Clinical and molecular insights into primary pediatric liver cancer
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General introduction to primary pediatric liver cancer and introduction to part I – novel clinical series of primary pediatric liver cancer
Epidemiology and Etiology

Liver cancer comprises 0.5-2% of pediatric solid cancers, implying that the liver is a rare anatomical site for pediatric cancer (1, 2). Hepatoblastoma (HB) and hepatocellular carcinoma (HCC) are the two most common pediatric malignant liver tumors.

Hepatoblastoma

HB occurs mainly in infants and very young children (3). It is the most common liver cancer in children in the western world although the worldwide incidence is only 0.5-1.5 per million (4). HB is reportedly more common in boys (5, 6). As a result of recent advances in treatment, particularly in surgical and advanced radiotherapeutic approaches, prognosis of pediatric HB has improved, even when diagnosed in advanced stages (7). Current three-year overall survival (OS) is 82% for PRETEXT (PRETreatment EXTent of disease pediatric liver tumor staging system) stage IV HB and 79% for metastatic HB in the most recent trial from Childhood Liver Tumours Strategy Group (SIOPEL) (8). Associated risk factors for HB include low birth weight, familial adenomatosis polyposis (FAP), Beckwith-Wiedemann syndrome, glycogen storage disease I-IV, and trisomy 18 (5, 6).

Pediatric Hepatocellular Carcinoma and Fibrolamellar Hepatocellular Carcinoma

HCC is the most common malignant pediatric liver tumor in the developing world, although the exact incidence in these regions is not found in the literature (9). HCC, including its rare histologically distinct variant fibrolamellar hepatocellular carcinoma (FL-HCC), occurs mostly in older children and adolescents (3,10). A claim that FL-HCC would more often occur in girls (11) could not be substantiated in a larger series by SIOPEL (5, 6, 12 – chapter 3). Despite recent advances in treatment, prognosis of pediatric HCC diagnosed in advanced stages remains much poorer than prognosis of HB, with five-year OS of only 17-22% for all stages of pediatric HCC including FL-HCC, in recent trials from SIOPEL and the Children’s Oncology Group (COG) (13, Murawski M et al. Submitted - chapter 2). Risk factors for pediatric HCC include hepatitis B (HBV), hepatitis C (HCV), Glycogen storage disease I-IV, Alagille Syndrome, tyrosinemia and familial progressive intrahepatic cholestasis (14). Pediatric HCC has commonly been reported to originate in healthy livers in patients in western countries, whereas in areas where HBV is endemic, the majority of pediatric HCC patients are chronically infected with HBV (5, 15, 16). Importantly, this does not necessarily mean that these tumors develop in cirrhotic livers, as HBV may lead to HCC independently of cirrhosis through activation of the protein LAMTOR5 (a.k.a. HBV X-interacting protein) or through integration of HBV DNA into the hepatocyte genome leading to chromosomal instability, suppression of tumor suppressor genes and activation of oncogenes (17, 18). For FL-HCC, no risk factors such as underlying liver disease or hepatic viruses have been established (12 – chapter 3).
ADULT HEPATOCELLULAR CARCINOMA

With a worldwide incidence of approximately 15:100,000 in males and 5:100,000 in females, HCC is the most common primary liver cancer in adults, and the third most common cause of cancer-related deaths worldwide (19, 20). Particularly in the Western world the incidence is rising due to increasing incidence of chronic HCV, alcoholic liver disease and non-alcoholic fatty liver disease (18, 21, 22). Adult five-year OS remains below twelve percent in the United States (18). A worldwide survival rate beyond a range of several months was not found in the literature (23). The exceedingly poor outcome may be related to heterogeneity in clinical circumstances; in many parts of the world most cases are still detected in advanced stages, where they are no longer amenable to curative treatment. Furthermore, underlying liver disease may limit curative treatment options.

The much higher incidence of HCC in adults compared to children was exploited in a translational research project as part of this thesis (chapter 8). A series of adult HCCs large enough to allow for significant research results was analyzed. Subsequently, results were compared to findings in smaller series of the rare pediatric liver tumors.

