Cytomegalovirus in Hematological Malignancies

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Cytomegalovirus (CMV) infection frequently causes cytopenia in hematopoietic stem cell transplant setting where there are clear cut recommendations for prophylaxis, screening and pre-emptive treatment of CMV infection [1]. However, evidence of CMV infection in hematological malignancies other than stem cell transplant setting is lacking. A retrospective, single centre study of autopsied patients of acute leukemia, chronic leukemia or myelodysplastic syndrome (without stem cell transplant), reported a low, but rising prevalence of CMV pneumonitis over a 5-year period, with a case fatality rate of 57% [2].

Kanvinde, *et al*. [3] describe 13 episodes of CMV in 11 cases of hematological malignancy, which were treated with intravenous gancyclovir. These cases were diagnosed based on detection of antigen or DNA, of which, nearly half were diagnosed by a qualitative PCR which is not the standard method for diagnosing CMV infection. Further, none of these cases had demonstration of virus by culture or histopathology. Few of these episodes were associated with other documented viral or bacterial infections which by themselves are known to cause prolonged cytopenias. Further, two of these patients had resolution of their symptoms even before initiation of gancyclovir. It would be reasonable to state that these patients may have had evidence of CMV infection but certainly CMV disease was not demonstrated in any case, and thus none of these patients can be attributed to have CMV-related cytopenia.

Even the term "CMV syndrome" should be avoided. Although it is recognized that CMV can cause the combination of fever and bone marrow suppression that is usually used to define the disease entity, the same symptoms can have several other different viral etiologies such as human herpesvirus 6 (HHV-6), possibly human herpesvirus 7, and adenovirus infections. Antiviral drugs might have some effect against these viruses, making the interpretation of causality difficult. Thus, if the term "CMV syndrome" is to be used, it must be used only after testing has been done for HHV-6, at the very least [4].

Intravenous gancyclovir remains the standard of care for symptomatic CMV infection and/or CMV disease. But there are limitation of gancyclovir treatment as it causes myelosupression which may lead to superadded bacterial or fungal infection. It is important not to treat every episode of asymptomatic CMV infection to avoid undesired toxicity. This argument is supported by Ng, *et al.* [5], who described 35 patients with CMV DNAemia, with six having CMV disease; in this series, none of the untreated 20 patients developed CMV infection or disease on follow-up.

In countries with population congestion like India, where CMV seropositivity is as high as 90%, CMV reactivation may be more common than in the Western world. It is possible that many of our patients have undiagnosed asymptomatic CMV infection, as they are not routinely screened for CMV. But at the same time, they may also be recovering from CMV infection without any antiviral therapy as described by Ng, *et al.* [5]. If CMV infection or disease has to be evaluated in hematological malignancies, then perhaps these patients should be serially tested from diagnosis for change in viral load, if any, from diagnosis and to attempt diagnostic biopsies in suspected cases of CMV disease. A previous study showed that on serial monitoring, 15.3% patients of acute lymphoblastic leukemia showed evidence of CMV reactivation but none of these patients at reactivation or thereafter showed evidence of CMV disease [6]. Thus, in the absence of strong evidence of CMV disease, it may not be appropriate to initiate gancyclovir therapy for patients with hematological malignancies who have either a positive pp65 antigen or PCR positivity, as toxicity of intravenous gancyclovir outweighs the effectiveness.

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Alleviating Pain in Neonates – What is The Best?

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Newborns are often exposed to minor invasive procedures such as venepuncture. Current evidence suggests that neonates are able to perceive pain. Studies have documented that babies born at less than 32 weeks of gestation are exposed to 10-15 painful procedures each day during the first few weeks of life, and in almost 80%, no treatment for pain relief is offered [1]. Pain in neonates is known to cause adverse short and long-term effects. Prolonged or repeated pain also increases the response elicited by future painful stimuli (hyperalgesia) and even by usually non-painful stimuli (allodynia). The consequences include altered pain sensitivity (which may last into adolescence) and permanent neuro-anatomical, behavioral, emotional and learning disabilities [2].

Healthcare providers are constantly on the lookout for a safe and effective pharmacological or non-pharmacological method to alleviate pain in neonates. Orally administered sweet solutions such as glucose and sucrose have been shown to be effective in reducing procedural pain in neonates. One Cochrane review examined 44 randomized trials enrolling 3496 infants for efficacy, effect of dose and safety of sucrose for relieving procedural pain in neonates [3]. Despite significant clinical heterogenicity in the dose of sucrose and tools used to measure effect of pain, there was significant reduction in total cry time and composite pain scores during heel lancing. Expressed breast milk (EBM) which contains 7% lactose is a good physiological alternative [4]. Studies have reported the analgesic effect of breastfeeding before, during and after venepuncture [5].

Despite convincing evidence, routine measurement of indicators of pain and use of pain-relieving measures is limited. Non-availability of sucrose in India and aversion of many neonatologists to administering anything other than breast milk to neonates may be contributing factors. In this issue, Sahoo, *et al*. [6] report reduced cry duration and pain score on using EBM or 25% dextrose before venepuncture. Their study shows 25% dextrose was more effective; EBM also significantly reduced the cry duration and pain score. Although, this is a well-conducted randomized controlled trial, exclusion of eligible subjects after obtaining consent and allocation of study group is undesirable. Probability of selection bias in such a scenario defeats the purpose of randomization. Administration of high concentration of dextrose can potentially cause hyperglycemia, rebound hypoglycemia and difficulty in subsequent breastfeeding. It is not clear whether investigators looked for these side effects.

There are inherent difficulties in conducting studies on neonatal pain. Standardization of dose of exposure (amount of pain) is difficult. Amount of pain inflicted is dependent on who conducted venepuncture, with what type/brand of needle and how the prick was given. Another concern with studies evaluating measures to reduce pain in neonates is about choice of a valid measure to detect and quantify pain. A recent study has suggested that although sucrose decreases clinical observation scores, there is no reduction in nociceptive brain activity and magnitude or latency of the spinal nociceptive reflex withdrawal response [7]. Whether the ability of sucrose to reduce the pain score or the duration of cry can be interpreted as reduced pain is not clear. Further studies are needed to evaluate the effect of sucrose, breast milk or other non-pharmacological measures in high-risk groups like extreme premature neonates exposed to repeated