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A novel perspective for an orphan problem: Old and new drugs for the medical management of malignant ascites

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Abstract

Malignant ascites is defined as a condition in which fluid containing cancer cells accumulates in the abdomen. The cancers most commonly associated to ascites are ovarian (37%), pancreato-biliary (21%), gastric (18%), oesophageal (4%), colorectal (4%), and breast (3%). Treatment of malignant ascites remains a challenge. In the majority of patients systemic chemotherapy is ineffective and diuretics and paracentesis are still the only approaches, but new promising option are appearing, as cytoreductive debulking surgery and intraperitoneal (IP) or intravenous biological (target) therapies. More promising, after the recognition of potential epithelial targets as Epithelial Cell Adhesion Molecule (EpCAM), are the trifunctional antibodies able to bind these cell adhesion molecules and, at the same, time the immune system cells. These agents have been developed for malignant ascites with the aim also to

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prolong the need for subsequent paracentesis. So patients with malignant ascites may look at the future with hope and growing optimism.

Keywords: Malignant ascites; Paracentesis; Diuretics; Intraperitoneal chemotherapy; Bispecific antibodies; Antiangiogenetic agents; Biological therapies

1. Epidemiology of malignant ascites

Malignant ascites is defined by the National Cancer Institute as a condition in which fluid containing cancer cells collects in the abdomen. This can occur either by direct invasion of the peritoneum, such as in peritoneal carcinomatosis, or as a secondary effect of the local biologic activity of tumours, portal hypertension or mechanical compression of the inferior vena cava. Development of malignant ascites has various clinical implications: the discovery of small quantities of IP fluid has staging and prognostic significance and may alter a planned surgical intervention. Symptomatic ascites often reflects end-stage disease, hence palliative options should be considered first. However malignant ascites does not necessary imply shortened survival and may be part of a clinical scenario amenable to curative attempts, as for example in ovarian cancer. So pure palliative strategies (aimed at removing ascites from the abdominal cavity to relieve distension and then the patient's suffering) must be differentiated from potentially curative aim (attempted to reduce the bulky of peritoneal disease with systemic and/or locoregional therapies).

Cancer is the second etiological cause of the syndrome after cirrhosis, and accounts for 10% of all ascites cases. A review of 209 patients [1] showed that malignant ascites was more common in females than males (67% vs. 33%), probably due to the high prevalence of ascites in ovarian cancer. The cancers most commonly associated to ascites were in fact ovarian (37%), pancreato-biliary (21%), gastric (18%), oesophageal (4%), colorectal (4%), and breast (3%). Ascites was the initial presenting sign or symptom in 54% of patients. Not surprisingly, more than 95% of patients with malignant ascites also had measurable metastatic disease in the peritoneum (90%), liver (27%), bone (12%), and lung (8%). Except than in ovarian cancer, malignant ascites confers a poor prognosis, with a median survival of 5.7 months. Patients with malignant ascites secondary to ovarian cancer represent an exception because they have a significantly better survival, with a median of almost 2 years, than those with gastrointestinal cancer, in whom median survival was almost 3 months ($p = 0.0001$). The median survival of patients with symptomatic malignant ascites remain few months [2].

2. Medical treatment of malignant ascites

Management of malignant ascites must be multidisciplinary. Standard and experimental treatments in fact cover various branches of internal medicine, including hepatology, palliative care, oncology, interventional radiology, and surgery. Treatment of the primary tumour with antineoplastic therapy should always be considered first. There are no standard criteria of efficacy or response, an issue most relevant to the design and interpretation of clinical trials. Many strategies have been used to achieve palliation rather than cure, because the presence of malignant ascites is perceived as a sign of incurable disease. Paracentesis can effectively and rapidly palliate the symptoms of malignant ascites [3]. A survey of practising physicians suggested that the most common means of managing malignant ascites was paracentesis, which was also felt to be the most effective [4]. After paracentesis, diuretics and peritoneo-venous shunting were most commonly used. In particular cases, radical surgical procedures or aggressive intracavitary therapies have been attempted; however, to date few prospective randomized trials have been performed to compare alternative treatments. The encouraging results reported by many phase I or II studies involving intracavitary instillation of chemotherapeutic agents have generally not matured into randomized phase III trials [3]. In general, for non-ovarian malignant ascites, the goal of treatment is palliation of symptoms.

According to Souter et al., [6] a patient with malignant ascites whose only considered therapeutic goal is palliation should first undergo repeated paracentesis and medical management with diuretics. If the rate of fluid re-accrual is rapid, the fluid is not viscous or bloody, there is no evidence of intracavitary loculation, and the expected survival time is greater than 3 months, shunting should be considered [5,7]. We will revisit vvarious systemic and loco regional therapeutic strategies for malignant ascites with mention to the more aggressive cytoreductive surgery procedures. As a general consideration, treatment of malignant ascites is palliative with the aim of improve quality of life.

2.1. Symptomatic treatment: diuretics, paracentesis and shunts

Although malignant ascites may be highly resistant to diuretic use, diuretics and salt restriction have been recommended as first line treatment in selected patients. Specifically, patients with ascites related to portal hypertension due to hepatic metastasis are more likely to respond to diuretics. Becker evaluated 5 studies, with a total of 113 patients with a variety of tumour types, and found that approximately 43% of patients attained relief of symptoms associated with ascites by diuretic management [8]. Most data on diuretic treatment have been obtained from studies