Risk of cytomegalovirus transmission by blood products to immunocompromised patients and means for reduction

Cytomegalovirus (CMV) transmission remains a particular concern for immunocompromised patients, such as those undergoing bone marrow transplantation or receiving chemotherapy. It is of major importance for CMV seronegative patients that the risk of CMV transmission with blood products is minimized. The currently available techniques, use of CMV-seronegative blood products and leucocyte-reduction by filtration, have limitations. Pathogen inactivation is the newest approach to making blood safer. Several technologies are already available or in development. The final choice of a technique will most likely depend on the risk for severe CMV disease in the patient population as well as efficacy, safety, and costs of the chosen techniques.

Cytomegalovirus (CMV) is a highly cell-associated virus, which normally causes an asymptomatic infection in the immune competent host. After a primary infection, the virus persists in a latent state, from which it can be reactivated under certain conditions. Since CMV can cause severe illness and even death in immunocompromised patients, such as patients undergoing haematopoietic stem cell transplantation, solid organ transplantation, and patients suffering from leukaemia or lymphoma, the spread of CMV through blood products should be prevented. The risk for a viral infection through blood products can be limited by an improved selection of the donor-population. However the high prevalence of CMV seropositive individuals in the donor-population of many countries represents a particular problem since an increasing demand for CMV-free blood products may be difficult to meet if CMV positive donors are excluded. In addition, the cost of maintaining a CMV-negative blood supply can often be high.

White blood cell (WBC) reduction has been shown to reduce the risk of transmission of CMV via blood products to a level within the same order of magnitude as by selection of CMV negative blood products (Bowden *et al*, 1995; Ljungman *et al*, 2002). There is no consensus whether the techniques are equivalent, what conclusions should be drawn regarding CMV testing of blood products and whether different techniques should be used in patient groups at varying risks for CMV disease.

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The aim of this review is to discuss the risk for CMV infection through blood products in different immunosuppressed patient populations to compare different methods for preventing CMV transmission including viral detection, leucoreduction and pathogen inactivation.

Clinical picture of CMV infection

The clinical symptoms of a CMV infection are generally mild or absent in a normal immune competent individual. A mononucleosis-like syndrome with fever, malaise, myalgia, liver dysfunction and heterophil antibody negative lymphocytosis may occur several weeks after exposure (Klemola & Kaariainen, 1965). In contrast, CMV infection in transplant patients may lead to severe illness (Ljungman, 2002) including hepatitis, thrombocytopenia, haemolytic anaemia and pneumonia (Neiman *et al*, 1977; Meyers *et al*, 1982, 1990; Paya *et al*, 1989; Sayage *et al*, 1989) with potentially lethal outcome, despite modern antiviral therapy (Ljungman *et al*, 1992, 2001; Einsele *et al*, 2000; Machado *et al*, 2000; Limaye *et al*, 2001; Boeckh *et al*, 2003). The severity of the CMV infection correlates directly with the degree of immunosuppression for each transplant setting and/or patient condition, as well as with the serological status of patients and, in the transplant situation, of their donors (Smyth *et al*, 1991; Egan *et al*, 1998; Hertz *et al*, 1998; Ljungman *et al*, 1998; Lowance *et al*, 1999; Einsele *et al*, 2000; Hebart *et al*, 2001; Junghanss *et al*, 2002). Data on the importance of CMV infection in non-transplant cancer patients are limited. Among adults with acute leukaemia, CMV pneumonia was reported to occur in 2·9% of patients with a case-fatality rate of 57% (Nguyen *et al*, 2001). There is an increased risk for CMV infections and also for CMV-associated disease in lymphoma patients receiving T-cell suppressive therapy, such as fludarabine (Anaissie *et al*, 1998) or anti-CD52 antibodies (Campath) (Bowen *et al*, 1997; Lundin *et al*, 2002; Nguyen *et al*, 2002).

