PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #333
TRANSPLANT MEDICATION MANAGEMENT FOR PATIENTS NEARING END-OF-LIFE
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The decision to withdraw immunosuppression medications in solid organ transplant (SOT) patients dying from a comorbid illness arises frequently. This *Fast Fact* offers guidance in immunosuppressant management for SOT patients nearing death from a comorbid illness. The bioethics of the voluntary cessation of immunosuppressants to hasten death or the withholding of other life prolonging treatment for easily treatable transplant-related complications are beyond the scope of this *Fast Fact*.

Background on Immunosuppression Medications: The main clinical targets of these medications in SOT patients is to prevent antibody-mediated hyperacute rejection immediately after transplantation, lymphocyte-mediated acute rejection during the first-year post-transplantation, and chronic rejection thereafter. Commonly used agents include: cyclosporine, tacrolimus, sirolimus, mycophenolic acid, azathioprine, and corticosteroids. As the availability and management of immunosuppression medications have improved, so has the life expectancy of transplant recipients.

Continuation of Medications: When patients enroll in hospice or change the focus of their care to comfort they are often overwhelmed with many changes, including the introduction of new care teams and philosophies of care. Discontinuation of immunosuppressants may be met with resistance and possibly interpreted as medical abandonment by patients or their families, as the importance of immunosuppressant adherence is often routinely stressed by treating clinicians. If cost and side effects are manageable, some hospice interdisciplinary teams may opt to continue these medications in the hopes of building rapport and easing the transition of care.

Discontinuation of Medications: The monthly expense of immunosuppressants and other transplant-specific medications is more than $2,500 for many SOT patients. Furthermore, immunosuppressants place patients at increased risk for cancer and infection, require strict lab monitoring because of their narrow therapeutic window, and are usually available only in oral formulations (1-3). These factors may make them prohibitive for many dying patients receiving hospice care. Stopping these medications, however, may lead to acute rejection within days to weeks of roughly one quarter to one-half of SOT patients (4,5). For many of these patients, the signs and symptoms of acute rejection closely resemble the dying process and include delirium, pain, fever, and malaise. Therefore, clinicians may opt to discontinue immunosuppressants and palliate symptoms as they arise.

Substitution of Immunosuppressants: Discontinuation of immunosuppressants, unfortunately, can also lead to graft failure and abrupt onset of more significant organ related symptoms which may hinder the dying process: e.g. oliguria [renal], hepatosplenomegaly and abdominal pain [liver], shortness of breath and cough [lungs], left ventricular dysfunction [heart] (6-9). Though data on the incidence of these symptoms are scant, patients may fear the symptom burden brought about by stopping immunosuppressants. Instead of stopping all immunosuppressive agents, a rotation to a high-dosed corticosteroid could be considered when significant symptomatology is anticipated. Corticosteroids are less costly, available via more routes, more useful in palliating common symptoms at the end of life (e.g. pain, nausea) than other immunosuppressants. Plus, they do not require lab monitoring.

- Studies support oral prednisone or oral/IV/IM methylprednisolone for treating acute rejection (10-13). There is less clinical evidence supporting the use of dexamethasone.
- One care option is to discontinue all immunosuppressants and start prednisone at 50-80 mg per day (dose equivalent methylprednisolone 40-60 mg per day) to prevent acute rejection. Subsequent corticosteroid tapering could be considered on a case-by-case basis.
- Alternatively, all immunosuppression could be discontinued and the patient monitored clinically. Should symptoms arise, an empiric burst of IV methylprednisolone 3-5 mg/kg for 3-5 days could be considered.
- Higher corticosteroid doses (e.g. methylprednisolone 1 gm/day) may be required for heart, lung, or liver transplant patients (13).

Other Clinical Factors:

- Failed allografts: when the patient's transplanted organ is no longer functioning, the goal of preventing rejection no longer exists and discontinuing immunosuppression is reasonable.
- Organ type: heart and lung grafts are at highest risk to be rejected rapidly, followed by kidney then liver (14). For heart or lung transplant patients, stronger consideration should be given to continuing immunosuppressants or immediate substitution with corticosteroids.
- Comorbid conditions: If a patient is having recurrent infections, dying of sepsis, or experiencing worsening renal failure, it may make more clinical sense to stop immunosuppression altogether. If a patient has a concurrent malignancy, rotation to a corticosteroid should be considered given the potential concurrent symptom benefits for pain and nausea.
- Prognosis: for patients with a prognosis as short as hours to days, stopping all immunosuppression is reasonable as it is unlikely that acute rejection will hinder their dying process. For patients with an anticipated survival of several weeks to months, continuation of previous immunosuppressants or rotation to corticosteroids should be considered to prevent acute rejection.

Summary Recommendations: The decision to stop immunosuppression in SOT recipients does not automatically lead to imminent death and suffering. Considering the care complexities involved, collaboration with pharmacists and the patient's transplant team is crucial.

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