The biological background in which primary liver tumors arise in children and in adults appears similar: in both patient groups the disease process is the result of a vicious cycle of cell damage and repair; although in most HCCs arising in adults, decades of compounded cell damage and repair due to chronic hepatic viral infection, alcohol abuse or nonalcoholic fatty liver disease result in its end-stage: cirrhosis (18).

HISTOLOGY

HEPATOBLASTOMA

The histology of HB can be either purely epithelial in which case the phenotype is classified as pure fetal, pure embryonic, mixed fetal/embryonic, macrotrabecular or small cell undifferentiated (SCUD); or it can be mixed epithelial and mesenchymal with or without teratoid features (5, 24). HB is generally understood to arise from pluripotent stem cells in the liver during its development, and thus the majority of cases occur early in life (25). Although the histological typing of HB thus far has not been regarded to have definitive prognostic significance, pure fetal histology seems to have a better clinical outlook (26, 27) and SCUD histology may be associated with poor prognosis (28, 29).

PEDIATRIC AND ADULT HEPATOCELLULAR CARCINOMA

The histology of HCC in pediatric patients resembles that of HCC in adults, with well differentiated tumor tissue consisting of large pleomorphic cells with prominent nucleoli, phenotypically similar to mature hepatocytes with a compact or trabecular growth pattern (30, 31). Although HB and HCC are distinct entities, they may rarely co-exist in a mixed fashion.
within one lesion, termed transitional liver cell tumor (TLCT), which is most prevalent in adolescents \(6, 15, 32, 33\). The origin of HCC is subject to debate \(34\). Several hypotheses are found in the literature. Some claim that the two main hypotheses of HCC development, dedifferentiation of mature hepatocytes and maturation arrest of liver stem cells, can co-exist in a nonexclusive manner \(35\). They argue that alterations in rodent liver tissue after exposure to hepatocarcinogens support both theories \(35\). According to this concept, changes in liver architecture (formation of foci and nodules) induced by carcinogens would support dedifferentiation. Meanwhile, proliferation of bipotential hepatic progenitor cells that can differentiate into either hepatocytes or cholangiocytes upon exposure to carcinogens would support a maturation arrest of stem cells \(35\). In a more recent study, higher expression of progenitor cell markers KRT7 (a.k.a. cytokeratin 7) and KRT19 (a.k.a. cytokeratin 19) in HB-like HCC was found \(36\). However, these findings of increased expression do not confirm stem cell origination \(36\). The authors acknowledged that these findings could result from dedifferentiation of mature hepatocytes as well \(36\). Furthermore, they found that the majority of the 139 human HCCs analyzed in the study were derived from hepatocytes \(36\). Others take a firm stance for maturation arrest of stem cells as the sole origin of certain cases of HCC \(34, 37\). A largely overlapping gene expression pattern between intrahepatic cholangiocarcinoma and HCC with high MAPK8 (a.k.a. JNK1) levels, was advanced to suggest shared origin from bipotential hepatic progenitor cells \(37\). Overlap between gene signature of stratified cohorts of HB and HCC suggests that certain cases of HCC may indeed arise from liver stem cells or hepatic progenitor cells \(36, 38, 39\). In that perspective, HB may represent an early stage of this type of HCC \(40\).

**FIBROLAMELLAR HEPATOCELLULAR CARCINOMA**

FL-HCC is characterized by a histologic appearance of lamellar stroma containing large polygonal cells composed of deeply eosinophilic cytoplasm that may contain pale bodies and hyaline globules, with large nuclei comprising marginalized chromatin and prominent nucleoli \(10, 41\). A recent report indicates that stem cells may play a significant role in FL-HCC pathogenesis \(42\). Certain molecular components aberrantly expressed in FL-HCC (discussed below) also indicate that this tumor could have its origins in precursor cells that may differentiate into hepatocytes and biliary cells \(43\).