Recent data indicate that infection with CMV may not only cause a viral disease syndrome, but also a more general impairment of the cellular immune response (Grigoleit *et al*, 2002). This hypothesis is supported by the observation that infection of dendritic cells with CMV may not only cause an immune response sufficient to control infection with CMV, but also a down regulation of major histocompatibility complex (MHC) class I and II, which could explain why bone-marrow recipients who become infected with CMV show

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a delay in immune reconstitution (Grigoleit *et al*, 2002). This is illustrated by the fact that CMV seronegative recipients of stem cell transplants (SCTs) from CMV seropositive donors are at a significantly increased risk for death due to bacterial and fungal infections. Mortality due to bacteraemia or invasive fungal infection was 18·3% for CMV seronegative stem cell recipients of seropositive donations, and 9·7% for seronegative stem cell recipients receiving from seronegative donors. These numbers indicate a possible immunomodulatory effect of primary CMV infection independent of the direct CMV associated morbidity (Nichols *et al*, 2002).

Risk of contracting CMV via transfusion and transplantation

The importance of a primary infection in immunosuppressed individuals varies between different patient populations. Primary infection is an important risk factor for CMV disease and also for rejection in solid organ transplant recipients (Rubin, 1990; Gane *et al*, 1997; Flechner *et al*, 1998; Lowance *et al*, 1999). The major risk factor for CMV disease in allogeneic SCT patients is CMV seropositivity of the patient, however primary infection is also associated with a significant risk for development of CMV disease. The importance of primary infection in other patient populations, such as acute leukaemia patients, undergoing induction chemotherapy and autologous SCT recipients is less well known.

The main source of CMV transmission to a seronegative organ or SCT recipient is the donor infectivity (Bowden *et al*, 1986, 1991a; Balfour *et al*, 1989; Smyth *et al*, 1991; Bailey *et al*, 1992; Merigan *et al*, 1992; Snydman *et al*, 1993; Conti *et al*, 1994; Rostaing *et al*, 1997; Ljungman *et al*, 1998; Lowance *et al*, 1999). However, transmission from blood products has also been documented to be an important source of primary CMV infection unless preventive measures are taken (Bowden *et al*, 1986, 1991b). An incidence of primary CMV infection of 23% has been reported following the administration of CMV unscreened blood to autologous SCT recipients (Reusser *et al*, 1990). Seronegative patients receiving grafts from CMV seronegative stem cell donors have a similar risk, with incidence figures between 32% and 37% (Bowden *et al*, 1986; Miller *et al*, 1991). However, the use of CMV seronegative blood products has no, or a very limited, impact on the risk for CMV infections in CMV seronegative allogeneic SCT patients with CMV seropositive donors (Bowden *et al*, 1986; Miller *et al*, 1991). The risk in less immunosuppressed patients than SCT recipients might be lower. In CMV seronegative organ transplant recipients receiving organs from CMV seronegative donors, the risk for CMV transmission from unscreened, non-leucocyte-depleted blood products is rather low (Preiksaitis *et al*, 2002) and the consequences might be less severe than after CMV infection transmitted from the organ donor (Falagas *et al*, 1996). In seronegative children with malignancies, no transfusion-associated CMV infection was found regardless of whether the patients received leucocyte-depleted or standard blood products (Preiksaitis *et al*, 1997). The risk in non-immunocompromised patients of transfusion-associated CMV disease is low (0·9%) (Preiksaitis *et al*, 1988).

What is the risk of CMV transmission to an already CMV seropositive individual? Contact with blood products containing CMV may cause reactivation of latent CMV virus in a state of immunosuppression. Another possibility is reinfection with a new strain of CMV, as demonstrated in patients with the human immunodeficiency virus (HIV) and organ transplant recipients (Chou, 1987; Grundy *et al*, 1988). A higher risk for a severe CMV infection has been suggested following infection with a second strain of CMV (Grundy *et al*, 1988). It is very difficult to assess with certainty the importance of CMV transmission by blood products into already CMV seropositive patients. Whether CMV disease occurring in seropositive patients is more or less frequently caused by a reactivation of a previous strain or by reinfection of a new strain is unknown but is likely to be strongly influenced by the existing CMV immunity in the patient (and the donor) (Nichols *et al*, 2002; Ljungman *et al*, 2003).

