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Advances in the conventional clinical treatment for hepatoblastoma and therapeutic innovation

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ABSTRACT

Background Hepatoblastoma (HB) is a rare malignancy usually occurring in children under 3 years old. With advancements in surgical techniques and molecular biology, new treatments have been developed.

Data resources The recent literatures on new treatments, molecular mechanisms and clinical trials for HB were searched and reviewed.

Results Surgical resection remains the main option for treatment of HB. Although complete resection is recommended, a resection with microscopical positive margins (R1) may have similar 5-year overall survival and 5-year event-free survival (EFS) rates after cisplatin chemotherapy and the control of metastasis, as only once described so far. Indocyanine green-guided surgery can help achieve precise resection. Additionally, associating liver partition and portal vein ligation for staged hepatectomy can rapidly increase future liver remnant volume compared with portal vein ligation or embolization. Cisplatin-containing chemotherapies slightly differ among the guidelines from the International Childhood Liver Tumors Strategy Group (SIOPEL), Children's Oncology Group (COG) and Chinese Anti-Cancer Association Pediatric Committee (CCCG), and the 3-year EFS rate of patients in SIOPEL and CCCG studies was recently shown to be higher than that in COG studies. Liver transplantation is an option for patients with unresectable HB, and successful cases of autologous liver transplantation have been reported. In addition, effective inhibitors of important targets, such as the mTOR (mammalian target of rapamycin) inhibitor rapamycin, β-catenin inhibitor celecoxib and EpCAM (epithelial cell adhesion molecule) inhibitor catumaxomab, have been demonstrated to reduce the activity of HB cells and to control metastasis in experimental research and clinical trials.

Conclusion These advances in surgical and medical treatment provide better outcomes for children with HB, and identifying novel targets may lead to the development of future targeted therapies and immunotherapies.

INTRODUCTION

Hepatoblastoma (HB) is a rare childhood malignant tumor with an incidence rate of 0.4 per 100 000 people per year.[1] It often arises in teenagers under the age of 15 years, especially in children under 3 years old, and is relatively rare in adults,[2] with only 47 cases reported in English articles from 1958 to 2016.[3] Due to its non-specific clinical manifestations, most patients are diagnosed at an advanced stage. Currently, the international pediatric liver tumor collaboration groups include the Children's Oncology Group (COG), International Childhood Liver Tumors Strategy Group (SIOPEL),[4] Society for Pediatric Oncology and Hematology (GPOH), and Japanese Pediatric Liver Tumors Group (JPLT). Among them, the guidelines of the first two groups are widely accepted due to their rational therapeutic schemes. The Children's Hepatic Tumor International Collaboration (CHIC) has incorporated their data into a collaborative database.[5] In China, a consensus has been reached on the diagnosis and treatment of HB (CCCG-HB-2016)[6] based on COG, SIOPEL and their personal experiences. At present, the main treatment strategies for patients with HB include surgical resection, autologous or allogeneic liver transplantation, and chemotherapy. Advances in surgical techniques and therapeutic strategies have improved the precision of hepatectomy and patient prognosis. Additionally, the recent breakthroughs in molecular biology and immunology will facilitate the clinical use of immunotherapies and targeted therapies in HB. In this review, we mainly focused on the progress in conventional clinical treatments and potential laboratory targets or pathways for future therapeutic interventions.

CLINICAL TREATMENT

Staging

There are two widely accepted staging systems: the preoperative SIOPEL system[4] based on imaging assessments and the postoperative COG staging system[7] based on pathology.[8] The Chinese Anti-Cancer Association Pediatric Committee (CCCG) accepted the PRE Treatment EXTent of disease (PRETEXT)/POST-Treatment EXTent of disease (POSTTEXT) system and further modified the COG staging system (table 1) and risk stratification

Table 1 Modified COG Evans staging system (CCCG-HB-2016)[6]

Stage	Definition
Stage Ia	Complete resection, PFH.
Stage Ib	Complete resection, non-PFH.
Stage II	Incomplete resection with microscopic residue.
Stage III	Incomplete resection with macroscopic residue. Incomplete resection with positive lymph nodes. Tumor rupture or intraperitoneal bleeding.
Stage IV	Distant metastasis at diagnosis, whether primary lesion resection or not.

