Perioperative Management of a Recipient of Allogenic Hematopoietic Stem Cell Transplant Undergoing Neurosurgery

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J Neuroanaesthesiol Crit Care

Hematopoietic stem cell transplant (HSCT) is a potentially curative therapy for a wide variety of diseases including various hematological malignancies. The complex immunobiology of HSCT warrants multiple special considerations.1

A 29-year-old man presented with headache and diplopia for last 15 days. He had undergone an allogeneic HSCT to treat pure red cell aplasia when he was 3.5 years old. He developed severe skin GVHD (graft vs. host disease) within 6 months after the HSCT, which gradually improved, and immunomodulatory medications along with steroids were gradually stopped after 2 years. He achieved delayed developmental milestones and had severe eye dryness, skin pigmentation, and alopecia probably because of GHVD. Since the age of 16 years, he started developing multiple attacks of tonic-clonic convulsions. Absence seizures were also diagnosed with hypothyroidism at the same time. He was receiving brivaracetam, clobazam, and oxcarbazepine. After his recent presentation to the hospital, a magnetic resonance imaging revealed a right intraventricular tumor measuring 45 × 30 × 26 mm, without any midline shift. Surgical removal of the tumor via the anterior interhemispheric approach was planned. His airway and systemic examinations were unremarkable. His Glasgow coma scale (GCS) preoperatively was E4VTM6.

We kept a vein finding device (VeinViewer Flex) and ultrasound as adjuncts for difficult cannulation. Cell saver was kept to salvage autologous blood in order to reduce allogeneic transfusion. For anesthesia induction, we used propofol (2.5 mg/kg), fentanyl (2 mcg/kg), and cisatracurium (0.10 mg/kg). Anesthetic depth was maintained using a combination of oxygen, air, and sevoflurane to maintain minimum alveolar concentration of 0.8 to 1. Train-of-four and bispectral index (BIS) monitor was also employed for the possibility of further need for total intravenous anesthesia (TIVA). We maintained the BIS value between 40 and 60. Since his donor (grandmother) had blood group A Rh “D” positive, and his pretransplant blood group was B Rh “D” positive, the transfusion medicine experts detected a bidirectional ABO incompatibility and suggested the use of group O Rh “D” positive, leuco-depleted and irradiated packed red blood cells (PRBCs), group AB irradiated platelets, and group AB plasma products. However, transfusion of blood products was not required. The patient was shifted to the intensive care unit (ICU) in an intubated condition in view of his poor sensorium at the end of an otherwise uneventful surgery (E2VTM5). In view of the development of intraventricular hemorrhage, an external ventricular drain (EVD) was placed intraoperatively. The next morning, the drain showed no output, for which a fresh EVD was inserted in the operation theater using a similar anesthetic technique uneventfully. Postoperatively a small venous infarct was developed in the right periventricular region for which he was conservatively managed. The sensorium gradually improved (E4VTM6), and the trachea was extubated on the third postoperative day, and he was subsequently discharged from the ICU in a fully conscious state. Informed and written consent was obtained before writing the case report. Histopathological examination of the specimen revealed an atypical central neurocytoma.

After an allogenic HSCT, there is a complex interplay between the donor antigen presenting cells (APC), lymphocytes, and the recipient's lymphocytes, natural killer (NK) cells. A chronic interaction between the donor cells and the tumor cells provides a protective effect in the form of a graft versus tumor effect. On the contrary, the immunological interplay between the host and the donor cells culminates into GVHD.1 In the preoperative preparation, along with the concerns regarding the primary disease, special focus should be given on the effects of GVHD for example, posttransplant...
lymphoproliferative disorders (PTLDs), veno-occlusive disease in the liver, hepatitis, pneumonitis, interstitial lung disease, skin and mucosal involvement, etc. PTLD can involve different lymphoid tissue in the oropharynx and nasopharynx, for example, tonsils, posterior pharyngeal wall, etc., and pose challenges in the airway management. GVHD can rarely affect both the central and peripheral nervous systems in the form of cerebrovascular disease, demyelinating disease, immune-mediated encephalitis, PTLDs, myositis, neuropathies, and myasthenia gravis.\(^2\)

There are specific concerns regarding different chemotherapeutic agents, which are extensively discussed elsewhere.\(^3\) The anesthetic implications of the different immunomodulatory agents and radiotherapy are described in Table 1. Depending on the stem cell donor and recipient’s blood group, HSCT can lead to major, minor, or bidirectional ABO