**CYTOGENETICS AND MOLECULAR BACKGROUND**

Knowledge of the histologic background of a tumor is crucial to make a correct diagnosis and, as in the case of HB, may assist in predicting biological tumor behavior and determining an accurate prognosis \(44\). For pediatric HCC, such specific associations between subtypes of histology and prognosis have not been made \(15\). Furthermore, discerning HB from HCC is not always straightforward. Especially when alpha-fetoprotein (AFP, the main diagnostic marker in HB and HCC) is low, differentiating can be challenging. Thus, research efforts
are directed at elucidating cytogenetic background, molecular biology and other diagnostic markers of these tumors. Results from such efforts are discussed in the following sections. All cytogenetic and molecular aberrations and correlations mentioned in the following sections are significant findings from the respective studies. HUGO Gene Nomenclature Committee (HGNC) approved abbreviations are used throughout; full names and/or aliases can be found in the list of abbreviations (Appendix).

HEPATOBLASTOMA
On the cytogenetic level, chromosomes 1, 2, 8 and 20 are frequently altered in HB, with gains more prevalent than losses (24, 44-47). In terms of molecular aberrations, the WNT pathway is frequently activated in an aberrant way in HB, in particular in aggressive HBs (24, 44-47). CTNNB1 (a.k.a. beta-catenin) is the most commonly deregulated component of the pathway (44-46). Other reported deregulated pathways in HB are the NOTCH, SHH (a.k.a. Sonic Hedgehog), TGFB1, and EPHB2 (formerly known as ERK) pathways (47-56). EPHB2 deregulation is associated with aggressive epithelial HBs with a small cell component (24). Apoptosis and cell cycle pathways are also reportedly aberrant in HB (24, 39, 57-59).

PEDIATRIC HEPATOCELLULAR CARCINOMA
Few studies were done on the cytogenetic and molecular background of HCC in the pediatric population. One study comparing nine childhood and nine adult HBV-positive cases found more frequent loss of heterozygosity (LOH) of 13q in pediatric HCC, LOH of 8p and 17p with similar frequencies in pediatric and adult cases, lower levels of CCND1 (a.k.a. Cyclin D) in childhood HCC and similar levels of CDK4 (cyclin dependent kinase 4) and CCNE1 (a.k.a. Cyclin E) – which is believed to substitute for CCND1 function in its absence (60). Interestingly, 13q contains the locus of the tumor suppressor geneRB1, which is involved in cell cycle control when functional, and associated with late progression and more aggressive HCC when disabled (61). Another comparison of ten childhood HCCs with sixteen adult HCC cases, 21 cholangiocarcinomas and 28 HBs, found the proto-oncogenMETexclusively mutated in pediatric HCCs (62). The MET/HGF pathway (hepatic growth factor) is involved in development, cell function and tissue homeostasis (63).

FIBROLAMELLAR HEPATOCELLULAR CARCINOMA
The combination of gain of chromosome 4q and losses at 9p, 16p and Xq is specifically found in FL-HCC (64). Hepatobiliary precursor cell markers KRT7, ETFA, CEACAM5, ILL13RA2 (interleukin 13 receptor subunit alpha 2), and EPCAM (epithelial cell adhesion molecule) are aberrantly expressed in FL-HCC. These markers may assist in distinguishing between FL-HCC and HCC, as they are expressed in a minority subset of HCC only (43). Furthermore, theCTNNB1 andTP53 (a.k.a. p53) mutations of HCC are not typically found in FL-HCC (65). However, the distinction of FL-HCC from cholangiocarcinoma can be difficult, as both tumor types display biliary markers and have low AFP levels. Other molecular aberrations detected in FL-HCC include high levels of embryonic development markerAGR2 (anterior
gradient 2), which is scarcely found in HCC, and high levels of phosphorylated NFKB1 (Nuclear Factor kappa B), which may serve as a diagnostic marker as it is absent from non-neoplastic liver tissue (66, 67). Furthermore, an increase in the cell cycle regulator CDKN2A (cyclin-dependent kinase 2A, a.k.a. p16INK4) in FL-HCC is associated with G0-G1 cell cycle arrest (68).

ADULT HEPATOCELLULAR CARCINOMA

Most cases of adult human HCC are aneuploid. Recurrent gains are reported at 1q, 6p, 8q, and 20q (69-75). Common losses in adult HCC are found at 4q, 8p, 13q, 16q and 17p (64, 69-75). In one study, loss of 8p was found to be specific for HCC; it did not occur in evaluated FL-HCC or HB cases (64). The amplified regions of 1q, 6p and 17q contain genes with roles in angiogenesis such as VEGFA (vascular endothelial growth factor A), and in development and differentiation such as RPS6KB1 (ribosomal protein S6 kinase), while the region of loss at 4q contains apoptosis-related CASP3 (Caspase 3) (76).

