Surgery 165 (2019) 281–285

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Clinical Review

What is transplant oncology?

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ARTICLE INFO

Article history:
Accepted 11 October 2018
Available online 22 November 2018

Introduction

Transplant oncology is a new concept encompassing multiple disciplines of transplantation medicine and oncology designed to push the envelope of the treatment and research of hepatobiliary cancers.[1,2] Liver transplantation (LT) for hepatobiliary malignancies constitutes only a part of this concept, and all of the following form critical components of transplant oncology: application of transplantation techniques in cancer surgery to extend the limit of conventional resection and the bridge linking tumor and transplant immunology, which thereby pave the way to a novel, anticancer strategy and a platform for conducting genomic studies based on new insights on cancer immunogenomics. This mini review is designed to illustrate this new field of transplant oncology and to underscore the importance of convening all the relevant experts in transplantation medicine and oncology, including transplantation and hepatobiliary surgeons, medical and radiation oncologists, hepatologists and gastroenterologists, immunologists, etc, to maximize the care and cure of cancer patients.

Transplant oncology accelerates the evolution of multidisciplinary treatment

Hepatocellular carcinoma

The landmark paper by Mazzaferro et al[3] from Milan, Italy, proposed that transplantability for unresectable hepatocellular carcinoma (HCC) should follow the Milan criteria (≤3 tumors with none >3 cm in diameter or a single tumor ≤5 cm in diameter, with no vascular invasion or extrahepatic metastases). This paper serves as an outstanding prototype of transplant oncology and continues to be held as the gold reference. Because the criteria were relatively stringent—and some researchers believed that patients with more advanced disease could benefit from LT—vigorous attempts have been made to carefully expand the Milan criteria.[2,4] More recently, based on further study, Mazzaferro et al[5] have expanded these criteria to include the serum α-fetoprotein (AFP) level, tumor size, and tumor number to determine the risk of HCC-related death. These and other studies were meant to refine the model "beyond" the Milan criteria to select other groups of patients who have acceptable risks of recurrence and still preserve the best use of the limited source of donor livers.

Because of the underlying liver disease that predisposes so many patients to hepatic recurrence or a new primary HCC, in an ideal world, LT represents the best treatment for many—if not most—HCCs with 5-year survival rates of ~75% in patients meeting the Milan criteria. The main limitation for the application of LT is the scarcity of organs, which depends on each jurisdiction.[4] Therefore, it seems important to determine the minimum survival that should be achieved when utilizing such a precious but limited source. Some investigators originally proposed 50% 5-year survival, and more recently, a 50% 10-year survival has been suggested.[6] Whether the acceptable cutoff level should be equivalent between living and deceased donor LT also remains a matter of considerable controversy[7] and establishing universal criteria of LT for HCC has become increasingly difficult.

The grim reality is that a new primary HCC will recur in a certain number of recipients after LT (~15%–20%), leading to dismal prognoses.[8] An outstanding model of risk estimation—the RETREAT score incorporating AFP, tumor size, and explant pathology—has been established by a multicenter North American study[9] and that model has been validated by the United Network for Organ Sharing (UNOS) database.[10] This score predicts the risk of recurrence once a patient has received LT. If recurrence occurs, the concept of transplant oncology can be utilized again. A systematic review has demonstrated that aggressive resection, with a curative intent, in selected patients with HCC recurrence (either intrahepatic or extrahepatic) after LT provides prolonged survival with a median of

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https://doi.org/10.1016/j.surg.2018.10.024

42 months.[8] In a retrospective study (the largest series to date) of 121 patients with HCC recurrence after LT, overall survival at 5 years approached ~50% in those who underwent treatments with curative intent (surgical resection or ablation intended to achieve no evidence of disease) after a multidisciplinary meeting.[11]

Perihilar cholangiocarcinoma

Complete resection remains the only curative option for perihilar cholangiocarcinoma (PhCCA).[12] In the 1990s, initial attempts to perform LT for unresectable PhCCA resulted in unacceptably high recurrence rates; however, with the use of potent neoadjuvant therapy, the University of Nebraska (patient enrollment began in 1987)[13] and the Mayo Clinic (1993)[14] groups demonstrated significantly improved outcomes of this concept. In 2005, Rea et al[15] from Mayo Clinic reported an update of their aggressive multidisciplinary approach for highly selected patients with unresectable PhCCA or with underlying primary sclerosing cholangitis. It consisted of external beam radiation therapy with a target dose of 45 Gy combined with fluorouracil (5-FU). Thereafter, brachytherapy with iridium-192 with a target dose of 20–30 Gy was employed. A 5-fluorouracil infusion, which in later years was replaced by oral capecitabine, was continued as tolerated until LT. All patients were required to undergo a staging operation after completion of brachytherapy to exclude nodal and extrahepatic metastases and local extension of disease to adjacent organs. In patients who underwent LT, the overall survival rate at 5 years exceeded an almost unbelievable 80% and the results favored patients with underlying primary sclerosing cholangitis when compared with de novo PhCCA. The success led to a multicenter, retrospective study in 2012, compiling the experience of 12 US transplant centers with variable neoadjuvant protocols, which reproduced excellent outcomes.[16]

