Blood salvage use in gynecologic oncology

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BACKGROUND: Blood salvage allows for collection and processing of surgical blood loss with the eventual reinfusion of washed red blood cells (RBCs) back to the patient. The use of blood salvage in patients undergoing surgery for malignancy is off-label. Controversy exists as to the risk of potential cancer dissemination resulting from the reinfusion of the processed blood, but no data are available to confirm this risk. Recent studies have demonstrated that filtering the salvaged blood using a leukoreduction filter (LRF) significantly decreases the number of cancer cells in the recovered RBC aliquot in a variety of cancer types.

STUDY DESIGN AND METHODS: Patients on the gynecologic oncology service as part of the bloodless surgery program at Englewood Hospital and Medical Center from April 1998 to April 2007 were identified. Three patients that had reinfusion of cell salvage blood (all reinfusions were performed after filtration with a LRF) were studied further with emphasis placed on long-term outcomes.

RESULTS: Two of the three patients did not show any evidence of metastases after surgery. The only patient that developed evidence of hematogenous progression had known liver metastases at the time of her initial diagnosis and therefore had hematogenous dissemination before her index surgery.

CONCLUSION: In this series of patients undergoing surgery for malignancies on the gynecologic oncology service, blood salvage with LRF was not definitively associated with hematogenous dissemination. Further large controlled studies are needed to demonstrate the clinical safety of the use of blood salvage in this setting.

Blood management optimizes outcomes in patients undergoing surgical procedures who wish to avoid allogeneic transfusion. Blood management is the philosophy to improve patient outcomes by integrating all available techniques to reduce or eliminate allogeneic blood transfusions. It is a patient-centered, multidisciplinary, multimodal, planned approach to patient care. Using a series of interventions and management strategies related to this goal, patients who were previously considered extremely high risk or inoperable without a blood transfusion can now undergo complex surgical procedures with acceptable outcomes.

Blood salvage (also known as intraoperative autologous blood collection with autotransfusion, or cell saver) is one of the techniques utilized in blood management, which allows for collection and processing of surgical blood loss with the eventual reinfusion of this blood intravenously (IV) into the patient. In certain circumstances, blood salvage may be necessary to prevent life-threatening consequences of severe blood loss anemia during surgery in patients that refuse allogeneic transfusion (e.g., Jehovah’s Witness patients). Preoperative counseling is critical in utilizing blood management techniques, and recently we demonstrated that blood salvage (when used in a continuous circuit with the

ABBREVIATIONS: CT = computed tomography; LRF(s) = leukoreduction filter(s).

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BLOOD SALVAGE IN GYNECOLOGIC ONCOLOGY

patient) is widely accepted by the Jehovah’s Witness population. The use of blood salvage in patients undergoing surgery for malignancy has not been advocated since it represents off-label use of current available equipment. Although never definitively demonstrated, use of this process has been thought to include dissemination of cancer cells with resultant metastatic disease. Recent in vitro and in vivo studies have suggested that filtering the salvaged blood using a leukoreduction filter (LRF) may significantly decrease the amount of cancer cells in the concentrated red blood cells (RBCs) for infusion and thus reduce or eliminate the risk of dissemination in a variety of cancer cell types including, but not limited to, gastric, colon, liver, prostate, renal cell, and transitional cell cancers. Therefore, as part of our blood management protocol on the gynecologic oncology service, all patients with suspected malignancy routinely have blood salvaged with a LRF before reinfusion. We report our experience of three patients on the gynecologic oncology service that had reinfusion of salvaged blood while undergoing surgery as part of our blood management protocol with emphasis placed on long-term outcomes and evaluation of potential hematogenous dissemination of cancer cells.

MATERIALS AND METHODS

Patients undergoing surgical procedures on the gynecologic oncology service as part of the blood management program at Englewood Hospital and Medical Center were identified from April 1998 to April 2007 (from an institutional review board–approved bloodless database maintained by the anesthesiology research department). For the cases identified, charts were reviewed and information was collected regarding the patient’s general characteristics, as well as pertinent aspects of the surgeries performed. Preoperative, intraoperative, and postoperative interventions and techniques specifically related to blood management were recorded. Patients undergoing blood salvage techniques during their surgery were identified and studied further with emphasis on long-term outcomes.

RESULTS

We identified 41 patients that had surgery on the gynecologic oncology service under the blood management protocol during the study time period (all were Jehovah’s Witnesses and refused allogeneic blood transfusion). Of the 41 patients, all Jehovah’s Witnesses, three patients with malignancy received reinfusion of salvaged RBCs (all reinfusions were performed after filtration with a LRF). These cases are presented below.

