

Esophagectomy postallogenic hematopoietic stem cell transplantation for hematologic malignancy: A case series



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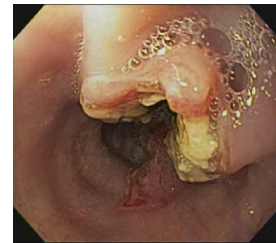
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Survival rates following allogenic hematopoietic stem cell transplantation (AHSCT) for hematologic malignancies continue to improve.¹ Patients undergo aggressive chemotherapy with or without radiation therapy, followed by relapse of their primary disease, leading to AHSCT. Preparation for transplantation requires intensive preconditioning with immune suppression and chemotherapy, followed by long-term immune suppression to modulate complications such as graft versus host disease (GvHD), an independent risk factor for solid-organ malignancy.¹ These patients form a difficult cohort for esophagectomy due to their previous chemotherapy or radiation therapy in addition to necessary ongoing immune modulation. This series reports 3 consecutive patients, all with AHSCT and significant GvHD, developing interval esophageal squamous cell carcinoma (SCC) at varying remote intervals from their primary diagnosis and undergoing minimally invasive esophagectomy (MIE).

CASE SERIES

Our institutional database was reviewed to identify appropriate cases. Patients provide consent for inclusion in this database and any research activity arising from it at diagnosis. Patient demographics and broad treatment approaches are outlined in [Table 1](#). Patient 1 was initially diagnosed with chronic lymphocytic leukemia, which subsequently underwent transformation to non-Hodgkin lymphoma. Following relapse with non-Hodgkin lymphoma, he had induction therapy with busulfan and cyclophosphamide, followed by human leukocyte antigen–matched AHSCT. He had GvHD of the oral mucosa, connective tissue, and skin and 18 years following transplant was diagnosed with a T3N1 SCC due to symptomatic dysphagia. Following neoadjuvant CROSS chemoradiotherapy



Esophageal SCC following allogenic haematopoietic stem cell transplant.

Esophageal SCC following hematopoietic stem cell transplant.

CENTRAL MESSAGE

Esophagectomy is feasible in high-risk patients following allogenic hematopoietic stem cell transplantation for hematologic malignancy.

(41.4-Gy radiation with carboplatin and paclitaxel), he underwent an uncomplicated 2-field MIE with a 7-day hospital stay. His final histopathology showed a T2N1 tumor. He remains disease-free 3 years' postresection.

Patient 2 was initially diagnosed with acute lymphoblastic leukemia (ALL) aged 50 years. Following chemotherapy, and total brain irradiation, she relapsed and underwent induction therapy with busulfan and cyclophosphamide and total body irradiation with 400 cGy and successful human leukocyte antigen–matched AHSCT. She had GvHD affecting the oral mucosa (frequent ulcers), skin, and alimentary tract, with a benign esophageal stricture requiring multiple serial dilations over 2 years and occasional cramps. During endoscopy, she was incidentally found to have a T1bN0 SCC of the midesophagus. Staging investigations also showed an incidental floor of mouth SCC. She progressed straight to surgical resection of her dual primary pathologies. She underwent an uncomplicated 2-field MIE with a floor of mouth resection, flap reconstruction, and elective tracheostomy due to limited mouth opening with a 14-day hospital stay. Final histopathology showed a T1bN0 esophageal SCC and a T2N0 oral SCC with a close deep margin. Unfortunately, this patient developed

TABLE 1. Patient details for those with esophageal cancer following allogeneic hematopoietic stem cell transplantation