CCCG-HB-2016, Chinese Anti-Cancer Association Pediatric Committee Hepatoblastoma consensus 2016; COG, Children's Oncology Group; HB, hepatoblastoma; PFH, pure fetal histology.

system (table 2) on the basis of their personal experience. Analysis of patient data in the CHIC data set verified the reliability and hierarchy of most traditional prognostic indicators, such as old age (especially >8 years), lower or higher alpha fetoprotein (AFP) serum levels (<100 ng/mL or ≥1 000 000 ng/mL), PRETEXT annotation factors and distant metastasis.[9 10] The lung is the most common site of metastasis and recurrence site. For patients with HB with lung metastasis, chemotherapy is recommended first, and lung metastasectomy is feasible if it does not achieve complete resection (CR). The outcome of those that achieve CR by chemotherapy only is relatively better resulting from the JPLT-2, SIOPEL-3 and SIOPEL-4 studies.[11 12]

Surgical margins and long-term outcomes

The integrity of resection plays a decisive role in the subsequent disease progression and prognosis. R0 resection (microscopically margin negative) is recommended, but the negative impact of R1 resection (microscopically margin positive) on the survival rate of children remains controversial.[13 14] In early 2004, Dicken *et al*[15] preliminarily observed no significant difference in survival between margins <1 cm of grossly uninvolved liver parenchyma and ≥1 cm after controlling pulmonary metastasis in 23 patients treated for primary HB. Instead, extrahepatic disease and macrovascular involvement were identified as poorer prognosis predictors.[15 16] In recent long-term follow-up studies, the 5-year overall survival and 5-year event-free survival (EFS) rates of PRETEXT III/IV stage patients with R1 section were shown to be similar to those in patients with CR,[14 16 17] when postoperative chemotherapy was administered, with normal AFP serum levels and imaging manifestations.[14] Ren *et al*[17] recently stratified the data from 2005 to 2017. They found that R1 resection might be associated with decreased survival in children with mixed epithelial/mesenchymal HB compared with R0 resection and not affect survival outcomes in those with an epithelial subtype without metastasis, confirming the greater importance of conventional prognostic indicators for survival outcomes compared with R0/R1 resection. Therefore, although R0 resection remains the primary aim, R1 resection or surgery with 'planned close margins', that is, extreme resections,[13] might also have good outcomes and be valuable when orthotopic liver transplantation is not possible.

Table 2 Risk stratification system (CCCG-HB-2016)[6]

Risk group		AFP (ng/mL)	PRETEXT staging system	COG staging system	Pathological type	P+/V+/M+/E+/H+/N+	Note
Very low risk				Stage I	Differentiated PFH		Both met simultaneously.
Low risk	1	≥100	Stage I/II			None	All met simultaneously.
	2			Stage I/II	Non-PFH and non-SUC		Both met simultaneously.
Intermediate risk	1		Stage III				
	2			Stage I/II	SUC		Both met simultaneously.
	3			Stage III			
High risk	1	<100					Satisfy any of them.
	2		Stage IV				
	3			Stage IV			
	4					P+/V+	

AFP, alpha fetoprotein; CCCG-HB-2016, Chinese Anti-Cancer Association Pediatric Committee Hepatoblastoma consensus 2016; COG, Children's Oncology Group; E+, extrahepatic and intra-abdominal diseases; H+, liver rupture or intraperitoneal bleeding; HB, hepatoblastoma; M+, instant metastasis; N+, lymph node involvement; P+, portal vein invasion; PFH, pure fetal histology; PRETEXT, PRE Treatment EXTent of disease; SUC, small cell undifferentiated; V+, inferior vena cava or hepatic vein invasion.

