Liver transplant in HCC

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and is the leading cause of death in cirrhotic individuals. 80% of HCC develops in cirrhotic patients. Unfortunately only 20 to 25% of patients can have a radical treatment, like resection, liver transplantation (LT), or percutaneous ablation. The other 75 to 80% of patients can only have supportive care.

There is no evidence to establish the optimal first-line treatment for early HCC (one tumor of 5 cm or less,) in patients with well preserved liver function, because of the lack of RCTs comparing these radical therapies. Resection and transplantation achieve a very good outcome (5-year survival of 60 to 70%) but with very different recurrence rates (60-70% and 15-20% respectively). Due to the lack of liver donors, these two techniques compete as the first option for treatment in cirrhotic patients with well preserved liver function and only one tumor.

There is no question in considering LT as the best option for patients with liver function impairment (Child-Pugh B-C patients) and early tumors (less than three tumors of less than three centimeters). LT provides cure of both the neoplastic disease and the underlying liver disease.

There are a few numbers of reports that shows a decrease in the overall survival, from an intention-to treat perspective as a result of the impact of dropouts from the waiting list because of death or progression. These numbers can be as high as 20%. Adjuvant therapies during the waiting period, although intuitively effective, have not had an impact on the outcome. Expansion of the accepted Milan criteria (single nodule <5 cm, two or three nodules <3 cm) has been advocated by some groups, but there are few data to support the benefit of this policy, which otherwise would make the management of the shortage of donors more difficult and less cost effective. Living donor liver transplantation (LDLT) has been mostly applied in patients beyond the Milan criteria, and thus the results should be analyzed with caution.

Maybe in the future, when other parameters of the tumor are incorporated in the preoperative protocol, like: tumor doubling time, micro vascular invasion, number of mitoses, and histological grading, the question of what patient really benefits of expanding criteria can be answer, the expansion of the standard criteria is going to be more benefit for the patient due to the less influence in prognosis.

Treatment of HCC to reduce waiting list dropout has become a priority at most centers. Ablative therapies (percutaneous or laparoscopic) and chemoembolization are the most frequently applied treatments, these treatments have been tested only in the setting of observational studies, and at present there is no evidence of survival benefit. Thus, randomized studies are clearly required.

Immunosupression in liver transplant for hepatocellular carcinoma

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The hepatocellular carcinoma (HCC) has turned into a frequent indication for liver transplant. The reports of different series indicate that it represents at least 12% of all liver transplants in Europe. But what kind of inmunosuppression is better in these patients is an unanswered question. Our intension with this review is to give basic information to

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define which would be the best immunosuppression alternative. There is enough information on the relationship between immunosuppression and cancer, as it is seen in states of primary immunodeficiency or infection with the Human Immunodeficiency virus (HIV).

The immune system offers a state of permanent guard to avoid the arousal of neoplasic diseases in immunocompetent patients and from this point of view it has been seen that in immunosuppressed patients there is an association with this condition and the development of lymphoproliferative disorders, which can range from reversible diseases (polyclonal proliferation of B type lymphocytes) to the development of a lymphoma and other types of tumors, like the ones observed in skin, genital region or oropharynx. Colon tumors and breast tumors have not been associated with immunosuppression. Immunosuppressive medication takes part in a different manner in the development of tumors, it has been said that steroids that are associated with some tumors, especially those regarding skin, paradoxically have a protective role in the development of lymph tissue tumors.

It has been said about Azathioprine and Mycophenolate mofetil (MMF) that its immunosuppressive effect is an antiproliferative type of immunosuppression, inhibiting the synthesis of purinic nucleotides, especially in lymphocytes. Azathioprine has been involved in the development of hepatic tumors, especially in the era previous to the use of inhibitors of calcineurin like Cyclosporine (CsA), especially because in that time the dosage of this medication was very high. MMF has a more selective role by inhibiting the new synthesis of purines and in some cases it has been assigned the role of the antitumor agent basically because it stops the adhesion of the tumor cells to the vascular endothelium and so a tendency to diminish tumors in these patients has been described but it is unclear if this is due to less severe treatment regimens or because this association really is related to diminishing neoplasms.

It has been reported that the inhibitors of calcineurin, either CsA or Tacrolimus (TAC), play an even more important role in the development of neoplasms, their immunosuppressive effect is given by the diminishing of interleukin-2, an important cytokine that participates in the activation and clone expansion of lymphocytes. Mayor number of tumors associated to the use of CsA has been reported, due to its interference with DNA repairing, also it seems to be that it increases the expression of the Tumor growth factor-B (TGF-b), which has a stimulating role in angiogenesis (process involved in tumor growth). There are studies that show the close relation between the use of CsA and the higher incidence of tumors, especially skin tumors and lymphoproliferative postransplant disease (PTLD).

There is less knowledge about TAC, it has been observed that hepatocellular tumors progress more quickly and in more quantity when TAC is used instead of CsA. There is even less knowledge of antibodies due to its poor utility in TH.

Sirolimus (Rapamicine) and everolimus deserve to be mentioned aside, they are a new type of immunosuppressors that stop proliferation of lymphocytes because it binds and inactivates a protein named the mammalian-target of Rapamicine (m-TOR) which participates in the proliferation of the cell, especially in the cycle starting in G1 until STAGE S. The antitumor role of this medication has been observed, and it ranges from stopping cellular transformation to proliferation and metastasis development. The most impressive aspect is the effect in diminish of angiogenesis because it lowers the production of VEGF which is a stimulating agent of endothelium cells.

Long termed observation shows diminish in the incidence of PTLD and skin tumors and in renal transplant patients due to Kaposi tumors that receive Sirolimus. Due to the previous information it appears to be that Sirulimus is the best option for immunosuppressor in transplant patients due to CHC. Different variables participate in the reappearance of CHC in postransplant time; poor selection; inappropriate immunosuppression and even bad luck. It is suggested to use the immunosuppression protocol that is established in the moment, without caring if the patient has CHC, and change to Sirolimus when recurrence is proven or when there are adverse characteristics of the tumor in the explant (e.g. microscopic vascular invasion, o more of "symmetric 5s and 3s" for the size of the tumor and number of nodules from the extended Barcelona criteria.