

Limits of anti-infectious chemoprophylaxis

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Limitations of non-specific drug prophylaxis	Limitations of specific drug prophylaxis
<p>Gut decontamination has no benefit on survival and poses resistance and compliance problems.</p> <p>The benefit of IVIG in preventing infection is not particularly high.</p> <p>Isolation poses problems of cost, maintenance, and psychological impact.</p>	<p>Drugs used in STC* transplantation are not effective enough, induce resistance, and many of them, particularly against fungi and viruses, have too many side effects.</p> <p>Anti-infectious prophylaxis is generally accepted against <i>Herpes simplex</i> (aciclovir), <i>Pneumocystis jerevecci</i> (Trim-sulfa) and maybe <i>Candida albicans</i> (fluconazole).</p> <p>However, there are problems with prophylaxis against viruses that require T-cell control (e.g. CMV, EBV, and adenovirus), viruses for which good prophylactic agents are lacking (EBV, adenovirus, paraflu), bacterial infections (pneumococcal resistance to various antibacterial drugs), and most fungal infections.</p>

* Stem Cell

CMV: a good example of the “limits of chemoprophylaxis”

CMV problems are rare in HLA-identical sibling transplant recipients but much more frequent in patients with mismatch or unrelated donors. (Ljungman *et al.*, 1998)

It is important where possible, to select a CMV seronegative donor for a CMV seronegative patient to reduce the risk for:

- CMV infection and disease
- fatal bacterial and fungal infections.

CMV seems to have immunosuppressive properties. (Nichols *et al.*, J Infect Dis 2002; 185: 273-82)

The influence of the donor CMV serological status in a CMV seropositive patient is controversial. However, in a recent study seropositive patients with a seropositive unrelated donor had improved survival and reduced transplant-related mortality compared to those with a seronegative donor (Ljungman *et al.*, Blood 2003).

The positive effect of a seropositive status was mediated mainly through a reduced risk for death from all types of infections. It was also dependent on transfer of specific donor T-cells. This indicates that patients receiving grafts from non-immune donors have poorer control of CMV and are therefore at risk for secondary events to CMV immunosuppressive effects.

Strategy for prevention of CMV reactivation/disease: treating all patients

Several approaches:

- treatment with immune globulins, or either low potency (acyclovir, valaciclovir [Prentice *et al.* 1994]) or high potency (ganciclovir, foscarnet) prophylactic antiviral agents.

One limitation of this approach is that reasonable, but not complete suppression of the virus may occur (Ljungman *et al.*, Blood 2002).

- valaciclovir (renal transplant) could strongly reduce the risk for CMV disease in the high-risk group of seronegative recipients with a seropositive donor, but not in the seropositive recipient group (Lowance *et al.*, New Engl J Med 1999).

Results were similar for the risk of acute rejection.

- ganciclovir prophylaxis given at the time of engraftment helped reduce the probability of CMV infection and disease (Goodrich *et al.* $p < 0.001$; Winston *et al.* $p = 0.06$). Associated with delayed reconstitution of the specific immune response (Li *et al.* 1994) and the development of late occurring CMV disease, it has become less common.

Mostly used in patients at particularly high risk for CMV disease (targeted prophylaxis).

Valganciclovir, a prodrug to ganciclovir, is more readily absorbed from the gut and has more favorable pharmacokinetics but further studies in SCT patients are needed.

Strategy for prevention of CMV reactivation/disease: treatment of selected patients

Ganciclovir prophylaxis and preemptive therapy based on antigenemia were compared in a randomized study (Boeckh *et al.*, 1996, 1999) that showed that ganciclovir prophylaxis gave more late CMV disease and a higher risk for invasive fungal disease presumably due to ganciclovir-induced neutropenia.

Overall survival was not different.

Resistance

Relatively infrequent in SCT patients: the more potent the immunosuppression, the more quickly the virus replicates and the more likely this patient is to develop CMV resistance.

Which strategy should we choose?

- Low potency prophylaxis (aciclovir, valaciclovir) + preemptive therapy?
- Preemptive therapy + secondary prophylaxis?
- High potency prophylaxis followed by preemptive therapy?

Decisions depend on the virus laboratory, the techniques used, and the patient population treated.