Case 1

A 52-year-old woman, para 1, presented for evaluation and management of a 40-cm pelvic mass and refractory anemia (preoperative hemoglobin [Hb] was 7.1 g/dL). The patient was initially begun on a regimen of weekly erythropoietin (EPO), oral iron, and folate acid therapy. The patient underwent attempted bilateral uterine artery embolization preoperatively by interventional radiology; however, only the right uterine artery could be successfully embolized. Despite continued attempts at preoperative Hb optimization, the Hb of the patient was found to be steadily decreasing, and by the third week after presentation, she was switched to daily EPO with IV iron supplementation. She was enrolled into the blood management program at our institution and underwent an exploratory laparotomy, hysterectomy, bilateral salpingo-oophorectomy, sigmoid colon resection with side-to-side primary reanastomosis, ventral hernia repair, lysis of adhesions, bilateral ureterolysis, and therapeutic panciclectomy (to aid in surgical access and postoperative wound healing). The decision to perform a supracervical hysterectomy was made intraoperatively given the already significant blood loss. Recombinant Factor VIIa was administered at a dose of 90 µg/kg IV intraoperatively. Acute normovolemic hemodilution was not performed secondary to the patient’s low starting Hb of 7.1 g/dL. Final pathology revealed a 12.7-kg uterine leiomyosarcoma with spread to a left periureteral lymph node. The estimated blood loss from the procedure was 2500 mL, and the patient’s intraoperative and postoperative Hb was 2.5 g/dL. Approximately 280 mL of salvaged RBCs were reinfused after filtering through a LRF.

Postoperatively, the patient was managed in the intensive care unit with aggressive fluid resuscitation and supportive care (secondary to her severe anemia and significant comorbidities). Importantly, the patient also had a right renal mass, which was removed at a planned subsequent procedure several weeks after her initial procedure and was found to be a renal cell carcinoma. The patient received six cycles of gemcitabine and docetaxel chemotherapy and achieved a full recovery with no neurologic or cardiovascular deficit.

During her 2-year follow-up, the patient underwent several diagnostic studies including an examination under anesthesia as well as a series of positron emission tomography and computed tomography (CT) scans. Although she did develop a recurrent pelvic mass measuring 20 × 17 × 20 cm, she did not develop any evidence of hematogenous recurrence.

Case 2

A 58-year-old patient, para 5, presented with increasing abdominal swelling over the past several weeks. A CT scan of the chest, abdomen, and pelvis revealed a 7-cm right hepatic lobe lesion consistent with metastatic disease, bilateral pleural effusions, and an 18-cm solid pelvic mass with marked ascites. Paracentesis was performed and
cytology revealed adenocarcinoma with papillary serous features. Given the patient’s large volume of metastatic disease (Stage IV ovarian adenocarcinoma) and the fact that she would not accept allogeneic blood transfusions, the patient was offered neoadjuvant chemotherapy with a plan for interval cytoreduction. After five cycles of platinum-based combination chemotherapy, the patient was found to have marked improvement of her disease status as demonstrated by CT imaging (including complete resolution of the liver lesion) and normalization of her CA-125 levels (from 1750 to 18.4 U/mL). The patient underwent an interval cytoreduction and staging procedure including an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and paraaortic lymph node dissection, appendectomy, omentectomy, and optimal cytoreduction. In compliance with the bloodless protocol, intraoperative blood salvage with reinfusion (after filtration with a LRF) was performed. The patient’s preoperative Hb was 13.4 g/dL, and her estimated blood loss during surgery was 900 mL. Blood salvage was performed and approximately 400 mL of RBCs were reinfused. Her postoperative Hb was 9.3 g/dL. The patient did well postoperatively and received three additional cycles of platinum-based combination chemotherapy.

Approximately 1 year later, the patient developed recurrent disease and was found to have a solitary 1.5-cm pulmonary nodule and two hepatic masses measuring 6.5 and 7 cm, respectively. There was also biochemical progression evident by an increase in CA-125 level to 464 U/mL. She was treated with IV topotecan.

Case 3
A 49-year-old female presented with a magnetic resonance imaging of the pelvis demonstrating a pelvic mass measuring 13.4 × 13.1 cm, an enlarging fibroid uterus (compared to a previous study), two separate hemorrhagic adnexal masses measuring 10.7 and 1.8 cm, and a 4.5-cm dilated small bowel loop. There was no evidence of pulmonary, liver, or spleen metastases based on CT imaging. The patient was taken to the operating room and underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, paraaortic lymph node dissection, and small bowel resection with a functional end-to-end primary reanastomosis. Findings at surgery included a 4-cm mesenteric mass in the jejunum and paraaortic lymphadenopathy. Final pathology revealed a gastrointestinal stromal tumor of the small bowel with all remaining specimens revealing benign changes. Blood salvage was performed using a LRF and approximately 170 mL of salvaged RBCs were reinfused. The patient’s preoperative Hb was 6.5 g/dL, and estimated blood loss during surgery was 2000 mL. Her postoperative Hb was 5.7 g/dL, and she was managed in the intensive care unit postoperatively and achieved a full recovery. She did not receive any adjuvant treatment and currently remains free of disease 2 years since her diagnosis.

