Commentary

Safety of intraoperative blood salvage in cancer surgery: what is new?

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Cell salvage (CS), alternatively known as "auto-transfusion", is a medical procedure that scavenges, processes and concentrates blood from operative fields or wound sites, and re-infuses the processed patient's own red blood cells back into the patient. Cell salvage was first performed on humans in 1818, though it was initially linked to a very high mortality rate. It wasn't until the 1960s that the modern version of CS emerged, becoming an increasingly vital component of perioperative blood management strategies. Particularly, during surgery with increased blood loss CS is commonly used. Studies comparing the effectiveness of allogeneic *vs* autologous red blood cell concentrates indicate that salvaged red blood cells better maintain their biconcave shape and have higher levels of 2,3-diphosphoglycerate and ATP[1]. Consequently, tissue oxygenation is more efficient with salvaged red cells compared to stored allogeneic ones. Additionally, salvaged red blood cells do not trigger a negative immunomodulatory response during the perioperative period, unlike the immune modulation observed with stored allogeneic red blood cell transfusions[2]. The amount of free hemoglobin in salvaged blood products is minimal and likely lower than in allogeneic transfusions[3].

However, CS is not routinely applied in oncological surgery. As no RCT has been performed, existing studies do not clearly demonstrate whether the reinfusion of salvaged blood in cancer patients may contribute to dissemination of malignant tumor cells and metastatic growth. The spread of tumor cells during surgery may result from residual tumor cells at the resection site, accidental rupture of the tumor, the presence of tumor cells in the peritoneal cavity prior to surgery, or intraoperative release into the bloodstream due to pressure.

As medicine advances, new techniques are established, better healthcare is provided, and promising strategies emerge in the market. Modern CS devices provide the usage of so-called leukocyte reduction or depletion filter (LRF/LDF) in order to reduce contamination from tumor cells. Catling and colleagues investigated the efficacy of LDF in eliminating tumor cells in salvaged blood of patients undergoing gynecological cancer surgery. The authors found no viable, nucleated malignant cells after passing the LDF[4].

In addition to LDF, the use of antibodies to eliminate tumor cells from salvaged blood is one of the most promising strategies for applying CS during oncological surgery. Catumaxomab (Trion Research GmbH, Puchheim, Germany) is a biologically engineered, bispecific monoclonal antibody, and one of its binding arms specifically targets the epithelial cell adhesion molecule (EpCAM), which is overexpressed on many tumor cells such as ovarian, gastric, colonic, pancreatic, bladder, prostate, endometrial,

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and non-small cell lung cancers, with an expression rate of over 90%[5,6]. The other arm of Catumaxomab binds to CD3 on T-cells, which helps recruit immune cells to attack the tumor cells[7].

Recently, Winter and colleagues elucidated the efficiency of the CATUVAB® device (Lindis Blood Care GmbH, Hennigsdorf, Germany) in removing EpCAM-positive tumor cells from salvaged blood of patients undergoing oncological surgery. The CATUVAB® device functions by using Catumaxomab to crosslink EpCAM-positive tumor cells with CD3-positive T-cells and Fc-gamma receptor-positive immune cells. These cell aggregates are removed during a centrifugation step from the salvaged blood, and any residual tumor cell-containing aggregates were subsequently removed during a final filtration step using LDF (Haemonetics Corporation, Munich, Germany). In total, salvaged blood of 16 oncological patients were analyzed. The salvaged blood in the reservoir, the red blood cell concentrates, and the post-filtration samples were screened for the presence of EpCAM-positive tumor cells. The number of detected tumor cells ranged from 0 to 263,076 in the salvaged blood reservoir, and from 0 to 6,835 in the red blood cell concentrate, whereas it was zero after filtration of the red cell concentrate. Catumaxomab is associated with the activation of different types of immune cells and an increase in proinflammatory cytokines. However, the levels of interleukin-6 and interleukin-8 were markedly reduced, indicating a cytokine washout effect from the procedure. This pilot *ex-vivo* study demonstrated that the CATUVAB® device was effective in significantly reducing the number of EpCAM-positive tumor cells in salvaged blood during oncological surgeries. In addition, the processed blood, after removing the tumor cells, was deemed safer for reinfusion into the patient, potentially reducing the risk of tumor cell dissemination[8]. Finally, the pilot study provided a proof of concept for the device's function in a clinical setting and its potential role in improving intraoperative blood management during cancer surgeries. Overall, this study lays the groundwork for safer blood management strategies during cancer surgery, with the potential to impact patient recovery and long-term survival.

Based on these results the authors proceed with the "Removal of EpCAM-positive tumor cells during intraoperative blood salvage (REMOVE)" study. This multicenter pivotal, confirmatory open-label, multicenter clinical study was performed to validate these results. The REMOVE study is focused on evaluating the effectiveness of the CATUVAB® device, which uses Catumaxomab, in removing EpCAM-positive tumor cells from blood salvaged during major oncological surgeries. The main aim of the study is to determine if the CATUVAB® device effectively eliminates EpCAM-positive tumor cells from salvaged blood in cancer surgeries and to evaluate the safety of re-transfusing this filtered blood to patients and monitor its impact on post-surgical outcomes (data have not yet been published).

If successful, the CATUVAB® device could become a key tool in managing blood during oncological surgeries by allowing safe autotransfusion. It may also help reducing the risk of tumor spread through circulating tumor cells during surgery, potentially improving long-term survival and reducing metastasis. In view of the continuous improvement of medical devices the concept of the REMOVE study could lead to broader applications in various types of cancer surgeries where blood loss and tumor cell dissemination are concerns.

DISCLOSURE OF CONFLICTS OF INTEREST

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