Indocyanine green in surgical resection

Indocyanine green (ICG) fluorescent imaging[18] helps surgeons achieve precise primary resection and metastasectomy. When injected preoperatively, ICG is cleared by normal liver cells and is excreted into the biliary tract but remains in tumor cells for a relatively long time. Clinically, ICG molecular fluorescence imaging is applied to detect primary lesions and metastases that cannot be visualized by the naked eye, making negative resection margins possible. The dose and timing of ICG injections for HB have not been standardized,[19] but ICG is generally injected intravenously at a dose of 0.5 mg/kg 72 hours before surgery.[18 20–22] Because ICG is only visible in the near-infrared mode, frequent switching between the normal white-light mode and near-infrared mode is required to resect the stained tumor during surgery. To further improve the feasibility of real-time operations, the PINPOINT endoscope fluorescence imaging system with the same focal distance between the white-light mode and the near-infrared mode has been applied. This system overlays both modes and displays HB metastases injected with ICG on the white-light image in high definition, which simplifies the surgical steps without frequent screen switching.[21] Furthermore, projection mapping technology has also been used in some cases of HB with lung metastasis. The Medical Imaging Projection System projects the fluorescence image obtained by CT onto the surface of the target organ. With this system, the use of monitors and a dark environment are not required.[23]

Associating liver partition and portal vein ligation for staged hepatectomy

Extensive liver resection may lead to severe posthepatectomy liver failure due to an insufficient volume of the future liver remnant (FLR).[24] The greatest advantage of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is the rapid increase in the FLR volume compared with portal vein ligation or embolization.[25 26] ALPPS is a two-stage hepatectomy procedure, including portal vein ligation and staged liver resection.[10 27] During the first stage, the liver is completely divided from the FLR with concomitant portal vein ligation of the lobe that will be removed, and the biliary tract system and the blood vessels are well preserved. During the second stage, hepatectomy is performed after achieving adequate FLR (at least 50% of the total liver volume).[27 28] ALPPS has shown promising results in adults with hepatobiliary malignancies, but pediatric cases are rarely reported. Chan *et al*[29] in 2014, Wiederkehr *et al*[27] in 2015 and Hong *et al*[24] in 2017 successively performed ALPPS or monosegmental ALPPS in pediatric patients with HB with PRETEXT stage III/IV, and most of them showed a rapid increase in FLR and a decrease in AFP serum levels. In August 2020, Akhaladze *et al*[25] reported the first case of pure laparoscopic first-stage ALPPS in a child and showed the feasibility of a laparoscopic approach. In summary, ALPPS provides a better opportunity for CR in patients with primarily unresectable liver tumors, but may also be related to complications such as multifocal recurrence,[30] pleural effusion and pneumonia.[28] Therefore, the use of ALPPS in pediatric patients deserves further evaluation.

Liver transplantation

The indications for liver transplantation are similar in several groups including COG, SIOPEL, JPLT and CCCG. When the POST-TEXT evaluation of patients is the POST-TEXT IV or P2 (involvement of the main portal vein) or V3 (involvement of all three hepatic veins and/or the inferior vena cava) in POST-TEXT, liver transplantation is recommended.[4 6 31 32] In other words, those who respond to chemotherapy but have unresectable tumors and no evidence of persistent extrahepatic disease should be considered for liver transplantation. The CCCG consensus indicates that liver transplantation can be applied after the distant metastasis is removed by surgery or chemotherapy, so the lung metastasis is not the contraindication for orthotopic liver transplantation.[6 33] For the unresectable HB, liver transplantation may be effective, with a long-term survival rate of 80% after combination treatment.[34–36] Shi *et al*[37] successfully implemented ex vivo liver resection and autotransplantation for children with HB. The procedure includes removal of the malignancy in vitro or semi-in vivo, transplanting the remaining liver and anastomosing the superior and inferior vena cava, bile duct and other duct systems to restore the liver blood supply.[38] Compared with allogeneic liver transplantation, this approach overcomes the limitations of liver resource scarcity and rejection. Besides, living-related liver transplantation is another better choice to avoid the waiting time for deceased donor liver. The liver graft procured from donor relatives for pediatric recipient always includes the left lateral segment without inferior vena cava,[39 40] and the reconstruction of inferior vena cava cannot be avoided. Because the Dacron synthetic blood vessel cannot adapt to the growth of children, it is necessary to find a large lumen vein graft (such as the autogenous iliac vein, recanalized umbilical vein and donor internal jugular vein) to reconstruct the vena cava.[41–43] Regarding the timing of liver transplantation, Isono *et al*[44] suggested that liver transplantation could be performed when the AFP level remained stable after the last chemotherapy treatment.