Strikingly, when comparing chromosome imbalances in adult HCC with those in HB, gains in chromosomes 1, 8 and 20 are common in both tumor types. However, too little data is available to draw conclusions on similarities in imbalances between adult HCC and pediatric HCC or FL-HCC. Although clinical characteristics of pediatric and adult patients with primary liver cancer are clearly different, it becomes apparent from the overview of most frequently aberrant pathways that many similarities in molecular background between pediatric and adult primary liver cancer exist (57, 60). In adult HCC, like in pediatric HB and HCC, the main aberrantly activated or repressed pathways include pathways involved in growth, development and differentiation: the WNT/CTNNB1, EPHB2 and TGFB1/MTOR (mechanistic target of rapamycin) signaling routes (77). Furthermore, angiogenesis and apoptosis pathways are often deregulated (77). Ubiquitination and ubiquitination-like pathways were relatively recently discovered to play a role in HCC; these pathways will be discussed in more detail after a short overview of other important aberrant pathways.

WNT/CTNNB1 PATHWAY

Like in HB, mutation of CTNNB1 is a major genetic alteration in HCC, together with the below described mutation of TP53, accounting for the two main genetic alterations commonly described (44, 79-81). Interestingly, CTNNB1 mutation in HCC correlates with a high differentiation grade and absence of underlying liver disease, which may translate clinically in patients presenting with larger tumors (65, 82).

EPHB2 PATHWAY

An evaluation of RASA1 involvement in HCC showed a role in more differentiated HCC and early carcinogenesis of FL-HCC (81, 83, 84). In contrast, increased RAF1 is found in late stages of HCC. EPHB2 expression has been associated with HCC disease progression (84-87). One group reported mutation of the MET oncogene exclusively in pediatric cases (62),
whereas upregulation of the MET receptor (a.k.a. hepatic growth factor receptor, HGFR), was reported in adult HCC by others (88, 89). Moreover, MET overexpression was associated with increased vascular invasion and poor prognosis (88, 89).

**TGFB1/MTOR PATHWAY**

Loss of the tumor suppressor phosphatase gene PTEN correlates with increased levels of phosphorylated AKT1 and phosphorylated MTOR in HCC (90, 91). These PIK3CA (a.k.a. PI3K)/PTEN/AKT1/MTOR pathway aberrations were associated with advanced tumor grade, increased intrahepatic metastasis, vascular invasion, a higher TNM stage and a high MKI67 (a.k.a. Ki-67) index (90, 91).

**ANGIOGENESIS PATHWAY**

Conflicting data are available regarding the role of TGFA (transforming growth factor, alpha) in HCC. High expression of TGFA, which acts on EGFR (epidermal growth factor receptor), may correlate with proliferation of neoplastic hepatocytes (92). However, others found that TGFA levels were high in hardly dividing, well-differentiated HCC (93), while a third group found similar TGFA levels in HCC and adjacent noncancerous tissue (94). Yet another study found a relationship between tissue TGFA concentration and severity of liver dysfunction, with levels in cirrhotic tissue surpassing those in HCC (95). These results would imply that TGFA serves as a marker for deregulation of liver function rather than a specific HCC marker. EGFR was reported to be lower in HCC than in noncancerous tissue in one study (96), and specifically high in poorly differentiated HCC in another study (93). Increased KDR (a.k.a. vascular endothelial growth factor receptor, VEGFR) expression was found to correlate with male gender, higher tumor differentiation grade, HbsAg positivity, and cirrhosis (89, 97). Increased PDGFRB (platelet derived growth factor receptor B) expression was shown to correlate with plasma AFP concentration, tumor size, cirrhosis, and overall survival (89, 98).