The definition of "unresectable disease," however, is not universal, and some centers would potentially resect patients deemed unresectable in a different institution. The criteria of unresectability, as defined by the Mayo Clinic group, were bilateral invasion of second-order biliary radicals (ie, Bismuth type IV tumors), encasement of the main portal vein and unilateral segmental ductal extension with contralateral vascular encasement, or insufficient hepatic reserve. Recently, the group from Nagoya University reported a 5-year survival rate of 53% in patients with Bismuth type IV PhCCA and pN0M0 disease, who underwent resection which was similar to that of patients with de novo cancer who underwent LT at Mayo Clinic.[17] In contrast, Ethun et al[18] described significantly worse outcomes in patients who underwent hepatic resection for PhCCA who met the criteria for LT (<3 cm and lymph node-negative disease), using data obtained from the US Extrahepatic Biliary Malignancy Consortium registry, when compared with those who received neoadjuvant therapy followed by LT, based on the Mayo Clinic protocol discussed earlier in this review. An interesting concept is currently being tested in resectable patients: The TRANSPHIL (NCT02232932) trial is a prospective, randomized, multicenter study comparing neoadjuvant chemoradiotherapy followed by LT and conventional operative resection for resectable PhCCA.

Intrahepatic cholangiocarcinoma

LT for intrahepatic cholangiocarcinoma (ICCA) has been contraindicated in most centers based on the poor results reported in the late 1980s and early 2000s.[1,2] The main caveat with those studies was the relatively small number of patients, the combined analysis of patients with PhCCA and ICCA, and the inclusion of cirrhotic and noncirrhotic patients. Sapisochin et al[19] demonstrated in a multicenter, retrospective study conducted in Spain and validated in an international study[20] that LT for "very early" ICCA (single tumor and up to 2 cm) in cirrhotic patients achieved excellent 5-year overall survival and recurrence rates (73% and 0% in the Spanish cohort and 65% and 18% in the international cohort). Currently, a single-arm, prospective, international multicenter study to evaluate the effectiveness of LT for very early ICCA in cirrhotic patients is underway (NCT02878473).

Lunsford et al[21] described 6 highly selected patients with locally advanced ICCA in a noncirrhotic liver not amenable to resectional therapy but without extrahepatic disease, who ultimately underwent LT after confirmed disease stability for ≥6 months while on gemcitabine/cisplatin-based neoadjuvant chemotherapy (1 had previously undergone radiotherapy). During a median follow-up of 36 months after transplantation, the overall and recurrence-free survival at 5 years were 83% and 50%, respectively. A total of 3 patients relapsed at a median of 7.6 months: 1 died at 14.5 months after LT because of diffuse metastases to the lung, liver, and bone, and the other 2 remain alive under systemic therapy at 32 and 54 months after recurrence at the time of the report. Their observation is in accordance with an earlier publication from a group at the University of California in Los Angeles that described relatively improved outcomes with the use of neoadjuvant/adjuvant chemotherapy combined with LT in the treatment of ICCA and PhCCA, particularly in patients with a low risk of recurrence estimated by a predictive index based on 7 factors (multifocal tumor, perineural invasion, infiltrative subtype, lack of neoadjuvant and/or adjuvant therapies, history of primary sclerosing cholangitis, PhCCA, and lymphovascular invasion).[22] It is noteworthy that in the prospective case series by Lunsford et al,[21] the tumor burden of 3 patients was downstaged to resectable disease after neoadjuvant chemotherapy, thereby precluding LT. Successful downsizing chemotherapy for initially unresectable, locally advanced ICCA has also been reported by the Chiba University group,[23] highlighting the paramount importance of multidisciplinary discussion under the transplant oncology concept. Similar to the case of PhCCA, the definition of resectability of locally advanced ICCA remains ambiguous, particularly when "advanced techniques," such as in situ resection with hypothermic perfusion and ex vivo resection and autotransplantation are taken into consideration.[24]