The location of CMV in different blood cells

Leucocytes are the most likely vehicle of transmission for the highly cell-associated CMV in blood products (Einhorn & Öst, 1984; Rice *et al*, 1984). CMV transcripts have been demonstrated in a subset of $CD33^+$ cells of the bone marrow of naturally infected CMV seropositive subjects (Kondo *et al*, 1994; Kondo & Mocarski, 1995). Granulocyte transfusions have also been associated with a high risk of CMV transmission (Hersman *et al*, 1982a). CMV can be demonstrated in granulocytes either by culture, immunostaining or by direct DNA detection (Gerna *et al*, 1991, 1992; Boland *et al*, 1992). Following incubation with high titres of CMV, *in vitro* monocytes and CD8 lymphocytes can be infected (Einhorn & Öst, 1984; Braun & Reiser, 1986). Monocytes seem to be a very important source of CMV in blood products of healthy seropositive individuals (Taylor-Wiedeman *et al*, 1991), particularly in the terminally differentiated $CD14^+$ monocytes of the myeloid/granulocyte lineage (Bolovan-Fritts *et al*, 1999).

It has been difficult to isolate CMV from fresh blood or leucocytes from healthy blood donors (Hersman *et al*, 1982b). The high risk for transmission through blood products is therefore likely to be caused by factors stimulating CMV reactivation. One such effect is the allogeneic effect. *In vitro* data indicate that allogeneic stimulation can reactivate CMV from both seropositive and seronegative blood donors (Söderberg-Naucler *et al*, 1997). This effect is most likely to be mediated through cytokine stimulation in the allogeneic situation. In the immune competent CMV seropositive host, CMV reactivation is most likely to be directly controlled by the pre-existing immune response. However, in severely immunocompromised individuals, this control function might fail.

The risk for CMV disease when blood products transmit a primary infection is difficult to determine. It will most likely

depend on the immunosuppressed state of the patient, the viral load transmitted by the blood product, and the preventive measures taken against CMV (antiviral prophylaxis, monitoring and pre-emptive therapy). In a randomized study comparing CMV seronegative blood products to leucocyte-depleted blood products, Bowden *et al* (1995) found a similar risk of CMV infection and disease. The risk for CMV transmission by erythrocyte or platelet transfusion is probably related to the number of leucocytes present in these products. Although the concentration of leucocytes in unfiltered erythrocyte preparations is generally 10 times higher than in platelet preparations, due to multiple transfusion of platelet preparations the risk of CMV transmission is probably greater for platelet recipients (Bowden, 1995). Fresh frozen plasma does not seem to transmit CMV infection, possibly because the few leucocytes found in the plasma are disrupted during the freezing procedure (Bowden & Sayers, 1990; Bowden, 1995).

Detection of CMV

It is important to differentiate between the detection of pre-existing CMV infection, i.e. seropositivity, and ongoing CMV infection. The important risk factor for transmission of CMV is existing seropositivity in the blood donor population. The prevalence of CMV antibodies in a healthy donor population varies greatly, and figures between 20% and 100% have been presented (Bowden, 1995). Approximately 50–80% of the blood donor populations in the USA are CMV seropositive (Krajden *et al*, 1996). Since primary CMV infection in the immune competent host rarely causes any characteristic symptoms, the history of CMV infection in a blood donor is unreliable. CMV antibody was detected in 37% of a volunteer donor population that did not give a history of CMV infection (Zhang *et al*, 1995).