<table>
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<th>Agents</th>
<th>Side effects</th>
<th>Interactions with anesthetic drugs and concerns</th>
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| Cyclosporine (CyA) | Hypertension, diabetes, neurotoxicity, nephropathy, gingival hypertrophy | ● CyA can increase blood level of benzodiazepines, statins, factor Xa inhibitor  
● Analgesic effect of fentanyl and effect of muscle relaxants enhanced  
● Amiodarone, lidocaine, quinidine, verapamil, amlodipine, sulfonyleurea, biguanides, azoles (antifungal), nonsteroidal anti-inflammatory drugs (NSAIDs), haloperidol, fluoxetine, etc., can increase serum levels of CyA  
● Isoflurane reduces oral clearance of CyA  
● Carbamazepine, bosentan reduces CyA levels  
● Propofol, etomidate, thiopentone do not have any effect on blood levels  
● Blood concentration monitoring to maintain therapeutic levels is crucial |
| Tacrolimus (Tac) | Hypertension, diabetes, metabolic syndrome, neurotoxicity, nephropathy, electrolyte imbalance (hyperkalemia, hyponatremia) | ● Amiodarone, lidocaine, quinidine, verapamil, amlodipine, NSAIDs, haloperidol, fluoxetine can increase serum Tac levels  
● Carbamazepine, bosentan reduce Tac levels  
● Both CyA and Tac reduce seizure threshold: caution during hyperventilation  
● Risk of renal insufficiency during coadministration of amphotericin, aminoglycosides, NSAIDs |
| Cyclophosphamide | Vomiting, hemorrhagic cystitis, syndrome of inappropriate antidiuretic hormone (SIADH), skin lesions, heart failure | Look for serum electrolytes, urine osmolarity |
| Mycophenolate mofetil | Hypertension, diabetes, neurotoxicity | Blood pressure, sugar charting |
| ATG (antithymocyte globulin) | Pancytopenia | Complete blood count, asepsis |
| OKT3 (monoclonal antibodies directed against CD-3 antigen on the surface of human T-lymphocytes) | Fever, anaphylaxis, leucopenia | Complete blood count, asepsis, rule out infective reasons |
| Steroids | Gastric ulcer, cataract, skin changes, Cushing’s syndrome, hypertension, diabetes mellitus | Blood pressure, sugar charting, cautious airway management for possible osteoporosis |
| Newer monoclonal antibodies | Endocrinopathies including inflammation of the pituitary gland, hypothyroidism, adrenal suppression, diabetes insipidus, hypogonadism, pneumonitis, progressive multifocal leukoencephalopathy (PML), myocarditis, neurotoxicity | Hormonal profile |
| Radiotherapy | Pericarditis, arrhythmias, pericardial effusion, pulmonary fibrosis, mucositis, dermatitis, airway complications due to fibrosis | Cautious airway management with adjuncts like video laryngoscope, fiberoptic bronchoscope |

Table 1 Perioperative concerns of different immunomodulatory agents
incompatibility.\textsuperscript{4} Judicious use of blood products after consultation with the transfusion experts remains the key. Surgery is known to cause a transient attenuation in the immunity. The immunomodulatory effects of individual anesthetic agents on cancer biology are still unclear. Inhaled volatile anesthetics were found to be proinflammatory, whereas intravenous anesthetics have shown anti-inflammatory action at the molecular level. Possible immunosuppressive effects of opioids versus the detrimental effect of poor analgesia on immunity should be balanced. Although propofol-based TIVA may improve survival in patients undergoing major cancer surgeries, the possible effects of individual anesthetic agents on cancer recurrence, relapse, or progression especially when used for noncancer surgeries are still a matter of debate.\textsuperscript{5} In summary, the neuroanesthetic goal shall be to maintain cerebral blood flow, to avoid any acute rise in intracranial pressure, to avoid major hemodynamic fluctuations, and at the same time using anesthetic agents that will have minimum or no long-term detrimental effect on the immunobiology of the GVHD or the primary malignancy. For the ease of titration and the risk of unpredictable metabolism of drugs in patients who are receiving multiple chemotherapeutic or immunomodulatory agents, short acting anesthetic drugs are preferable. It is advised to wait for elective surgeries till engraftment is complete and the patient has satisfactorily recovered from the effect of cytotoxic and immunosuppressive drugs. When time permits, prehabilitation along with nutritional optimization, psychological support, and exercise training to improve functional status are instrumental. Maintaining sterility during any invasive procedure is of utmost importance in these patients as they may have compromised immunity owing to the original disease and the effect of different immunomodulatory and chemotherapeutic agents including steroids and inadequate engraftment.

Our case describes a successful anesthetic administration in a post-HSCT patient. There exist a small number of articles regarding the anesthetic implications of HSCT. Further research is warranted particularly to elucidate the effect of different anesthetic agents on the outcome of GVHD, disease relapse or immunological complications, and the role of opioid-free anesthesia in such patients.

Conflict of Interest
None declared.

References
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