The ABCs of LTX for BAC

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Lung transplantation (LTX) is an effective form of palliative therapy for a variety of end-stage lung diseases, but access to LTX is severely limited by a scarcity of suitable donors. Fewer than 900 LTX procedures are performed annually in the United States although over 4000 patients are currently listed for LTX.¹ In part, because of the scarcity of donors, strict listing criteria for potential LTX recipients are espoused.² Current malignancy is considered an absolute contraindication to LTX, because of the concern that poor prognosis due to the malignancy and possible acceleration of tumor growth secondary to immunosuppression would surely jeopardize long-term survival. As deaths on the waiting list increase, there is growing pressure not to squander such a scarce and precious resource as transplantable lungs.

In this issue of the *Journal*, Zorn and associates³ challenge this paradigm by reporting their experience with LTX for a subset of patients with bronchioalveolar carcinoma (BAC). They tested the hypothesis that total lung replacement could be curative for the diffuse form of BAC by transplanting 9 patients presumed to have this diagnosis. One of the 9 was found to have adenocarcinoma, not BAC, after lung replacement, and so was not included in the Kaplan-Meier survival analysis. Arguably, by intention-to-treat analysis, this patient should have been included, because if LTX is to be recommended as a therapy for BAC, then this misdiagnosis would presumably occur with a similar frequency as it did in this report. This inclusion would not change the provocative finding that survival of patients with BAC who underwent LTX was similar to that of patients having LTX for other indications.

The fact that patients with BAC did just as well as patients with other indications for LTX is just as much a sad commentary on the long-term results of LTX as it is a sterling recommendation for this strategy as a therapy for BAC. Zorn and associates titillate with their impressive survival statistics and aggressive surgical approach to disease recurrence, but leave the reader to speculate just how many patients with lung cancer were evaluated to select the 9 study patients. How realistic is this option for those with diffuse BAC? How many patients were eliminated because of metastatic disease or mediastinal lymph node involvement? Two of their 9 patients who had LTX had positive N2 nodes at operation (although only 1 of these patients had “true” BAC). The recurrence rate was disappointing, with 6 of 8 patients having recurrent disease, and many of their patients ultimately died of BAC. Thus, it would appear that their hypothesis was not true; LTX is not a “curative” strategy for BAC. However, LTX is not a curative therapy for *any* end-stage lung disease. As a form of palliation, LTX for selected patients with BAC may have merit, based on this initial report in a small number of presumably highly selected patients.

The authors report that they have abandoned LTX for BAC because of the high

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recurrence rate and the increasing wait time for transplantation. Despite the recurrence rate, however, excellent palliation of incapacitating dyspnea was achieved for a time in virtually all patients. Should LTX be performed for diseases that recur? At first blush, the intuitive answer is a resounding “NO!” But LTX is routinely offered to patients with end-stage lung disease due to sarcoidosis and lymphangioleiomyomatosis (LAM); both diseases recur in LTX recipients.^{4,5} Alpha-1 antitrypsin deficiency emphysema would presumably recur in transplanted lungs if patients with this disease survived long enough after LTX. Because LTX is really not a cure for *any* lung disease, we must ask ourselves: what is the measure of success among LTX recipients? If one patient is just as likely to survive as long as another, does it matter whether the recipient diagnosis is malignant? And we must address the thorny issue of who should be offered a lung transplant, particularly given the vexing shortage of suitable donor lungs.

The Department of Health and Human Services has required that United Network for Organ Sharing (UNOS) organ allocation policies place less importance on waiting time and geography, and consider equity and utility in amending organ allocation algorithms. The ideal would be to attempt to provide organs to those more at risk of death, balanced by the desire not to waste organs by transplanting them into hopelessly ill individuals with significantly compromised opportunity for survival. The Lung Allocation subcommittee of the UNOS Thoracic Organ Committee has made substantial progress on identifying factors associated with increased risk of death on the UNOS LTX waiting list,⁶ as well as factors associated with an increased risk of death within 1 year of LTX.⁷ Using this and similar information, the UNOS Thoracic Organ Committee hopes to recommend a lung distribution algorithm that places more importance on saving and extending lives rather than on the ability to survive a long wait with lung disease. Perhaps if such an algorithm were in place, LTX for BAC would be a practical option because waiting time would no longer be the principal variable in lung allocation.