The most common techniques for screening for a previous CMV infection are serological assays based on passive particle agglutination and latex agglutination. Both are quite sensitive and quick, and are therefore suitable for screening. There are some limitations to serological testing. One is the possibility of a 'window period' between becoming infected with CMV and seroconversion. Analysis of IgM antibodies might shorten the duration of this 'window period' by enabling earlier detection of a primary infection before IgG seronconversion has occurred. The second limitation existing for all screening tests is the risk of false negative results. This might be due to genotypic variation of the virus giving rise to antibodies not detected by the assay used or waning of the antibodies giving titres that are too low for detection by the assay used (Laupacis *et al*, 2001). Different assays have different levels of sensitivity. For example, the risk of false negative results is approximately 4% for the 'immunofluorescent antibody test' and 25% for the complement fixation test (Bowden, 1995).

The risk for incorrect serological assignation to seropositive or seronegative of course exists both for patients, organ or stem cell donors, or blood donors. The risk is most probably highest for immunocompromised patients, since these might have an impaired capacity to mount an antibody response to CMV. Finally, it has been suggested that abortive infections with CMV exist that do not give rise to a serological immune response and unless the individuals are exposed to replicating virus, this prior infection may interfere with seroconversion (Zhang *et al*, 1995).

Instead of detecting antibodies, another option is to try to detect viral antigens or viral nucleic acids in the peripheral blood. It has been shown that it is possible to detect CMV DNA or RNA in both seropositive and seronegative healthy blood donors (Table I) It is not known whether blood products from CMV seropositive donors, from which CMV DNA or RNA can be detected, give a different risk of CMV transmission than blood products that are CMV DNA or RNA negative. However, it has been shown that the likelihood of detecting CMV is highest early after primary infection. CMV viraemia, as indicated by positive viral culture, was detected in leucocyte samples of one out of six patients within 9–10 weeks after infection (Zanghellini *et al*, 1999), while CMV DNA was detected in the leucocytes of five of the six patients during the first 16 weeks of infection with a successive decline, although one of six patients were still positive at 48 weeks after infection. One study of 52 immunocompetent individuals (including 40 pregnant women) with a symptomatic primary CMV infection showed that CMV DNA was detected in leucocytes in all patients during the first month after an acute CMV infection. A steady decline of the viral DNA was thereafter demonstrated during 6 months follow-up. Thereafter no viral DNA could be detected (Revello *et al*, 1998).

The detection of CMV DNA or RNA in blood products from CMV seronegative donors could explain the observation that seroconversion occurs in 4–6% of recipients of CMV negative blood products (Bowden *et al*, 1986; Miller *et al*, 1991). However, it should be noted that the studies showing a high detection frequency of CMV DNA or RNA from seronegative blood component donors are the oldest and more recent studies have shown a very low frequency in both seronegative and seropositive blood component donors. This might be due to the development in technology for nucleic

Table I. Detection of CMV DNA and RNA in blood products from CMV seropositive and seronegative individuals.

Product (reference)	CMV seropositive	CMV seronegative
Blood samples (Greenlee *et al*, 2002)	0/110 DNA	0/93 DNA
Whole blood (Krajden *et al*, 1996)	8/101 DNA	
Whole blood (Smith *et al*, 1993)	7/86 DNA	
Heparinized plasma (Nitsche *et al*, 2000)	0/5 DNA	5/22 DNA
Buffy coat samples (Larsson *et al*, 1998)	60/145 DNA	19/140 DNA
Buffy coat samples (Zhang *et al*, 1995)	50/117 RNA 3/113 DNA	86/196 RNA
Heparinized plasma (Roback *et al*, 2003)	2/456 DNA	0/514 DNA

acid detection. It is also likely that the risk for transmission from a so-called seronegative donor is dependent on the serological assay used for screening, in that a more insensitive assay might misclassify a donor with a low antibody titre as seronegative.