**APOPTOSIS PATHWAY**

Loss of TP53 and CDKN2A is associated with advanced stage (99). Mutation of TP53 is highly common in HCC and TP53 mutations together with CTNNB1 and WNT mutations constitute the most prevalent genetic alterations in HCC (79, 80). Hepatocarcinogenesis induced by Aflatoxin-B1 contaminated food and HBV is specifically linked to an arginine to serine substitution at codon 249 of exon 7 of TP53. (100, 101)

**CELL CYCLE CONTROL PATHWAYS**

Expression of the cell proliferation marker PCNA and the cell cycle regulators CDK4, CCNB1 (Cyclin B1), CCNA2 (Cyclin A2), and CKS2 (CDC28 protein kinase 2) was found in a low survival subclass of HCC in a gene expression profiling effort in 89 HCCs (102).
UBIQUITINATION AND UBIQUITINATION-LIKE PATHWAYS

In a study in which distinct subclasses of HCCs were distinguished, upregulation of genes involved in the ubiquitination and ubiquitination-like pathways was found in the subclass with ominous prognosis, suggesting etiologic involvement of these signaling routes in disease progression (102).

Taken together, analyses of cytogenetics and molecular biology of primary liver cancer have elucidated a number of putative diagnostic and prognostic markers, which should allow selection of specific cases for targeted therapy. However, by evaluating these findings it becomes apparent that available data are heterogeneous and scattered and full-scale knowledge of essential aberrations is not yet available (103, 104). The thus far limited benefits of these developments are discussed below.

CURRENT TREATMENT MODALITIES

Surgery has a crucial role in the management of all hepatic tumors discussed here, as complete resection is the key to cure (105-108). Currently, in countries following the treatment guidelines of SIOPEL, in most cases of HB as well as HCC, surgery is preceded by chemotherapy (15, 109). Primary surgery may be performed in lower stages of HB and complete resection alone suffices in cases of pure fetal histology with low mitotic index (27, 109). Current chemotherapy regimens for HB consist of one or more of the proven effective agents cisplatin, vincristine, 5-fluoro-uracil, cyclophosphamide and doxorubicine, although, due to toxicity, the latter may be better reserved for advanced or recurrent cases (110). Unresectable HB is treated with chemotherapy and then evaluated for resectability or orthotopic liver transplantation (OLT) (110). In HCC diagnosed in lower/earlier stages, complete tumor resection with or without OLT, radio-frequency ablation, and (chemo-)embolization provide a chance for cure (5, 110). In a recent study evaluating treatment strategies of primary pediatric liver tumors, primary OLT was performed in two HBs and four HCCs, and secondary OLT in one TLCT and one HCC (111). After more than one year, four children were alive without evidence of disease (one from the HB group, three from the HCC group, of whom one had undergone secondary OLT), whereas four patients had died, of whom three of noncancer causes (111). Given the generally poor outlook for pediatric patients in whom OLT is indicated, these results are relatively promising. Especially in pediatric HCC, the liberal use of liver transplantation omitting the Milan criteria is more and more advocated (16). The Milan criteria comprise as requirements that the cancerous process does not consist of more than one solitary nodule with a maximum diameter of five centimeter, or three nodules measuring each maximally three centimeter, and that no vascular invasion or extrahepatic manifestation is present (112).
For FL-HCC, regardless of stage at diagnosis, the only currently available effective treatment is complete resection at the earliest opportunity (12 – chapter 3). Unfortunately, also in advanced or recurring HCC the aforementioned treatment modalities rarely yield results. Although many agents targeting specific molecular players in advanced HB and HCC have been developed and tested, efficacious chemotherapeutic options are still limited. Considerable differences in clinical background and genetic make up between cases warrant the search for a wider range of standard treatments to strive for management options in all cases (77).

