOGICAL TREATMENT

Dietary Therapy

It is a reasonable approach for patients in whom the cause was not found and if they were not responding to treatment of the underlying cause then they were recommended to the nutritional therapy. It is common in practice to recommend bowel rest and dietary modification, and the use of total parenteral nutrition. The goal of nutrition therapy is to decrease the production of chyle, replace fluid, electrolytes, and improve nutrition status. Low sodium diet is the first step towards the management of ascites. It is believed to reduce the associated water retention and help reduce edema. Long-term sodium restriction has been shown to reduce recurrences and prolong the symptom-free period [14].

MARKETED FORMULATIONS OF HERBAL DRUGS USED IN ASCITES CANCER

These are the drugs which is different from the allopathic drugs and they have potent anti-ascites cancer with anti-tumour effect. Recent studies showing, this drugs having a strong therapeutic effect at a minimum concentration with lesser side effects. There are number of herbal ingredients present to treat ascites cancer. The drugs used are as given below.

Table 1: *Plants Used for Treatment of Ascites Cancer.*

Name of the Plant	Family	Active Constituents
Comptotheca accuminata	*Nyssaceae*	Quinoline alkaloid, camtothecin, 10 hydroxy camptothecin, 10-Methoxy camptothecin
Catharanthus roseus	*Apocunaceae*	Vincristine, vinblastine, ajmalicine
Curcuma longa	*Zingiberaceae*	Curcuminoids, curcumin, volatile oil, starch
Taxus brevifolia	*Taxaceae*	Taxane, cephalomannine, 10-deacetylbaccatin, taxol
Taraxacum mongolicum	*Asteraceae*	Sesquiterpene lactones, phenyl propanoids, saponins, polysaccharides
Akebia quinata	*Lardizabalaceae*	Limonene, eugenol, octanol, monoterpenoids, saturated short chain aldehyde, hexanoic acid.

Table 2: *Marketed Formulations of Herbal Drugs Used in Ascites Cancer.*

Brand Name	Active Constituents	Dose
Curcumin Capsules	Curcuminoidsatlantone, bisdemethoxycurcumin, demethoxycurcumin	1 g/day
Wheat Grass Syrup	Chlorophyll, amino acid, minerals, vitamins and enzymes	4–6 drops/day
Planet Ayurveda Punarnava Capsules	b-Sitosterol, arachidic acid, palmitic acid, ester of b-sitosterol	1–2 tablets twice/daily
Phyllanthus Niruri	Flavonoids, alkaloids, terpenoids and saponins	0.5 mg/ml/day

GUIDELINE ON THE MANAGEMENT OF SYMPTOMATIC MALIGNANT ASCITES IN ADVANCED CANCER

1. Paracentesis is indicated to the patients that have symptoms of increasing intra-abdominal pressure. Available data show good, although temporary relief of symptoms in most patients. Symptoms like discomfort, dyspnoea, nausea and vomiting seem to be significantly relieved by drainage of up to 5 l of fluid.
2. When removing up to 5 l of fluid, intravenous fluids seem to be not routinely required.
3. If the patient is hypotensive or dehydrated or known to have severe renal impairment and paracentesis is still indicated, intravenous hydration should be considered. Infusion therapy is not sufficiently studied. The only investigated therapy in malignant ascites is an infusion of dextrose 5%. There is no evidence of concurrent albumin infusions in patients with malignant ascites.
4. To avoid repeated paracenteses a peritoneovenous shunting may be considered. Major complications have to be expected in about 6% of patients.
5. There are no randomized controlled trials assessing the efficacy of diuretic therapy in malignant ascites. The available data are controversial and there are no clear predictors to identify which patients would benefit from diuretics. The use of diuretics therefore should be considered in all patients but has to be evaluated individually. Patients with malignant ascites due to massive hepatic metastasis seem to respond more likely to diuretics than patients with malignant ascites caused by peritoneal carcinomatosis or chylous ascites.
6. Choice of diuretics is not evaluated. As available data suggest that the efficacy of diuretics in malignant ascites depends on plasma renin/aldosterone concentration, aldosterone antagonists like spironolactone should be used, either alone or in combination with a loop diuretic.
7. Dose regimens of diuretics are not evaluated in patient's malignant ascites. There is no evidence to diverge from standard clinical practice. Therefore dosage should be performed according to manufacturer's instructions and package inserts [15].

CONCLUSION

Ascites cancer is a dangerous disease, which is common all over the world. Its early detection is necessary to ensure effective management without any complications. The management of malignant ascites is a significant challenge in medical oncology. Newer therapies are emerging in this review for the effective treatment of ascites cancer. The use of tri-functional antibodies represents a new approach to the management of both types of complications associated with advanced cancer, such as malignant pleural effusions as well as malignant ascites. The control of the immune system suggests that the implication of tri-functional antibody may not only be effective for advanced disease but may also be beneficial for patients with earlier stages of the disease. Medicinal plants also have contributed a rich health to human beings. This review has given some of the plants possessing anti ascites cancer activity for various types of cancer. This review can help others to explore herbs to further extent.

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