Colorectal liver metastases

LT for locally unresectable colorectal liver metastases (CRLM) had also been abandoned, given the dismal prognoses in the early 1990s.[1,2,25] In 2013, however, the SECA study revealed a 60% overall survival at 5 years among 21 patients with liver-only CRLM who underwent LT after at least 6 weeks of neoadjuvant chemotherapy. The prognoses were considerably better than those reported after chemotherapy alone in a similar cohort of patients; however, 19 of 21 patients developed recurrent disease in the liver graft. Overall survival after LT was significantly worse in patients with maximum tumor diameter >5.5 cm, time from primary cancer surgery <2 years, carcinoembryonic antigen levels >80 μg/L, and progressive disease on chemotherapy.[26] With the goal of optimizing the available grafts, the Norway group described an approach, referred to as the RAPID concept (Resection And Partial Liver Segment 2/3 Transplantation With Delayed Total Hepatectomy), that combines the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (the so-called ALPPS procedure) with living donor LT of segments 2 and 3, followed by total hepatectomy.[27] Along these lines, the Toronto group is currently conducting a similar, single-arm, prospective study to explore the utility of living donor LT for unresectable CRLM (NCT02864485), and the SECA (SEcondary CAncer)-II study (NCT01479608) includes a phase 3 trial, comparing deceased donor LT with liver resection in selected patients with 6 or more liver-only metastases from colorectal cancer

deemed technically resectable. Another randomized control trial (the TRANSMET study: Liver Transplantation in Patients With Unresectable Colorectal Liver Metastases Treated by Chemotherapy) is underway in France, comparing LT after standard chemotherapy and standard chemotherapy alone for unresectable CRLM (NCT02597348). The improved outcomes and renewed interest in LT for unresectable CRLM, compared with the initial experience 25 years ago, is attributed undoubtedly to more effective chemotherapy, recent advances in imaging (magnetic resonance imaging and positron emission tomography), precise understanding of tumor biology (eg, KRAS and BRAF mutation),[28] better perioperative management of LT itself, including the refinements in immunosuppressive regimen, and equally important a standardized patient selection.[24] With the development of precision (individualized) therapy, LT for unresectable CRLM may soon play an even more prominent role for the multidisciplinary management of this disease.

Neuroendocrine liver metastases

The available literature reporting the outcomes of LT for neuroendocrine liver metastases (NETLM) is limited by the number of patients studied. A recent systematic review reported 5-year overall survival after LT for locally advanced, unresectable NETLM, ranging from 50% to 70%, with a recurrence rate of 30%–60% at 5 years. More than 50% liver involvement, a high Ki67 index and pancreatic neuroendocrine tumor (NET) as the primary lesion were poor prognostic factors.[29] In 2007, Mazzaferro et al[30] proposed the Milan criteria for NETLM of a low-grade NET, including the primary tumor drained by the portal system, hepatic involvement of $\leq$50%, a good response or stable disease for at least 6 months, and age $\leq$55 years. These criteria were developed to select appropriate patients for LT, with the intent of cure rather than the palliation when liver resection or debulking was considered insufficient as a rescue treatment for debilitating symptoms attributable to large tumor burden or carcinoid syndrome.[30] They conducted a prospective study and described outstanding 5- and 10-year survival rates of 97% and 89%, respectively, in 42 highly selected patients who underwent LT between 1995 and 2010 compared with 51% and 22% in the 46 patients who did not undergo transplantation during the same period. This transplant survival benefit exceeded 3 years at 10 years posttransplant.[6] In the United States, United Network for Organ Sharing has adopted the Milan criteria and released guidelines for listing patients with unresectable NETLM for LT.[31] Several other guidelines have been proposed, including the European Neuroendocrine Tumor Society Consensus Guidelines and the National Comprehensive Cancer Network Guidelines, but the selection criteria remain ill defined and no true international consensus exists.[32–34] Several important but unanswered questions remain:

1. How should we incorporate quickly emerging, nonoperative treatments that have changed the landscape of treatment particularly for pancreatic NET, such as peptide receptor radionuclide therapy (PRRT) and molecular-targeted agents, with LT?[35]
2. What is an appropriate measurement outcome (overall versus recurrence-free survival, time to progression, etc.) when comparing LT with other treatment modalities, given the slow-growing, indolent biology of most NETs?
3. What defines unresectability? Or, should we be providing transplants to the patients with resectable but bulky disease?

Transplant oncology extends the limit of cancer surgery

Transplant surgery and surgical oncology in the hepatobiliary field have evolved in tandem. Several examples of operative techniques used in LT have been adopted for resections in the hepatopancreatobiliary arena. Transection of the suprahepatic inferior vena cava and anterior rotation of the liver, the so-called ante situm resection of the liver, combined with hypothermic perfusion with the use of total hepatic vascular exclusion and venoveno bypass was first described by Hannoun et al.[36] Autotransplantation of the liver with ex vivo "back table" resection for otherwise unresectable tumors began in 1988 with the pioneering work of Pichlmayr et al.[37] Indications for an aggressive approach have now been expanded from liver-only disease to intractable cancers involving the root of the superior mesenteric arteries and the celiac trunk.[38,39] Moreover, en bloc mobilization techniques involving 2 or more abdominal organs developed by the transplantation surgeons for organ procurement have been employed for resection of large tumors in the upper abdomen.[40] The true value of these "extreme" resections has yet to be defined and these procedures should only be considered for highly selected patients in a combined transplant and oncology program after an extensive, multidisciplinary discussion.[1,41]