Chemotherapy regimen

The SIOPEL and GPOH groups recommend preoperative chemotherapy for HB to achieve smaller resection, whereas the COG and CCCG groups recommend early and primary resection for localized HB and neoadjuvant chemotherapy for advanced stages. Regarding chemotherapy regimens, the COG and CCCG groups use the C5V regimen (cisplatin, fluorouracil and vincristine) as the standard care for low-risk patients and the C5VD regimen (cisplatin, fluorouracil, vincristine and doxorubicin) for intermediate-risk patients. There is a slight difference between COG and CCCG guidelines regarding the high-risk regimen. CCCG recommends

ifosfamide and etoposide to decrease the cumulative dose of cisplatin and doxorubicin,[6 45] whereas the VI regimen (vincristine+irinotecan) is introduced as upfront window therapy in the COG study AHEP0731.[46 47] The 3-year EFS of patients with high-risk HB was 49% in this COG study and 75.7% in a Chinese single-center study that followed the CCCG-HB-2016 consensus.[45–47] In comparison with these, the SIOPEL and GPOH groups focused more on the frequency and dose of platinum derivatives with or without doxorubicin.[12 48–50] In the SIOPEL-4 study of children with untreated high-risk HB, the children were given cisplatin, doxorubicin and carboplatin and the 3-year EFS was 76%.[4 6 10 45]

Cisplatin-induced ototoxicity

Ototoxicity is a severe complication of platinum-containing chemotherapy. Several ototoxicity criteria or grading systems, such as the National Cancer Institute Common Toxicity Criteria for Adverse Events, Brock Ototoxicity Grades and International Society of Pediatric Oncology (SIOP) Boston scale, have been developed. Among them, the SIOP scale may be more sensitive in classifying ototoxicity in children.[51 52] The accumulated dosage and single maximum dose of cisplatin have been reported to serve as independent predictors of moderate to severe hearing loss.[53] In the SIOPEL-6 trial, sodium thiosulfate (20 g/m^2) given 6 hours after cisplatin chemotherapy was demonstrated to effectively reduce hearing loss in patients with standard-risk HB,[54] which was consistent with the results of the COG study ACCL0431 which included heterogeneous samples.[55] In contrast, amifostine is not recommended because personal advantages or direct benefits were not observed in previous single-center studies or trials.[56 57] Other sodium diethyldithiocarbamate and intratympanic middle ear therapies are not currently recommended due to their low evidence quality.[56]

IMPORTANT TARGETS AND THEIR INHIBITORS

Tumor-related proteins and pathways have received increasing attention because understanding their function is essential for the development of novel targeted therapies and immunotherapies. Several key studies on classic signaling pathways and their inhibitors will be discussed in the following section (table 3).

The PI3K/Akt pathway

Phosphatidylinositol 3-kinase (PI3K) and its main downstream target serine-threonine kinase (Akt) constitute the PI3K/Akt pathway, which is a central regulator of numerous signal transduction pathways involved in tumorigenesis. Following activation by factors such as insulin-like growth factor-1 and epidermal growth factor, PI3K inhibits cell apoptosis by phosphorylating Akt.[58] PI3K and Akt are highly expressed in HB,[58] indicating the importance of the PI3K/Akt pathway in HB.