DISCUSSION
The field of blood management has been rapidly expanding over the past several years in response to a growing number of patients who refuse allogeneic transfusion due to personal beliefs. In addition, concerns regarding blood safety and both infectious and noninfectious risks have increased the search for methods to avoid blood product transfusion.21,22 Some of the techniques that have been utilized in perioperative blood conservation strategies include preoperative autologous donation, EPO therapy, antifibrinolytic medications, intraoperative acute normovolemic hemodilution, and intraoperative blood salvage.

Although the technology of blood salvage has evolved since its initial implementation in the 1970s, it remains most effective in patients with adequate preoperative Hb experiencing major surgical blood loss (1000 mL or greater).21 During the process of blood salvage, blood loss in the surgical field blood is collected, filtered, and washed to allow for autologous RBC transfusion to the patient. RBCs that are processed by cell salvage and are stored at room temperature can be safely transfused up to 4 hours after collection.24 Basic filtering systems and washing the collected blood helps remove contaminants such as cell fragments, fat globules, bone chips, some medications, and potassium leaked from hemolysis. The final washing step resuspends the RBCs in saline for preparation for transfusion into the patient.

The performance of blood salvage in oncologic surgeries is controversial because of the concern that cancer cells in the surgical field could contaminate the salvaged blood and lead to the hematogenous dissemination of cancer cells when the salvaged blood is reinfused IV into the patient.5,25 Hansen and colleagues25 showed that tumor cells remain in blood salvaged from the operative field. They analyzed blood shed from the surgical field during oncologic surgery for tumor cells in a series of 61 patients with cancer who underwent surgery for malignant tumors and blinded comparison with 15 patients with benign diseases undergoing surgery. In 57 of 61 patients, tumor cells were detected in the blood shed during oncologic surgery. They demonstrated proliferation capacity, invasiveness, and tumorigenicity. The total number of tumor cells identified ranged from 7 × 10⁶ to 1 × 10⁷ for Stage IV ovarian cancer, 1 × 10⁵ to 2 × 10⁷ for endometrial cancer, and 5 × 10⁶ to 1 × 10⁷ for gastric cancer (similar to the three cases in this case series) with no close correlation to the amount of blood loss. However, they also state that one should refrain from intraoperative autotransfusion in tumor surgery, unless methods such as
LRFs and irradiation techniques are used for the elimination of these cells.

Over the past several years, numerous in vitro studies have reported on the ability for LRF to remove tumor cells from blood, thereby reducing this concern and enhancing the safety of salvage in oncologic patients. All investigators who tested LRFs unanimously concluded that this method was effective in filtering cancer cells. These studies were primarily experimental in vitro studies on culture-derived cancerous cells. Unfortunately, there is a paucity of clinical data regarding the ability of LRFs to effectively prevent the hematogenous dissemination of malignant cells of gynecologic origin in patients undergoing blood salvage during open gynecologic cancer surgery with gross intraabdominal disease. Thus, the majority of our knowledge on the ability for LRFs to remove cancer cells from contaminated blood comes from in vitro studies. Other methods to remove cancer cells from contaminated blood have been studied with varied success including elimination of malignant cells by the centrifugal separation method, elimination of malignant cells by using anticancer drugs, and elimination of malignant cells by irradiation of cell salvage blood. Irradiation of salvaged blood is the second proposed method to eliminate tumor cells. This method has been studied exclusively by Hansen and coworkers; they concluded that a 50-Gy irradiation dose is sufficient to inactivate the proliferating tumor cells observed or expected in salvaged blood. Their results provide the experimental basis for the clinical application of blood irradiation for intraoperative blood salvage in cancer surgery.

