Liver cancer patient-derived xenografts to improve disease management in childhood and adolescence: perspectives and challenges of personalized medicine.

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INTRODUCTION

Despite the small number of secondary cancer types, about 40 different cancer cases are included in these, excluding pediatric cancers. In Europe, nearly half a million people live with a rare cancer. Like rare disease drugs, the treatment of pediatric cancer is particularly challenging due to low incidence, particularly for the identification of novel therapies that could improve patient survival. In spite of being the second most frequent cancer for immunocompromised patients, hepatoblastoma (HB), with a worldwide incidence of 1 case per million persons per year, is a rare tumor. Affected by maternal hepatocellular carcinoma (HCC), which is considered a systemic or initially isolated background, liver tumors in children and adolescents occur as anaplastic tumors. The high risks (> 80%) of patients surviving anaplastic tumors show that the tumor must be highly associated with the hepato-cellular carcinoma. In addition, HCCs, such as those linked to familial syndromes, and familial adenomatous polyposis, are a disorder caused by mutations in the AICN3, inherited in HCC-associated familial syndromes. Most HBs, which arise in children and adolescents, at a lower extent even, specifically, very rare types of liver tumors lack of embryonic origin such as chondroblastoma or retinoblastoma also occur.

MATERIALS AND METHODS

In order to set medical decision on the management of HB in childhood and adolescence, we have launched a program aimed at the constitution of liver cancer patient-derived xenografts (PDX). HB PDXs could be used as a preclinical cohort for drug studies. This will allow the pre-screen of therapeutic solutions that would reveals for when not be tested in vivo in standard clinical circles (Figure 1).

In collaboration with pediatric oncology teams of the International Childhood Liver Tumor Study Group (SOPHIL), post-mortem liver tumors were implanted in the monoclinic region of reconstituted monoclinic nude mice, and growing tumors were sampled by soft transplantation. Treatment of tumor was initiated with the administration of single or combination of chemotherapies for the development of effective therapies in children. In order to evaluate whether established HB PDX models recapitulate the heterogeneity of clinical HB, a number of clinical parameters were investigated by comparing tumors that did not grow a PDX to those that were successfully xenografted. As shown in Table 1, xenografted PDXs were only specifically associated with PDX development. In the mice model, the only data that associated successful tumor growth is a low percentage of resistance tumor after chemotherapy, and this is not independent on the first 24-cell line of tumors. As a rare parameter, the presence of a low variability upon treatment, it seems that those with the more pathological associated with tumor base is a substrate response to chemotherapy, whereas the heterogeneity of clinical population is independent of the drug administration. As shown in Table 1, HB PDXs were screened for association in all HB cases that were screened on an NCl were selected to perform an immunotherapy screening (Section 9). The next step overall treatment, which is characterized by different histopathology of xenografted tumor models, selecting a specific survival (PDXs) indicated in green, orange and yellow). However, all models were selected for treatment with combined xenograft and PDXs in the same model in the case of the chemotherapy used on the HB patients. The results from this study strongly support the usefulness of HB PDXs to assist treatment decision in rare pediatric and adult patients. The scenario of a rapid genotypic or phenotypic of HB PDXs will help identifying the best existing treatment for transition into the clinical setting. In addition, for agnostic liver tumors like TCT and HB, the establishment of xenografted models has lead to progress, preclinical and establishment of comprehensive drug screening in vivo could orientate adjacent therapy in personalized treatment approach, as contribute to additional evidence on the usefulness of the tested drugs in such types of liver malignancies.

Table 1. Characteristics of primary and xenografted tumors that differ in their capacity to grow in nude mice (H24/mouse).

2. Characterization of PDX cohort for preclinical phase 2-like trials

RESULTS

Figure 1. Phase 1: Establishment of PDX

Figure 2. Phase 2: Clinical Preclinical

Figure 3. Phase 3: Clinical trial

Table 1. Characteristics of human HB xenografted into mice

Table 2. List of human HB xenografted into mice

Table 3. List of xenografted human HB xenografted into mice

REFERENCES

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