Table 3 Promising targets and inhibitors for hepatoblastoma

Target	Inhibitor
mTOR	Rapamycin, polyphyllin VII
PI3K	LY294002
Akt	Emodin, FTY720, furazolidone
β-catenin	Celecoxib, R-etodolac, ICG001, miR-624-5p, let-7i-3p, miR-885-5p
NK1R	Aprepitant, L-733060, L-732138
EpCAM/CD326	Catumaxomab, IGN101, MT110
GPC3	Codrituzumab, vaccines EYILSLEEL and FVGEFFTDV

Akt, serine-threonine kinase; EpCAM/CD326, epithelial cell adhesion molecule; FTY720, fingolimod; GPC3, glypican-3; ICG001, (6S,9aS)-6-(4-hydroxybenzyl)-N-benzyl-8-(naphthalen-1-ylmethyl)-4,7-dioxo-hexahydro-2H-pyrazino[1,2-a]pyrimidine-1(6H)-carboxamide; IGN101, Al(OH)3-formulated Mab17-1A; LY294002, (2)-4-morpholinyl 8-phenyl-4h-1-benzopyran-4-one; MT110, solitomab; mTOR, mammalian target of rapamycin; NK1R, neurokinin receptor; PI3K, phosphodylinositol 3-kinase.

By inhibiting the upstream and downstream proteins in this signaling pathway, the metastasis of tumor cells can be effectively controlled. Classic targeted drugs include Ginkgol C17:1, which is coadministered with cisplatin to stimulate cisplatin-induced apoptosis,[59 60] the PI3K inhibitor LY294002[58] or the mTOR (mammalian target of rapamycin) inhibitor rapamycin.[61]

Molina *et al*[61] used an HB mouse model to observe the effect of rapamycin and found that rapamycin significantly reduced tumor burden in mice. The Chinese herb polyphyllin VII is an mTOR inhibitor and has been found to inhibit mTOR phosphorylation, promote autophagy and further induce HepG2 cell apoptosis.[62] mTOR inhibitors are often used in combination with sorafenib and have been shown to induce cell cycle arrest in the G1 phase and inhibit the invasion ability of tumor cells together with miRNA-378a.[63]

Akt is another key kinase, and inhibition of its phosphorylation effectively prevents signal transduction. Inhibitory drugs include emodin (a derivative of anthraquinone[64]), FTY720 (an immunomodulator of multiple sclerosis[65]) and furazolidone (a broad-spectrum antibiotic[66]). Among them, the immunosuppressive drug FTY720 (fingolimod) has been found to increase cisplatin sensitivity to effectively reduce the activity of HB cells and induce cell apoptosis in vitro and in vivo,[65] which may provide ideas for future clinical tumor treatments.

The Wnt/β-catenin pathway

The Wnt/β-catenin pathway plays an important role in normal development and HB formation. In healthy livers, β-catenin is degraded by the β-catenin destruction complex and proteasome in the absence of extracellular Wnt ligands. However, in the presence of Wnt ligands due to loss of the *APC* gene or mutations in the gene

CTNNB1 (76%–80% of HBs carry mutations in exon 3 of catenin-beta 1[67]), the degradation of β-catenin is inhibited, thus increasing the occurrence of HB.[68]

β-catenin serves as an important target in the treatment of HB. Indersie *et al*[67] established an HB-related microRNA library and screened nine miRNAs. They found that miR-624-5p, let-7i-3p and miR-885-5p inhibited the protein expression of β-catenin, thereby inactivating the Wnt pathway to prolong the G0/G1 phase and shorten the S phase. Among them, as the most effective inhibitor and preferred miRNA replacement therapy, miR-624-5p has been demonstrated to bind to the 3'-untranslated region of β-catenin and target three mRNA variants.[67] Other catenin inhibitors include celecoxib (which increases the cytoplasmic translocation and phosphorylation of β-catenin) and ICG001 (which binds cyclic AMP response element-binding protein to block β-catenin transcription). Combined with cisplatin, these inhibitors decreased the viability of the HB cell line HuU6.[69] In addition, flavonoids such as epigallocatechin gallate induce cytotoxicity in HB cells by downregulating the Wnt target genes *MYC* and *CCND1*.[70]

