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Fibrolamellar variant of hepatocellular carcinoma does not have a better survival than conventional hepatocellular carcinoma – Results and treatment recommendations from the Childhood Liver Tumour Strategy Group (SIOPEL) experience

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Abstract ***Purpose:*** Fibrolamellar hepatocellular carcinoma (FL-HCC) and conventional hepatocellular carcinoma (HCC) cases in two consecutive paediatric HCC trials were analysed to compare outcome and derive treatment implications.
Patients and methods: Data of 24 FL-HCC (24% PRETEXT IV) and 38 HCC (42% PRETEXT IV) cases from SIOPEL-2 and -3 (1995–1998, 1998–2006) were analysed. Patients were treated according to SIOPEL-2 and -3 high-risk protocol (carboplatin + doxorubicin alternating with cisplatin; seven preoperative, three postoperative cycles) or with primary surgery followed by chemotherapy as indicated.

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Results: Thirteen of 24 FL-HCC (54%) and 32/38 HCC (84%) were initially treated with chemotherapy. Eight FL-HCC (33%) and five HCC patients (13%) had primary surgery. Partial response was observed in 31% of FL-HCC versus 53% of HCC patients ($p = 0.17$). Complete resection was achieved in ten FL-HCC and seven HCC patients ($p = 0.08$). Three-year event free survival (EFS) was 22% for FL-HCC versus 28% for HCC. Overall survival (OS) was not significantly different at 3 years follow up (42% for FL-HCC versus 33% for HCC, $p = 0.24$). EFS/OS Kaplan–Meier curves did not differ significantly, with median follow up of 43 (FL-HCC) and 60 (HCC) months. No significant correlation was found between potential prognostic factors and OS. In the entire cohort nine out of 23 (39%) patients with complete resection or orthotopic liver transplantation versus 34/39 (87%) without successful surgical treatment, died.

Conclusions: Long-term OS in FL-HCC and HCC is similar. With low response rates, complete resection remains the treatment of choice.

1. Introduction

Fibrolamellar hepatocellular carcinoma (FL-HCC), a rare variant of conventional hepatocellular carcinoma (HCC), was first described by Edmondson in 1956 and accounts for approximately 5% of HCC cases.[1,2] The tumour is composed of large polygonal cells with large nuclei containing marginalized chromatin and prominent nucleoli and eosinophilic cytoplasm containing pale bodies, and hyaline globules, surrounded by distinctly lamellar stroma.[2,3] It is most common in the age group between 5 and 35 years.[3–7] Some studies report a female predilection.[4,6,8] Generally no underlying liver disease including cirrhosis is present in FL-HCC patients and in particular no link with hepatic viruses has been established.[2,9–12] While HCC is often multifocal and metastatic at diagnosis and associated with abdominal pain, FL-HCC is reputed to present as a single, large, slow-growing, painless mass.[6,11,13] Serum α-fetoprotein (AFP) levels are almost always normal in patients with FL-HCC.[2,5] The standard treatment when possible is surgery with lymphadenectomy, as FL-HCC is associated with a high rate of lymph node metastasis and lymph nodes are common sites of first disease recurrence.[11,14,15] Although FL-HCC is often diagnosed at a stage that would not allow for resection of HCC, aggressive resection may result in long-term survival.[11,13] Currently available non-surgical treatments are relatively ineffective. Earlier studies consistently reported a better prognosis of FL-HCC compared to HCC.[3,4,9,8,16,17] However, these studies lack accompanying analyses of non-cirrhotic HCC cases, and reported better outcomes of FL-HCC in adults may be confounded by absence of cirrhosis, a separate mortality risk factor in HCC.[2,5,6,18] Since the majority of reports regarding FL-HCC involves adult patients only, analysis of the paediatric experience in the SIOPEL-2 and -3 trials and treatment recommendations based on observations derived from these trials seemed warranted.

2. Patients and methods

2.1. Patients

Amongst 90 HCC patients registered in the SIOPEL database, only cases with a clear distinction in histological features during pathology review were selected in order to compare two well-defined groups of pathology proven FL-HCC and HCC. Sixty-two patients with either HCC ($n = 38$) or FL-HCC ($n = 24$) were selected from the SIOPEL-2 and -3 databases for analysis. An in depth analysis of the entire HCC group was performed separately.

SIOPEL-2 and -3 were international, prospective, cooperative clinical trials, open to registration of paediatric patients with primary liver tumours between October 1995 and May 1998 and June 1998 and December 2006, respectively.[19,20]

2.2. Patient information at diagnosis and pre-treatment extent of disease (PRETEXT) evaluation

Diagnostic biopsy of the primary tumour was mandatory in children (a) younger than 6 months, (b) older than 3 years or (c) with a normal serum AFP. In all other cases biopsy was strongly recommended. Tumour extension was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) for the abdomen, and X-ray and CT for the intra-thoracic lesions. Tumour stage was established with the PRE-Treatment EXTent of disease (PRETEXT) system, based on findings at diagnostic imaging.[21,22] Trials were approved by the institutional review boards of participating centres. Informed consent was obtained from patients and parents according to local requirements.

2.3. Treatment

All HCC cases (including FL-HCC) were classified as high risk. The SIOPEL-2 and -3 high risk regimen