A review of literature reveals seven clinical studies that have investigated patient survival after use of the cell saver in oncologic surgery. The population size of these studies ranged from 20 to 54 patients and included patients with gynecologic cancer (two studies), urologic cancer (three studies), and hepatic cancer (two studies; Table 1). None of these studies showed a difference in short- or medium-term survival and no metastatic dissemination. Two of the studies specifically evaluated patients with gynecologic cancers and the role of blood salvage in gynecologic oncology surgery. Connor and colleagues evaluated 71 patients undergoing radical hysterectomy with the use of blood salvage with respect to risk of recurrence in patients. Importantly, the salvaged blood in this study was not treated in any specific way for the purpose of removing cancer cells (LRFs were not used in this study). The risk of tumor cell cotransfusion was assessed intraoperatively with peritoneal cytology before blood collection and postoperatively with salvaged blood cytology. No study patient had positive peritoneal cytology based on the above assessments (thereby supporting the fact that these patients did not have gross intraabdominal disease). Thirty-one patients were autotransfused using blood salvage, whereas 40 patients were not autotransfused. There was no significant difference between these patients and a comparison group of 231 patients (age-matched historic controls) in terms of tumor recurrence rates. The authors concluded that blood salvage is well accepted by patients, decreases the need for allogeneic transfusions, and does not appear to cotransfuse tumor cells. In a similar study, Mirhashemi and colleagues published a retrospective study of 156 patients treated with Type III radical hysterectomy and lymphadenectomy. Fifty patients had intraoperative autologous blood transfusion using blood salvage (filtered using a 40-μm filter as LRFs were not available in the hospital where this study was performed), and 106 patients did not have blood salvage performed. There were no significant differences between the two groups of patients in terms of recurrence rates or patterns of recurrence. The authors concluded that the use of intraoperative autologous blood transfusions during Type III radical hysterectomy and lymphadenectomy is safe and effective without compromising cancer outcomes. Although these studies are important and demonstrate the safe use of blood salvage in gynecologic oncology patients, these studies do not address the far more challenging problem of how to manage blood salvage in patients with gross intraabdominal gynecologic malignancy.

Our case series is a retrospective chart review of three patients with gross intraabdominal malignancy undergoing open abdominal surgery on the gynecologic oncology service that received reinfusion of salvaged blood after filtration through a LRF. We were able to demonstrate that two of the three cases discussed above did not show any evidence of metastases over a long-term follow-up period. The only patient (Case 2-Stage IV ovarian cancer) that did develop evidence of hematogenous progression (including lung and liver metastases) had known liver metastases at the time of her initial diagnosis and therefore presumably had hematogenous dissemination before her index surgical procedure. Based on our

**TABLE 1. Clinical studies evaluating intraoperative blood salvage use in cancer patients**

<table>
<thead>
<tr>
<th>Study first author and year</th>
<th>Number of patients</th>
<th>Pathology</th>
<th>Median follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klimberg 1986</td>
<td>49</td>
<td>Prostate-bladder</td>
<td>12-24</td>
</tr>
<tr>
<td>Zulim 1993</td>
<td>39</td>
<td>Liver</td>
<td>36</td>
</tr>
<tr>
<td>Fujimoto 1993</td>
<td>54</td>
<td>Liver (HCC)</td>
<td>36</td>
</tr>
<tr>
<td>Connor 1995</td>
<td>31</td>
<td>Uterus</td>
<td>24</td>
</tr>
<tr>
<td>Jacobi 1997</td>
<td>24</td>
<td>Prostate</td>
<td>NS</td>
</tr>
<tr>
<td>Vagner 1998</td>
<td>20</td>
<td>Kidney</td>
<td>60</td>
</tr>
<tr>
<td>Mirhashemi 1999</td>
<td>50</td>
<td>Cervix</td>
<td>22</td>
</tr>
</tbody>
</table>

* None showed a change in short- or medium-term survival or any cancer dissemination. HCC = hepatocellular carcinoma; NS = not specified.
findings, blood salvage with filtration using a LRF may be acceptable in patients with gross intraabdominal gynecologic malignancies in whom allogeneic transfusion is not possible. These findings are supported by both in vitro and in vivo data in the literature among a variety of cancer cell types. In addition to the general AABB indications for the use of cell salvage, the types of gynecologic oncology cases where blood salvage is used should be individualized by the institution and surgeon performing the procedure. Blood salvage using a LRF should be considered in any patient refusing allogeneic transfusion that is undergoing surgery for a gynecologic malignancy. The avoidance of allogeneic transfusion is also important considering the issues of transfusion risks including immunomodulation affecting tumor growth. However, because the safety of cell salvage in patients with gross intraabdominal disease is still under investigation, we recommend the use of cell salvage in this population of patients when allogeneic transfusion is to be avoided.

Unfortunately, due to the off-label use, and theoretical but unsubstantiated risk of hematogenous dissemination of cancer cells during blood salvage, a randomized controlled trial evaluating the safety of blood salvage in patients with gross intraabdominal gynecologic malignancy is unlikely. Therefore, we must rely on the reporting of individual cases and case series such as this one to gain a better understanding about the safety of blood salvage in this patient population.

CONFLICT OF INTEREST

None of the authors have any conflict of interest for this manuscript.

REFERENCES

19. Vagner EA, Davidov MI. [Blood reinfusion during