Surely one of the most fascinating aspects of the report by Zorn and colleagues is what it potentially implies about the etiology of BAC. In an earlier publication, this group suggested that recurrence of BAC might be related to tumor cells left behind in the large airway that later migrated to the alveolar spaces to reappear as BAC recurrence.⁸ Indeed, aerogenous spread has been postulated as an explanation for the observation that approximately 60% of recurrences in cases of resected BAC involve only the remaining lung.⁹ Others postulate that BAC is the result of a stimulus (possibly viral) that has a propensity to cause multifocal sites of pulmonary involvement. In cases of resected BAC, only about 40% of all patients experience a recurrence, and approximately 40% of the recurrences involve distant sites.⁹

It is striking that recurrence was seen in 75% of patients who had lung transplantation for BAC, and that *all* of these involved *only* the lung. The higher incidence of recurrence among patients with BAC undergoing LTX may be because these patients had more extensive disease than patients who underwent resection alone. However, that would not explain the exclusive localization of recurrences to the lung. One could postulate that immunosuppression might contribute to a higher incidence of cancer recurrence, but this should lead to a higher recurrence rate elsewhere in the body as well.

A critical question is whether the malignant cells in the recurrent BAC are of recipient or donor origin. If the mechanism of recurrence involves aerogenous spread, the BAC cells should have the genotype of the recipient and be distinct from the donor. On the other hand, if the “recurrence” is a manifestation of a continued stimulus for alveolar proliferation that is now acting on the transplanted alveolar cells, then the genotype of the “recurrent” BAC should be the same as that of the donor.

The fact that the histologic appearance of the recurrent BAC was similar to the primary BAC before transplant does not address this issue adequately. In their earlier report, the authors used DNA polymorphisms¹⁰ from tissue specimens to attempt to identify the origin of the BAC and concluded that the recurrent BAC in 3 of their patients appeared to be of recipient genotype.⁸ However, the method of sampling of tumor was relatively crude. And the use of reverse transcriptase–polymerase chain reaction raises the possibility that contamination of the tumor cells with nonmalignant recipient leukocytes or alveolar macrophages might falsely identify tumor as being of recipient origin. Indeed, close inspection of the data in their earlier report suggests that their 3 patients showed *both* donor and recipient DNA in the recurrent tumor. More sophisticated techniques for tissue sampling, such as laser capture microdissection,¹¹ might answer the question definitively. Perhaps HLA class I antigens on tumor cells could be demonstrated by immunohistochemistry. The authors *must* make an effort to establish with more certainty whether recurrent BAC cells are of donor or recipient origin.

If recurrent BAC cells are of *donor* origin (which appears less likely from the DNA evidence), it would provide strong evidence that diffuse BAC is a response of alveolar epithelial cells to a stimulus that arises outside of the lung parenchyma. But what if the earlier analysis is correct and recurrent BAC cells are of *recipient* origin? How reasonable is it to postulate that BAC cells spread by aerogenous route when all lung tissue was removed? Did the cells crawl out of the alveoli and lie dormant for years before recurrence? Where? Did they hide somewhere distant and migrate back to the lung years later? If so, why did these patients not have metastases where the cells “hid away?”

The evidence presented in this small series of patients

suggests that BAC is a systemic disease manifested in the alveolar epithelium, or that BAC is a manifestation of a systemic stimulus that results in alveolar proliferation. This would explain the high rate of recurrence after LTX, although it is not clear why the incidence of recurrence or its distribution would be different from in patients who underwent resection of BAC *without* LTX. Recurrence of BAC after LTX may be virtually inevitable because the stimulus to undergo malignant transformation is still present in the recipient. Pulmonary alveolar macrophages may be the culprits, or some other marrow derived cells that interact with the pulmonary epithelium. Perhaps the malignancy is a disease of marrow-derived pulmonary epithelial stem cells that require a "hospitable" site to migrate to and undergo malignant transformation. The BAC LTX recipients who have so far avoided recurrence may have been transplanted with a genotype that has protected them from the stimulus to malignant transformation or made the alveoli inhospitable to recipient malignant stem cells.

Presumably LTX "starts the clock" again on the proliferation of the malignant cells. Does immunosuppression affect the natural history of BAC? Is time to recurrence and death altered by immunosuppression, or is time to recurrence simply a manifestation of latency for malignant cells to reach a critical mass to become obvious clinically?

Diffuse BAC is fortunately an unusual disease, but even if it represents only 3% of lung cancer cases, as reported by Zorn and associates, that would amount to almost 5000 cases a year in the United States. However, approximately 60% of these cases occur as a solitary nodule, while the rest involve infiltrative, multifocal, or diffuse presentations of the disease.⁹ Thus, 2000 BAC patients might be considered for LTX. Given the current shortage of donor lungs, LTX is currently not a practical therapeutic option. However, if LTX is feasible using lungs retrieved from circulation-arrested non-heart beating donors,¹² then an unlimited supply of donor lungs might make LTX a reasonable option for all of these unfortunate patients.

So what are the ABCs? Perhaps Alveolar epithelial cells undergo malignant transformation in response to an un-

known (Anonymous) stimulus that arises outside of the lung. Or, Bronchioalveolar carcinoma may not be a lung disease per se, but rather a manifestation of an Abnormality in another Cell population. Lung transplant for BAC is, as the authors point out, Controversial, but it is Certainly not Crazy, based on the encouraging data from their small series.

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