	Patient 1	Patient 2	Patient 3
Sex	Male	Female	Male
Primary hematologic malignancy	Chronic lymphocytic leukemia with transformation to non-Hodgkin lymphoma and immune mediated thrombocytopenia	Acute lymphoblastic leukemia	Acute lymphoblastic leukemia
Age at diagnosis, y	47	50	40
Primary chemotherapy	CHOP	Dana Farber induction protocol*	Dana Farber induction protocol*
Age at hematopoietic stem cell transplant, y	48	50	44
Induction regimen	Busulfan and cyclophosphamide	Busulfan and cyclophosphamide, TBI and whole-body irradiation with 400 cGy	Busulfan, fludarabine, TBI, and whole-body irradiation with 400 cGy
Maintenance immune suppression	Cyclosporine and methotrexate	Cyclosporine	None
Complications secondary to BMT	Chronic GvHD, predominantly affecting skin and subcutaneous tissues	GvHD, predominantly affecting skin, oral mucosa and causing benign esophageal stricture	GvHD affecting mouth, alimentary tract, liver, eyes and skin. AVN of both femoral heads
Interval to diagnosis of esophageal cancer, y	18	4	6
Histology	Moderately differentiated SCC distal esophagus	Moderately differentiated SCC of distal third of esophagus	Invasive moderately differentiated SCC of midesophagus
cTNM	cT3N1M0	cT1bN0M0	cT3N1M0
Perioperative therapy	CROSS	None, straight to surgery	CROSS
Operative intervention	2-field (Ivor Lewis with stapled intra-thoracic anastomosis) MIE	2-field (Ivor Lewis with stapled intra-thoracic anastomosis) MIE	3-field (McKeown with stapled modified Collard cervical anastomosis) MIE
Final TNM	ypT2N1Mx	pT1bN0Mx	ypTxN0Mx (complete pathologic response)
30-d morbidity	None	None	None
30-d mortality	No	No	No
Notes		Previous whole-brain irradiation. Also has synchronous floor of mouth SCC resected at time of MIE	Previous whole-brain irradiation

CHOP, Cyclophosphamide, doxorubicin, vincristine, prednisolone; TBI, total brain irradiation; BMT, bone marrow transplant; GvHD, graft versus host disease; AVN, avascular necrosis; SCC, squamous cell carcinoma; CROSS, 41.4-Gy radiation with carboplatin and paclitaxel; MIE, minimally invasive esophagectomy; TNM, tumor-node-metastasis. *Dana Farber induction protocol generally consists of doxorubicin, vincristine, dexamethasone, mercaptopurine, pegaspargase, methotrexate and subsequent intrathecal methotrexate, cytarabine, and hydrocortisone.

a recurrence of her oral cancer 6 months following surgery and was treated with palliative intent.

Patient 3 was diagnosed with ALL aged 40 years. He developed recurrent ALL 4 years later and underwent AHSCT. He had induction therapy with busulfan and fludarabine, total brain irradiation, and total body irradiation with 400 cGy. Following his transplant, he had significant GvHD affecting his oral mucosa with frequent ulcers, alimentary

tract (nausea, cramps), skin, and liver, and developed avascular necrosis of both femoral heads. Six years post-transplant, he was diagnosed with a T3N1 SCC of the mid-esophagus due to symptomatic dysphagia. He underwent neoadjuvant CROSS followed by an uncomplicated 3-field MIE with an 8-day hospital stay. He made an excellent recovery, and histopathology showed a complete pathologic response. He remains disease free over 1-year postresection.

COMMENT

Although survival following AHSCT continues to improve, consequences include the development of solid-organ malignancy such as esophageal SCC.^{2,3} Because of the chemotherapy, radiotherapy, and ongoing immune modulating therapy these patients receive for AHSCT, a role for definitive chemoradiotherapy has not been established, although it may be of use in selected cases.⁴ The authors feel that as the evidence base is limited, neoadjuvant therapy and resection should be the approach of choice. It is unclear if esophagogastric anastomosis in an esophagus affected by GvHD leads to greater perioperative complications, particularly a potentially devastating anastomotic leak. Kato and colleagues⁵ described 10 patients undergoing esophagectomy following AHSCT in a Japanese population and demonstrated a high rate of postoperative pneumonia. However, their patients received induction chemotherapy, and the majority underwent an open approach to esophagectomy. Herein, we demonstrate a series of 3 patients who underwent MIE with and without induction chemoradiotherapy without significant complication. Although our series is limited, there were no anastomotic complications.

Although long-term survival is achievable after esophageal resection in this context, patients must be monitored for development of other malignancies. As GvHD is an independent risk for SCC, surveillance of the esophageal remnant and gastric conduit is warranted for these patients. Following AHSCT, patients should undergo screening for oropharyngeal and esophageal cancers.

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