Prevention of CMV transmission

Since the risk for transmission by blood products of CMV is significant, several strategies have been investigated to decrease the risk. These include use of CMV seronegative blood donors, reduction of the number of leucocytes in the blood products, and postdonation treatment of the blood products to inactivate the virus. It should be recognized that each of these strategies has potential pitfalls including non-availability of screened products, incorrect ordering of the desired type of product, technical failure of depletion techniques, and the potential side-effects of the new techniques based on postdonation treatment of the blood products. It should also be recognized, as stated above, that break-throughs in all studies cited below could just as well be caused by failure of the serological testing of the patient (or the donor in a transplant situation), as the failure of the strategy of providing 'CMV-safe' blood products.

Use of CMV seronegative blood donors

The first introduced strategy was to screen blood donors for CMV and CMV seronegative donors for CMV seronegative patients. The disadvantages with this technique is that it might be difficult to provide CMV seronegative products from donor populations where the CMV prevalence is high, and the risk for false negative screening assays is still present, as discussed above.

Seronegative blood products strongly reduce the incidence of infection in CMV seronegative SCT patients with CMV seronegative stem cell donors to 0–7% (Bowden *et al*, 1986, 1995; Mackinnon *et al*, 1988). Similar results can be obtained after solid organ transplantation (Freeman *et al*, 1990)

Leucocyte depleted – 'filtered' – blood products

Since CMV is mainly a cell-associated virus and exists mainly in peripheral blood leucocytes, to reduce the number of transfused leucocytes might reduce the risk for transmission of CMV. Several studies were performed in different patient populations and showed that this was indeed the case. A 3-log reduction of CMV levels *in vitro* has been demonstrated following leucocyte reduction (Lau *et al*, 1998). More recently a 1·61-log reduction of CMV DNA copies in platelets and 2·96-log in whole blood following filtration has been reported (Rios Visconti *et al*, 2004).

In clinical studies, a significant risk reduction of CMV transmission was observed after the removal of leucocytes from blood products. Transfusion of leucocyte-reduced blood products from seropositive donors reduces the risk to levels similar to when products obtained from seronegative donors are used (Bowden *et al*, 1995; De Witte *et al*, 1990; Narvios *et al*, 1998; Narvios & Lichtiger, 2001; Ljungman *et al*, 2002).

The efficacy of filtered, leucocyte-reduced blood components depends on the reliability of the leucocyte reduction filters and the number of leucocytes remaining at transfusion. Laboratory assessments have suggested at least a 3-log reduction in the amount of infectious virus (Lau *et al*, 1998; Lipson *et al*, 2001). Many different factors influence the effectiveness of leucocyte removal including the properties of leuco-depletion filters, the blood components to be filtered (composition, age), and the filtration method (pre- or poststorage, temperature, flow rate) (Pietersz *et al*, 1998; van der Meer *et al*, 1999, 2001). Although the number of infected leucocytes required to transmit CMV infection is not known, the residual leucocytes carry a risk of viral transmission. In addition, specific subsets of WBCs may be removed by filtration with different efficiencies although overall the efficacy of removal has been shown to consistently be between 3 and 4 log 10 (Rider *et al*, 2000; Roback *et al*, 2000). Furthermore, leucocyte filters are not effective against cell-free CMV or the breakdown of intact, infected leucocytes (James *et al*, 1997). However, the detection rate of CMV DNA is lower in plasma than in whole blood or leucocytes (Table I), thus the significance of this might be limited.

There are other possible advantages of leucocyte depletion, such as reduction of the risk for transmission of other leucocyte-associated viruses, a possible lower risk for alloimmunization and for non-haemolytic febrile transfusion reactions. Other leucocyte-associated viruses that might theoretically be removed by leucocyte depletion include Epstein–Barr virus (EBV), human herpes virus (HHV)-6, HHV-7, and HHV-8 (Kaposi Sarcoma Associated Herpesvirus). No study has assessed the efficacy or importance of leucocyte depletion on infections with these viruses.