Transplant oncology elucidates recognition of self and nonself

To date, there is only one prospective, randomized trial of the use of antineoplastic immunosuppression (sirolimus) administered from 4 to 6 weeks after LT in recipients with HCC.[42] In this study, there was no difference in recurrence-free survival, and the study did not meet the primary endpoint. Therefore, this treatment should not be widely recommended at the moment. Nevertheless, subset analysis suggested an oncologic benefit in low-risk patients, interestingly. Meanwhile, it is well known that the innate component of the immune system, involving phagocytic leukocytes, dendritic cells, and natural killer cells, is not affected by immunosuppression. The group at Hiroshima University in Japan has introduced natural killer cell therapy for patients with HCC undergoing living donor LT in an attempt to decrease cancer recurrence in a clinical trial. Lymphocytes are extracted from the liver perfusate of the donor graft, and after stimulating lymphocytes with interlukin-2 (IL-2) and adding anti-CD3 monoclonal antibody for T cell depletion, these activated natural killer cells are administered intravenously to the recipient.[43] Moreover, precision medicine, including immunotherapy, is on the horizon in biliary tract cancers.[44] In the era of transplant oncology, these are great examples demonstrating the impending need of integrating tumor and transplant immunology, which ultimately should lead to the elucidation of the recognition of self and non-self.

Transplant oncology facilitates exploration of the biomechanisms of disease

Finally, new insights in cancer immunogenomics have taken cancer research to the next level,[45] and transplant oncology is expected to provide a strong platform for genomic studies to explore the various biomechanisms of disease by creating an international consortium of experts. For example, the interaction between MHC class I polypeptide-related sequence A gene (MICA) and natural killer group 2D (NKG2D) was shown to activate an antitumor response of innate natural killer cells and $CD8^+$ T cells.[46] Recently, Kumar et al[47] reported that single nucleotide polymorphisms of MICA are strongly associated with tumor surveillance in association with natural killer cells in HCC induced by the hepatitis C virus and that the natural killer cell–mediated cytotoxicity against HCC was enhanced by vorinostat (a histone deacetylase inhibitor) via the upregulation of MICA.[48] In addition, aforementioned novel approaches to hepatobiliary malignancies by integrating LT to multidisciplinary cancer care would enable the explanted liver, a cornucopia of cancerous lesions and background liver parenchyma (from normal liver to cirrhosis), to be fully available for large-scale

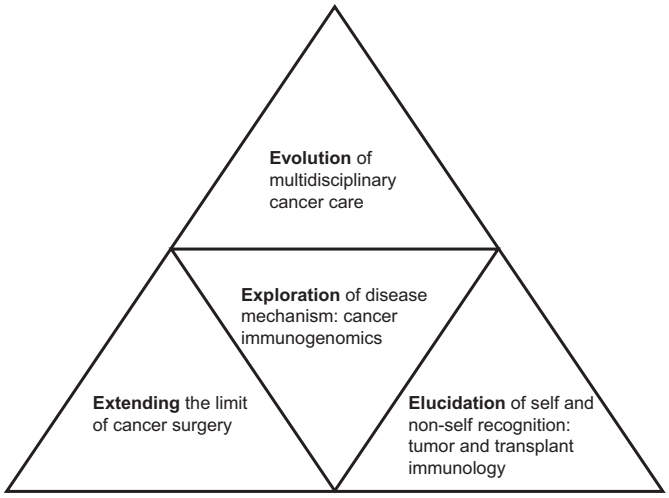

Fig. 1. The 4 Es of transplant oncology.

genomic studies. These examples show the powerful potential of transplant oncology.

Conclusions

The era of transplant oncology has just begun, and we are witnessing a paradigm shift in the treatment and research into hepatobiliary cancer. The 4 pillars (4 Es; Fig. 1) of transplant oncology are:

1. Evolution of multidisciplinary cancer care by integrating LT,
2. Extending the limit of safe hepatobiliary resections by applying transplantation techniques to cancer surgery,
3. Elucidation of self and nonself recognition system by linking tumor and transplant immunology, and
4. Exploration of biomechanism of disease through genomic studies.

The first consensus conference on transplant oncology, hosted by the International Liver Transplantation Society, is scheduled on February 7, 2019, in Rotterdam (https://ilts.org/meetings/consensus-conference/). It is the time to consolidate global efforts to discuss resectability, transplantability, and curability in a multidisciplinary setting under the concept of transplant oncology and to build a common language/understanding among all related experts in this field to ultimately conquer cancer.

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