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Role of Chemotherapeutic Agents in the Management of Cystic Echinococcosis

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Hydatid disease is caused by infection with the metacestode stage of *Echinococcus* tapeworms of the family Taeniidae. The primary carriers are dogs and wolves, and humans are accidental hosts that do not contribute to the normal life cycle of this organism. The liver is the most commonly involved organ in the body by cystic echinococcosis (CE) secondary to infection with *Echinococcus granulosus*. Management options for CE should depend on the World Health Organization (WHO) diagnostic classification. Small (<5 cm) WHO stage CE1 and CE3a cysts may be primarily treated with benzimidazoles; the first-choice drug is albendazole. In some situations the combination of albendazole and praziquantel may be preferred. Chemotherapy with a benzimidazole or albendazole plus praziquantel is also used as adjunctive treatment to surgery and percutaneous treatment. Drug treatments have been the indispensable therapeutic modalities for cystic echinococcosis.

Key words: Cystic echinococcosis – Drug treatment – Albendazole – Mebendazole – Praziquantel

Hydatid disease is caused by infection with the metacestode stage of *Echinococcus* tapeworms of the family Taeniidae. Four species of *Echinococcus* cause infection in humans: *Echinococcus granulosus* and *Echinococcus alveolaris* are the most common, causing cystic echinococcosis (CE) and alveolar echinococcosis, respectively. The primary carriers are dogs and wolves, and intermediate hosts are sheep, cattle, and deer, Humans are accidental hosts that do not contribute to the normal life cycle of this microorganism. Humans are infected by ingesting ova from soil or water

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contaminated by the feces of dogs. Hydatid cysts are common in societies where agriculture and raising animals are common, and hydatid disease continues to be a serious public health problem in many countries, including Turkey.[1–6] The most common site is the liver, followed in frequency by lung, kidney, and spleen.[7,8] The other, less common sites, such as the heart, pancreas, bone, brain, and muscles, are very rarely affected.[8–11] The first step in the prevention of hydatid disease is basic hygiene and the second step involves the approach to treatment. No consensus exists regarding the optimal treatment, although medical treatment is effective against larval *E granulosus*. In this study, we aim to discuss the effectiveness of medical treatment in the management of hydatid disease

Classification of Hydatid Cyst

The World Health Organization (WHO) expert working group on echinococcosis has classified ultrasound images of hepatic cystic echinococcosis and has grouped the disease into 5 major cyst types. Type CE1 (unilocular, simple cysts) and type CE2 (multivesicular, multiseptated cysts) are considered active because they are likely to contain viable protoscoleces. Type CE3 (unilocular cysts with detachment of laminated membrane or multiseptated cysts with partial hyperechoic content) are considered transitional and might represent the beginnings of cyst degeneration. Type CE4 (heterogeneous or hyperechoic degenerative contents) and type CE5 (calcified cysts) are considered inactive because the parasite tissue is likely to be of low viability.[12,13]

Treatment Approaches

Four approaches in clinical management exist: surgery, percutaneous techniques, and drug treatment for active cysts; and the so-called watch and wait approach for inactive cysts.[12–16] Allocation of patients to these treatments should be based on cyst stage, size, and location; available clinical expertise; and comorbidities. For CE, consensus has been obtained on an image-based, stage-specific approach, which is helpful for choosing one of the following options: (1) percutaneous treatment, (2) surgery, (3) anti-infection drug treatment, or (4) watch and wait. Clinical decision-making depends also on setting-specific aspects.[12]

Treatments With Benzimidazoles

The use of benzimidazoles in CE treatment started in the 1970s with mebendazole. In the early 1980s albendazole was introduced, and since then it has largely replaced mebendazole because of some its advantages, such as lower dosage and better intestinal absorption. In treatment centers mebendazole and albendazole are given at the WHO-recommended dosages [mebendazole, 40–50 mg/kg/d in 3 divided doses; albendazole, 10–15 mg/kg/d in 2 divided doses (the usual dose for an adult is 2 × 400 mg)] during fat-rich meals to increase bioavailability.[12–14] Albendazole is more completely absorbed, but it is almost undetectable in plasma because of its rapid conversion to an active sulfoxide metabolite. Chemotherapy for the treatment of CE was initially recommended for inoperable patients and patients with multiple-organ disease. During the past decade several studies, mainly case series, have been published suggesting that chemotherapy could be an alternative to surgery in patients with uncomplicated cysts, leading to an increased use of chemotherapy over the years.[12–15] Stojkovic *et al*[14] collected data from 711 treated patients with 1308 cysts from 6 centers. They found that 1 to 2 years after initiation of benzimidazole treatment, 50% to 75% of active C1 cysts were classified as inactive/disappeared, compared with 30% to 55% of CE2 and CE3 cysts. However, 25% of cysts reverted to active status within 1.5 to 2 years after having initially responded, and multiple relapses were observed. This study also suggested that small highly active cysts show the best initial treatment response, with a better response in highly active CE1 cysts. Another study showed that the larger a cyst is, the more late treatment response is.[15]

Drug therapy alone is appropriate for definitive treatment of cysts that are CE1 and CE3a (cysts with a single compartment) and have a diameter <5 cm, cysts in inoperable patients, deep cysts that are amenable to percutaneous treatment, and/or peritoneal cysts. Treatment should be administered continuously for 3 to 6 months. Chemotherapy is a useful adjunctive therapy to percutaneous treatment or surgery to prevent secondary CE; albendazole is initiated at least 4 days before surgery (WHO suggests 4–30 days preoperatively) and should be continued for at least 1 month following surgery or percoutaneous procedure. Drugs are not recomended for the treatment of inactive or calcified cysts. The watch and wait strategy is currently

advised in patients with uncomplicated CE4 and CE5 cysts.[13,17–19]

The usual adverse effects include nausea, hepatotoxicity, neutropenia, and occasionally alopecia. Thus, all patients should have regular monitoring of leukocyte counts and liver function tests. Contraindications to chemotherapy include pregnancy, chronic hepatic diseases, and bone marrow depression.[18]

Praziquantel

Albendazoleplus praziquantel is more effective than monotherapy with albendazole in the preoperative treatment of intra-abdominal hydatidosis. Praziquantel does not have a definitive role in primary drug therapy. However, it could be helpful perioperatively and in bone or disseminated CE.[16,18–21] Although albendazole is potentially teratogenic, praziquantel is safe in pregnancy.[22]

In conclusion, today chemotherapy is an indispensable therapeutic tool in the management of cystic echinococcosis.

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