**Table 1 CMV Disease incidence in the preemptive era. Incidence of CMV disease in the placebo groups in randomized trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Study** | **Nº Patients** | **CMV disease incidence** |
| **Maribavir** | Marty FM, Lancet ID 2011 (4) | **227** | **2.4% (at 6 months)** |
| **Brincidofovir** | Marty FM. NEJM 2013 (5) | **59** | **3.0% (at 3 months)** |
| **Letermovir** | Chemaly RF. NEJM 2014 (6) | **33** | **0% (at 3 months)** |
| **Valganciclovir** | Boeckh M, Ann I. Med. 2015 (7) | **89** | **2.0% (at 9 months)** |

**Table 2 CMV Indirect effects: impact of + serology** (from table 1,Boeckh M. Blood 2004;103:2003 with modifications\*)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author (year)** | **Patient Nº** | **TCD****%** | **UD****%** | **Results (P <0.01)****R+ vs R/D CMV (-)** |
| Broers (2000) | 115 | **95** | 0 | **24% ⇓ absolute OS** |
| Cornelissen(2001)  | 127 | 26 | **100** | **38% ⇓ relative DFS** |
| Craddock (2001) | 106 | **100** | **100** | **22% ⇓ absolute OS** |
| Doney (2003) | 182 | 0 | 52 | **99% ⇑ relative TRM** |
| Kollman (2001) | 6978 | 25 | **100** | **7% ⇓ absolute OS** |
| Kroger (2001) | 125 | **100** | **100** | **41% ⇓ absolute OS** |
| Ljungman\* (2014) (59) | 8801\*\* | **100** | **69** | **5% ⇓ absolute OS****13% ⇑ relative TRM** |
| MacGlave (2000) | 1423 | 23 | **100** | **20% ⇓ relative DFS** |
| Malaspina (2002) | 510 | 24 | **100** | **46% ⇓ relative DFS** |
| Meijer (2002) | 48 | **100** | **100** | **41% ⇑ absolute TRM** |
| Nichols (2002) | 1750 | 0 | 57 | **26% ⇓ relative OS** |
| Teira\* (2016) (58) | 9469 | 52 | 29 | **60 ⇑ relative TRM** |
| Yakoub-Agha\* (2006) (107) | 236 | 0 | 23 | **16% ⇓ absolute OS****14% ⇑ absolute TRM** |

TCD: T-cell depletion. UD: unrelated donor

\*\*: This is a subpopulation of the study, restricted to the impact of using a CMV Seropositive Donor for a CMV-Seronegative unrelated patient.

**Table 3 Guidelines for CMV management in SCT: Prevention of CMV disease in allogeneic-SCT. ECIL recommendations (68)**

**Diagnosis**

* The diagnosis of CMV disease must be based on symptoms and signs consistent with CMV disease together with detection of CMV by an appropriate method applied to a specimen from the involved tissue (A II)
	+ Symptoms of organ involvement + CMV detection in blood are not enough for diagnosis of CMV disease
* PCR is usually not appropriate for documentation of CMV disease in tissue specimens, as the PPV is too low (B III)

**Monitoring**

* All allogeneic-SCT patients, regardless of whether they receive CMV prophylaxis, should be monitored for CMV in peripheral blood at least weekly using either CMV antigenemia assay or a technique for the detection of either CMV DNA or RNA (AI).
* Use of a quantitative assay gives additional information valuable for patient management (B II).
* The duration of monitoring should be at least 100 days (BIII).
* Longer monitoring is recommended in patients with acute or chronic GVHD, in those having experienced CMV infection after SCT earlier and in those having undergone mismatched or unrelated donor transplantation (BII).

**Prevention**

* The strategy of choice: pre-emptive therapy
	+ Pre-emptive antiviral therapy based on detection of CMV antigen or nucleic acid (A I)
	+ Either intravenous ganciclovir or foscarnet can be used for first line pre-emptive therapy (A I)
	+ Valganciclovir might be used in place of i.v. agents especially in low-risk patients (provisional BII).
	+ Cidofovir can be considered for second-line pre-emptive therapy (3–5 mg/kg) but careful monitoring of renal function is required (BII).
* Prophylaxis
	+ Iv ganciclovir prophylaxis could be used in sub-groups of patients at high risk for CMV disease (BI) (not specified).
	+ Acyclovir or valacyclovir can be used as prophylaxis against CMV in allo-SCT patients (BI). However, their use must be combined with monitoring and the use of pre-emptive therapy (AI).
	+ Immune globulin has no role as prophylaxis against CMV infection (EII).
* Adoptive cellular immunotherapy
	+ Infusion of CMV specific lymphocytes or Dendritic cell vaccination are interesting options and should undergo controlled prospective clinical trials (C II)

**Table 4 Guidelines for CMV management in SCT: CMV disease treatment. ECIL recommendations (68)**

* CMV pneumonia (allo-SCT)
	+ Ganciclovir is recommended (AII)
	+ Foscarnet might be used in place of ganciclovir (AIII)
	+ The addition of immune globulin to antiviral therapy should be considered (CII)
	+ Cidofovir or the combination of foscarnet and ganciclovir can be used as second-line therapy (BII).
* Other types of CMV disease and in other patients groups
	+ Ganciclovir or foscarnet without Ig is recommended (BII)
	+ Cidofovir or the combination of i.v. ganciclovir and foscarnet can be used as second-line therapy for CMV disease (BII).

**Table 5 Present CMV antivirals**

 Drug Route Approval

High potency

* Ganciclovir (iv) 1989
* Foscarnet (iv) 1991 Aids
* Cidofovir (iv) 1996 Aids
* Valganciclovir (oral) 2001 Aids
(not registered for SCT) 2003 SOT
* Fomivirsen (intravitreal) 1998\*

Low potency

* Acyclovir (oral, iv) 1982
* Valacyclovir (oral) 1995

\* Was voluntarily withdrawn from the European market in 2002

**Table 6 New anti-CMV antivirals**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Mechanism of action** | **Route** | **Spectrum** | **Prophylactic studies in allogeneic SCT****Phase II Phase III** |
| **Maribavir** | UL 97 inhibition | ORAL | CMV and EBV | Winston DJ, 2008 (98): 111 patientsPrimary end-point: SuccessFailures: 7% vs. 46% placebo | Marty FM, 2011 (4): 681 patientsPrimary end-point: Failure |
| **Brincidofovir** | Viral DNA polymerase inhibition (UL 54) | Oral | The broadest (CMV, EBV, adenovirus,…) | Marty FM, 2013 (5): 230 patientsPrimary end-point: SuccessFailures: 10% vs. 37% placebo | Marty FM, 2016 (99): 458 patientsPrimary- end-point: Failure |
| **Letermovir** | CMV terminase complex inhibition (UL 56) | Oral& iv | CMV | Chemaly RF, 2014 (6): 132 patientsPrimary end-point: SuccessFailures: 29% vs. 64% placebo | Ongoing |