**NOVEL AGENTS IN CLINICAL TRIALS**

From the wide array of molecular players implicated in hepatocarcinogenesis, a number of attractive targets in human HCC have been established. Agents targeting these actors have been evaluated or are currently being evaluated in clinical trials. These include tyrosine-kinase inhibitors (TKI) with names ending in ‘nib’ and monoclonal antibodies with names ending in ‘mab’. Examples are agents targeting angiogenesis-related proteins such as VEGFA/KDR and PDGFRB (23). These include sorafenib (which also targets RAF1/MAP2K2/EPHB2), sunitinib, brivanib, bevacizumab, ramucirumab, TSU-68, linifanib, cediranib, pazopanib, lenvanib, lenalidomide, and axitinib (23, 104, 113). Agents targeting EGFR include erlotinib, gefitinib, lapatinib, and cetuximab (23, 104). Agents targeting PIK3CA/AKT1/MTOR targeting agents are everolimus, temsirolimus, sirolimus and rapamycin (23, 76, 104). MAP2K2 is targeted by selumetinib and refametinib (104). MET/HGF targeting agents are tivantinib and cabozantinib (104). Other examples are ganetespib targeting HSP90AA1, PI-88 targeting FGF1/HPSE, and mapatumumab for TNFRSF10A (tumor necrosis factor receptor superfamily, member 10a) (23). So far, the small molecule TKI sorafenib and its later modifications seem the most effective (114). Current chemotherapeutic treatment of adult patients with metastatic HCC (and an otherwise decent performance status) therefore consists of sorafenib or a sorafenib-based regimen (23). In a small retrospective study, the German Society for Pediatric Oncology and Hematology (GPOH) added sorafenib on a ‘compassionate use’-base to cisplatin and doxorubicin in pediatric HCC, with promising results (6/12 patients were in complete remission after a median follow up of 20 months) (115). A prospective trial evaluating the efficacy of sorafenib in relapsed or refractory pediatric HCC is currently run by COG and an international protocol by COG, SIOPEN, GPOH and Japanese Study Group for Pediatric Liver Tumors (JPLT) is in preparation (115, 116). However, acquired resistance to sorafenib, possibly through activation of PIK3CA signaling, is an important issue (117). The second generation TKI EKB-569, which in addition to EGFR and KDR also targets ERBB2 (a.k.a. HER2NEU), shows promise in multi-drug resistant cells in vitro (118). A synergistic effect was observed in highly resistant cells when a combination of EKB-569 and sorafenib was applied (118). Combining drugs to enhance the effect of sorafenib, while targeting multiple molecular pathways at once, may be the approach of choice in advanced HCC (23). Gain in survival and quality of life acquired with currently available agents is modest at best. Robust molecular biomarkers to predict
efficacy, toxicity and resistance and new, more effective targeting agents are needed to gain terrain in advanced primary liver tumors through so called 'precision' medicine (104).

CONCLUSIONS AND WAY FORWARD

Extensive knowledge of aberrantly activated and silenced molecular pathways in these tumors is required in order to develop new, more efficacious pharmacologic treatment strategies targeting important molecular components in advanced HB and pediatric HCC (119). Given the epidemiology, despite the current absent requirement of tissue biopsy to diagnose HCC in adults, obtaining large numbers of samples for evaluation of molecular biology is more attainable in the adult HCC patient group and arguably the next best option in the absence of large pediatric series (22, 120). However, it is frequently debated whether primary liver tumors in adult patients, arising in the background of cirrhosis, have the same biological behavior in pediatric patients (15). Pronounced aberrance of the angiogenesis pathway in adult patients but not in pediatric patients may be related to cirrhosis; high expression of KDR (VEGFR) was shown to correlate with hepatic cirrhosis (89). Even without definitive answers to confirm or reject such hypotheses, information gained from the adult patient group may be highly useful in obtaining insights in the most recurrent molecular abnormalities and the most successful treatment strategies addressing those. A good example of this approach is the efficacy of sorafenib in adults and its early promise in pediatric patients (23, 115). Furthermore, collaboration of national and international consortia, such as the COG, SIOPEL, JPLT and GPOH in initiatives such as Children’s Hepatoma International Collaboration (CHIC), are essential for future progress in the field of primary pediatric liver tumors in order to collect sufficient treatment data given the low incidence of these tumors (121). These groups are currently bundling forces to execute molecular background studies and analyze new treatment regimens in combined pediatric series.

SCOPE AND OUTLINE OF PART I OF THE THESIS

The current status of treatment and prognosis of pediatric liver tumors is discussed in the first part of this thesis, in chapters 2 and 3, by means of an analysis of the most recent treatment results of the most recent HCC series and a sub-analysis of FL-HCC versus conventional HCC derived from this series from the Childhood Liver Tumour Strategy Group (SIOPEL).
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