Granulocytes and granulocyte fragments are causes of non-haemolytic febrile transfusion reactions, whereas antigen presenting cells presenting both MHC class I and II antigens appear to induce alloimmunization. Since leucocytes cannot be completely removed from a blood component, an upper limit of residual leucocytes of $1–5 \times 10^6$ has been suggested to prevent side effects caused by leucocytes. However, the risk of damaging erythrocytes or platelets might increase with more efficient filters. Monitoring molecules released upon contact activation, cellular injury, aggregation, including annexin V and kallikrein-like enzymes can be used as screening or quantitative assay of the quality of the filtration process (Pietersz *et al*, 1998).

Comparing CMV seronegative blood products to leucocyte-depleted blood products

Since both the use of CMV seronegative blood products and leucocyte-depleted blood products are able to reduce the risk for CMV transmission, the question remains which method is

most effective. One randomized study has compared CMV negative blood products with leucocyte-depleted blood products in CMV seronegative SCT recipients receiving grafts from CMV seronegative donors (Bowden *et al*, 1995). In 502 bone marrow transplant patients, no significant differences could be found between the two groups. The risks for CMV infection were 1·3% and 2·4%, respectively, while the risks for CMV disease were 0% and 2·4%, respectively. All of the patients that were infected developed CMV disease and the outcome was poor, with fatal outcome of CMV disease in five of six patients. The authors concluded that a 3-log reduction of the number of leucocytes is as effective as the use of seronegative blood. The results of this study have been questioned for several reasons. It really was underpowered to detect a meaningful difference in CMV disease. Furthermore, 40% of the patients received autologous grafts and therefore were at a lower risk for CMV disease. The blood products were filtered poststorage and there was no quality control regarding the efficacy of filtration. However, the study has influenced the decision of many centres to replace CMV negative with filtered, leucocyte-depleted blood components.

Pamphilon *et al* (1999) reviewed the results from nine studies in SCT and acute leukaemia patients, including the randomized study by Bowden *et al* (1995). The risks for CMV infection were 0·8% for patients receiving CMV seronegative blood products, 0·5% for patients receiving leucocyte-depleted blood products, and 18% for patients receiving unscreened, non-leucocyte-depleted blood products (Pamphilon *et al*, 1999). After this review, three additional non-randomized studies using somewhat different strategies in SCT patients have been published. The results are summarized in Table II. The designs of the three studies were as follows: Ljungman *et al* (2002) compared a group of patients that only received leucocyte-depleted blood products with a historical control group given the combination of leucocyte-depleted and blood products from CMV seronegative donors. They used polymerase chain reaction (PCR) monitoring and preemptive therapy was adopted if the patients had two consecutive positive PCR tests. Ronghe *et al* (2002) studied a group of 93 CMV seronegative patients receiving a seronegative transplant and red cells from CMV seronegative donors with unscreened, random leucocyte-depleted platelets. None of these patients developed primary CMV infection (Ronghe *et al*, 2002). The authors compared this to a previously published cohort of patients receiving CMV seronegative blood products (Foot *et al*, 1998). Nichols *et al* (2003) studied a cohort of 807 CMV seronegative SCT recipients receiving two different protocols. During period 1 CMV seronegative blood products were used if available, otherwise filtered blood products were provided. During period 2, leucocyte-reduced platelets, obtained by aphaeresis, without filtration were used (Nichols *et al*, 2003). The overall risk for CMV infection was higher in the second cohort (Table II), while overall CMV disease occurred only in one patient (it was not reported whether this patient was treated during period 1 or 2).

CMV inactivation through postdonation treatment of blood products

During the last few years, techniques have been developed that treat blood products *in vitro* with the aim to reduce the risk for transmission of different infectious agents. These include bacteria-contaminated blood products as well as many different viral pathogens (Hepatitis B and C virus, HIV, CMV among others). These methods could be interesting alternatives for reducing the risk of CMV transmission.

