BACKGROUND INFORMATION FOR MEDIACL TRADE MEDIA

Malignant Ascites

The accumulation of fluid in the abdominal cavity caused by an imbalance of plasma flow into and out of the blood and lymphatic vessels is called ascites ("abdominal dropsy"). In approximately 80% of cases ascites is caused by cirrhotic liver disease, whereas diseases such as heart failure, nephrotic syndrome and pancreatitis play minor roles (1-3%). In about one in ten patients suffering from ascites the disease is due to cancer. In four out of five patients with malignant ascites it is caused by ovarian carcinoma or gastrointestinal tumors, as well as by breast, pulmonary, uterine and cervical tumors.[1] The spreading of tumor cells in the abdominal cavity results in dysregulation of flow at the peritoneum in several ways.

Generally, patients suffering from malignant ascites have a poor prognosis implying a median survival time of 1-4 months, depending greatly on the underlying type of tumor and its stage.[2] There are still no evidence based guidelines for treatment of malignant ascites even though it is associated with high morbidity. Therapeutic options are limited to palliative treatment and include puncture of the abdominal cavity (paracentesis), and systemic or intraperitoneal chemotherapy. These options, however, only temporarily alleviate the symptoms. Clinical trials are required to establish the benefit of existing and novel therapeutic options. Potential new treatments such as intraperitoneal immunotherapy with trifunctional antibodies, are currently being tested in clinical trials, and give rise to hope for improvement.

Below, a brief overview is given on the structure and the function of the peritoneum as well as on the pathophysiology, diagnosis and treatment of malignant ascites.

Structure and function of the peritoneum

The peritoneum forms the lining of the abdominal and pelvic cavity (parietal peritoneum) and covers the intra-abdominal organs (visceral peritoneum). It consists of mesothelial tissue with a simple squamous epithelium facing the abdominal cavity, which is supported by an inner layer of tissue, called lamina propria. The latter in turn adheres to the organ capsule and the abdominal wall

respectively. The squamous epithelium is not a closed layer but contains foramina allowing macromolecules and cells to enter the abdominal cavity. Furthermore, plasma filters into the abdominal cavity via the peritoneum's vascular capillaries (transudation), and drains off via open endings of lymphatic channels (stomata) in the serosa. In the healthy state, approximately 50-100 ml of fluid fills the peritoneal cavity allowing the organs to slide freely over each other.

Pathophysiology of malignant ascites

Generally, the development of malignant ascites can be traced back to the settlement of metastasizing cancer cells in the abdominal cavity. Ovarian carcinoma is the primary tumor in the majority of cancer patients with malignant ascites. Gastrointestinal tumors play also a substantial role and in one out of five patients suffering from malignant ascites the location of the primary tumor remains unknown (cancer of unknown primary, CUP).[3]

The infiltrating tumor cells disrupt the normal regulation of fluid flow in the peritoneal cavity by simultaneously causing a greater plasma inflow as well as a reduced lymphatic outflow. Infiltrating tumor cells and growing metastases have been demonstrated to

- Release Vascular Endothelial Growth Factor (VEGF) leading to tumor neovascularisation. Additionally, it has also been shown that VEGF causes an increased permeability of the tumor capillaries and has the same effect on the capillaries of the peritoneum. Consequently, the new tumor vessels as well as the vessels of the peritoneum contribute to an increased inflow of fluids.[4]
- Block lymphatic stomata leading to obstruction of lymphatic drainage and an accumulation of fluid in the abdominal cavity.[4]

Diagnosis

In addition to an increasing abdominal girth, symptoms of malignant ascites are abdominal pain as well as anorexia, frequently accompanied by nausea and occasionally by vomiting. Other symptoms include dyspnea, fatigue and swollen wrists or ankles. The accumulation of large quantities of fluid causes visible swelling at the sides of the abdomen, a positive fluid wave and shifting dullness.[3]

A simple physical examination will not provide an adequate basis for deciding whether the ascites is due to a malignant cause or another disease. Therefore diagnosis is based on blood tests, imaging diagnostics and an analysis of the ascites. With the help of blood tests, e.g. tumor marker tests for CEA or CA-125, an underlying malignancy may be identified.

Imaging diagnostics such as CT, MRI or ultrasonography are able to detect even small amounts of fluid in the abdominal cavity but they cannot differentiate between a benign or malignant form of ascites. Despite this limitation, they are valuable techniques for discovering a primary tumor or metastases.[3]

A microbiological examination of an ascites sample can exclude a bacteriologic or mycotic infection as a cause. Detecting tumor cells in the ascitic fluid is a highly specific indicator for a malignant cause. However, only about 60 percent of aspirates are cytologically positive and, therefore, the examination ought to be repeated if a malignant disease is suspected.[5] In cases of negative tumor cytology, biochemical markers in the ascites may indicate an underlying cancer disease. In addition to the tumor markers mentioned above, an increased protein or lactate dehydrogenase level as well as the serum-ascites albumin gradient may be used to help distinguish the underlying cause. However, these markers and a multitude of others are not highly specific to a tumor disease and display an extremely inconsistent sensitivity depending on the primary tumor.[3, 4]

Therapeutic options for malignant ascites

Palliative paracentesis und diuresis

Repeated peritoneal punctures and drainage of the ascites from the abdominal cavity is the most common method to alleviate the symptoms; however, this approach has several disadvantages. Its palliative effect, for instance, is very short and therefore has to be repeated every 10 days on average.[6] Furthermore, it can result in intestinal injuries, peritonitis or fistulas. Another risk of repeated puncture is the significant loss of protein (e.g. hypoalbuminemia) which may lead to metabolic disturbances and eventually to cachexia. In order to prevent hypovolemia, intravenous fluids have to be contemporaneously administered when extracting large quantities of ascitic fluid.[3] A puncture can take between 30 minutes and 72 hours depending on

the quantity, flow and location of the ascites. These differences can be attributed to different ascites volumes (see above), performance status of the patient and to the fact that the intervention is carried out differently in every hospital as there are no binding guidelines on palliative paracentesis to date.