Neurokinin receptor

Substance P (SP) is widely distributed in the central and peripheral nervous system[71] and is produced by self-stimulated tumor cells. Following specific binding to the neurokinin receptor (NK1R), SP promotes cancer cell proliferation, angiogenesis and migration and inhibits apoptosis. SP has been shown to be overexpressed in breast cancer.[72] In 2015, Berger *et al*[73] first identified overexpression of the truncated NK1R in the human HB cell lines HuU6 and HepG2. Additionally, NK1R antagonists (aprepitant, L-733060 and L-732138) were demonstrated to induce the apoptosis of HB cells and act synergistically with the chemotherapy drug doxorubicin.[73] Ilmer *et al*[74] further revealed the molecular regulatory mechanism of NK1R antagonists. After treatment of HB cell lines with aprepitant, NK1R inhibition downregulated the Wnt signaling pathway and reduced the expression levels of the β-catenin interaction factor FOXM1, thereby disrupting the interaction between FOXM1 and β-catenin.[75] The SP/NK1R complex provides novel therapeutic targets for HB. Aprepitant, one of the drugs used to treat vomiting after chemotherapy, may be applied to future targeted therapy in HB.

Epithelial cell adhesion molecule (EpCAM/CD326)

Epithelial adhesion/activation molecule (EpCAM/CD326) is a type I membrane protein and a potential immunotherapeutic target. Its expression has been observed in epithelial tumor areas in 70%–80% of patients with HB.[76] Armeanu-Ebinger *et al*[76] suggested that the anti-EpCAM bispecific antibody MT110 could simultaneously bind to EpCAM and CD3 and promote the T cell-mediated lysis of HB tumor cells, thereby impairing tumor development. At present, EpCAM antibodies, such as catumaxomab and IGN101, are being investigated in phase II/III clinical trials related to gastric cancer and small cell lung cancer.[77 78]

Glypican-3

Glypican-3 (GPC3), a surface carcinoembryonic antigen, is often overexpressed in solid malignant tumors in children. For example, the upregulation of GPC3 has been reported in 97% of HB cases.[79] GPC3 promotes tumor cell growth and inhibits cell proliferation by activating the Wnt/β-catenin pathway.[79] A Japanese team conducted a phase I clinical trial using GPC3-derived peptide vaccines (HLA-A*24:02-restricted GPC3298–306 peptide (EYILSLEEL) and HLA-A*02:01-restricted GPC3144–152 peptide (FVGEFFTDV)) in children with GPC3 overexpression and found that the vaccines induced a GPC3-specific cytotoxic T lymphocytes response.[80] In addition, monoclonal antibody immunotherapies, such as GC33 (GPC3 monoclonal antibody, also known as codrituzumab), have been shown to have antitumor effects on GPC3-positive tumors in phase I for hepatocellular carcinoma but less clinical benefit in the Ib/II trials.[81–84] These immunological antibodies might be further investigated in clinical trials for HB.

CONCLUSION

The CCCG-HB-2016 consensus based on the widely accepted SIOPEL and COG guidelines and their personal experiences modified the COG Evans staging system and risk stratification system and deserves mention. Cisplatin-containing chemotherapies differ slightly in SIOPEL, COG and CCCG guidelines, and the 3-year EFS of patients was recently shown to be higher in SIOPEL and CCCG studies compared with that in COG studies. Cisplatin-induced ototoxicity can be effectively reduced with sodium thiosulfate, as demonstrated in SIOPEL and COG studies. ICG-guided resection and ALPPS, which rapidly increase the FLR volume, have gained popularity among pediatric surgeons. These advances in surgical and medical treatment provide better outcomes for children with HB. Additionally, the immunotherapeutic drug catumaxomab (an EpCAM inhibitor) and GPC3-derived peptide vaccines have been investigated in clinical trials. The efficacy of other important inhibitors, such as the mTOR inhibitor rapamycin, Akt inhibitory drugs emodin and fingolimod, β-catenin inhibitor celecoxib and NK1R antagonist aprepitant, have been shown in animal experiments. These inhibitors may provide novel ideas for future targeted therapies and immunotherapies in HB.

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