The method that has been most extensively tested is based on the inactivation of nucleic acids by intercalating DNA and RNA from blood products, utilizing amotosalen HCl (a synthetic psoralen) and long-wavelength ultra-violet A (UVA) light. The effect on CMV infection has recently been demonstrated *in vitro* and in an animal model. The

Table II. Results of comparative studies between the use of CMV seronegative and leucocyte-depleted blood products.

Group	Number of patients	CMV infection	CMV disease	Preemptive therapy	Reference
Seronegative	252	2 (0·8%)* 4 (1·4%)†	0 (0%)* 0 (0%)†	Not used	Bowden *et al* (1995)
Leucocyte-depleted	250	3 (1·2%)* 6 (2·4%)†	3 (1·2%)* 6 (2·4%)†	Not used	
Combination	33	3 (%)	0	1	Ljungman *et al* (2002)
Leucocyte-depleted	49	6 (%)	0	2	
CMV negative or leucocyte-depleted	360	6 (1·7%)	Not given	Used	Nichols *et al* (2003)
CMV negative or leucocyte depleted red cells; apheresis platelets	447	18 (4·0%)	Not given	Used	
CMV negative red cells and leucocyte-depleted platelets	93	0%	0%	0%	Ronghe *et al* (2002)
CMV negative	110	1 (0·9%)	0 (0%)		Foot *et al* (1998)

*Primary endpoint; infections day 21–100 after SCT.
†Secondary endpoint; infections day 0–100 after SCT.

combination of amotosalen and UVA-treatment was able to inactivate $>10^{5.9 \pm 0.3}$ plaque-forming units/ml of CMV in full-sized therapeutic platelet concentrates. In an immunocompromised *in vivo* murine transfusion model, mice transfused with platelets contaminated with murine CMV (MCMV)-infected splenocytes became MCMV-positive, exhibited histological evidence of CMV disease, and died. Mice transfused with amotosalen-treated platelets contaminated with MCMV-infected splenocytes prior to treatment remained MCMV-negative with no histological evidence of CMV disease and remained healthy (Lin, 2001). Similar technologies that aim to inactivate blood transmissible pathogens are currently being tested and use nucleic acid targeting substances like riboflavin or PEN 110 (Corbin, 2002; Lazo *et al*, 2002).

This technology for pathogen inactivation in platelet concentrates has been tested in clinical trials for safety and haemostatic efficacy (van Rhenen *et al*, 2003) in the USA (unpublished data), and is now licensed for use on platelet concentrates in Europe. These studies were not powered to detect any difference in transmission of infections including CMV so the assumption of the efficacy against CMV is based on *in vitro* data and animal models. The amotosalen and UVA-inactivation technique for pathogen-inactivation of plasma and a similar nucleic-acid targeting platform technology for red blood cells are both in phase III clinical trials in the USA, while the technologies for pathogen-inactivation of red blood cells using riboflavin or PEN 110 are currently under development. All these techniques also have other effects on blood products, including the inactivation of leucocytes, and theoretically could reduce the risk for non-haemolytic transfusion reactions and allo-immunization. However, no such effect was documented in a randomized, controlled trial with amotosalen HCl (S-59) and UVA light-treated platelets performed in Europe (van Rhenen *et al*, 2003).

Summary and conclusions

CMV transmission remains a particular concern for immunocompromised patients, such as those undergoing bone marrow transplantation or receiving chemotherapy. It is of major importance for CMV seronegative patients that the risk for transmission of CMV with blood products is minimized. The currently available techniques, use of CMV-seronegative blood products and leucocyte-reduction by filtration, both have limitations. Pathogen inactivation is the newest approach to making blood safer. Several technologies are already available or in development and their efficacy in inactivating CMV has led to discussions on omitting CMV testing in the future. The final choice of a technique will most likely depend on the risk for severe CMV disease in the patient population as well as the efficacy, safety, and costs of the chosen techniques.

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