Diuretic therapy is also possible but in most patients it is only effective when used in non-malignant cases, such as cirrhosis. Malignant ascites due to liver metastases is an exception to this rule. In such cases a benefit similar to those seen in patients suffering form cirrhosis of the liver can be achieved by administering higher doses of spirolactone.[3, 4]

Peritoneo-venous shunt

A peritoneo-venous shunt may be created in patients suffering from ascites who are in relatively good condition. Placement of a shunt can prevent repeated punctures and their associated risks mentioned above. Commonly used shunts include the LeVeen and Denver shunts which direct fluid from the abdominal cavity into the vena cava. A unidirectional valve ensures that the ascites can only flow from the peritoneum into the vein.

Shunting alleviates symptoms in 70% of patients treated but has associated risks, too. Among these are shunt obstruction, sepsis, coagulatory dysfunction and spreading of tumor cells from the abdominal cavity. For patients suffering from gastrointestinal tumors a peritoneo-venous shunt is not an option, as those patients generally have a very unfavourable prognosis and the risks of the intervention would thus exceed its benefits.[3]

Systemic chemotherapy

For patients suffering from ascites secondary to a primary tumor of known origin, systemic chemotherapy is indicated in tumors with known chemosensitivity. This applies for example to patients suffering from ovarian carcinoma who develop malignant ascites. After tumor staging, cytoreduction and adequate combination therapy, a median survival time of 44 months could be achieved in patients with ovarian carcinoma stages IIb to IV.[7] Systemic chemotherapy should also be considered in patients with clinical signs and symptoms secondary to organ metastases. However, the benefit of systemic chemotherapy compared to the risk of its toxicity should be taken into account especially in this palliative treatment situation.

Intraperitoneal chemotherapy

Intraperitoneal chemotherapy is used to reach high cytotoxic concentrations of active agents in the abdominal cavity. This treatment option can achieve remission rates between 33-85% depending upon the chemotherapy administered and the type of tumor involved.[1] Active agents for intraperitoneal chemotherapy should be chosen based upon a slow uptake into the blood circulation and demonstrated ability to create a response during intravenous application. Besides eradicating tumor cells, cytostatics can cause tissue fibrosis resulting in a significantly lower inflow of plasma from tumor and peritoneal vessels.[4]

The success of intraperitoneal chemotherapy is limited by its low depth of penetration into existing tumor nodules.[4] In order to evenly disperse cytostatics throughout the abdominal cavity they must be administered via a large quantity of fluids (e.g. 1-2 litres of physiological saline solution).[1, 3]

Comparative clinical trials involving patients suffering from ovarian carcinoma have shown that intraperitoneal chemotherapy can be superior to systemic chemotherapy given alone (cf. below) with regard to progressionfree survival and median overall survival.[8, 9] One study showed that the combination of a systemic and an intraperitoneal chemotherapy was more effective than an exclusively intravenous treatment. Patients who were treated with paclitaxel intravenously and successively with cisplatin and paclitaxel intraperitoneally experienced a significantly longer median progression-free and overall survival when compared to patients treated with a systemic therapy based on paclitaxel and cisplatin exclusively.[10]

Intraperitoneal radiotherapy

The installation of radioactive gold or phosphorous isotopes (198Au, 32P) which was commonly used in the recent past is rarely used now. Even though objective remissions of 30 percent may be seen with the established radionuclide yttrium-90, it is rarely applied today due to the complex logistics involved.[1]

Intraperitoneal immunotherapy

Immunomodulators have also been investigated for the treatment of malignant ascites. For the most part they do not work as direct cytotoxics but instead

work by inducing cells of the immune system to destroy tumor cells. The first trials were conducted using cytokines such as interleukin-2, and interferon-α and β. Other approaches are the inhibition of VEGF by anti-VEGF or anti-VEGF-receptor antibodies, or the use of tumor-necrosis-factor (TNF).[3, 4]

Presently there is a new category of active agents being investigated in clinical trials for the intraperitoneal immunotherapy of malignant ascites: the so-called trifunctional antibodies. One of these antibodies has been designed to specifically adhere with one binding arm to the epithelial cell adhesion molecule (EpCAM) of carcinoma cells, with the second binding arm to CD3-receptors of T-cells and with its Fc portion to the Fcγ receptor of accessory cells such as macrophages and natural killer cells. The inductionof a complex immune response is one of the hopes linked to this method and could lead to an improved therapeutic effect.[11, 12] Smaller trials have already been conducted in the setting of ovarian carcinoma and gastrointestinal tumors.[13, 14] A phase II/III has recently been finished.

Conclusion

The treatment of malignant ascites is characterised by a multitude of different palliative therapeutic options which are of limited efficacy and associated with some degree of risk. None of these treatments have been established by evidence-based clinical trials enabling to demonstrate to be clinically superior so there are no binding therapeutic guidelines to date. In order to improve the treatment of malignant ascites validated therapies and new, meaningful studies on established therapeutic options are necessary.

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