Myelodysplastic Syndrome in Patients with Gastro-Pancreatic Malignancies: A Case Series and Review of Literature

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ABSTRACT

Patients who develop one primary neoplasm are at increased risk for second cancers. Chemotherapeutic agents can result in DNA damage leading to clonal hematopoiesis, thereby causing myelodysplastic syndrome (MDS). Alkylating agents and topoisomerase inhibitors are most frequently implicated in therapy-related MDS. We report four patients with gastro-pancreatic malignancies (two with pancreatic adenocarcinoma and two with gastric adenocarcinoma) who developed MDS during or after the treatment of their primary gastrointestinal (GI) malignancies. Two of these patients were diagnosed with MDS during maintenance therapy with ramucirumab. To our knowledge, development of MDS in association with ramucirumab has not been previously reported in the literature. Our findings also suggest that with continued improvement in survival of patients with GI and pancreatic malignancies, more cases of treatment-related MDS might be identified.

KEYWORDS

MDS; Leukemia; Chemotherapy; Alkylating agents; Anemia; Thrombocytopenia; Pancytopenia

1. INTRODUCTION

Multiple primary malignant neoplasms (MPMN) have been reported in 1% - 10% of cancer patients [1]. Cancer survivors have an increased risk for secondary malignancies [2,3]. This risk arises from interplay of genetic predisposition, behavioral factors and prior anti-neoplastic treatment. Additionally, improved survival and frequent diagnostic scrutiny contributes to higher diagnoses of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Secondary malignancies especially hematologic are rarely reported in patients with gastrointestinal (GI) cancers.

Patients with advanced upper gastrointestinal and pancreaticobiliary tumors usually have very poor long-term outcomes. Advances in surgical technique, earlier diagnosis and improved chemotherapy combinations have resulted in an incremental improvement in pancreatic cancer outcomes where 5-year survival rates in resected pancreatic cancer are now higher than 30% [4,5].

Chemotherapy can result in short and long-term hematological toxicities as a result of DNA damage leading to clonal hematopoiesis, secondary hematologic malignancies and bone marrow failure. Over 40% of
cancer patients receiving chemotherapy require blood product and growth factor support for the duration of their treatment [6,7]. Chemotherapeutic exposure with alkylating agents (latency period of 5-7 years) or topoisomerase inhibitors (latency period of 2-3 years) is known to increase the risk for MDS/AML [8,9].

As the treatment paradigms for GI malignancies continue to evolve and survival improves, more cases of secondary malignancies may be seen in patients with gastrointestinal malignancies. We describe in detail the presentation and management of four cases of MDS (Table 1) that were diagnosed in patients with GI malignancies.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td>64</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
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<tr>
<td>Smoking status</td>
<td>Active smoker</td>
<td>Former smoker</td>
<td>Former smoker</td>
</tr>
<tr>
<td>Primary cancer</td>
<td>Pancreatic adenocarcinoma</td>
<td>Gastric adenocarcinoma</td>
<td>Gastric adenocarcinoma</td>
</tr>
</tbody>
</table>

Table 1: Patient characteristics.

2. CASE 1
A 63-year-old female with a prior history of coronary artery disease and peripheral vascular disease presented with a 2-week history of fatigue, muscle weakness, and obstructive jaundice. Workup included endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP), which demonstrated a distal common bile duct obstruction from a 24.6 X 22.3 mm hypoechoic pancreatic head mass. A sphincterotomy with metal stent placement was performed, and EUS-guided biopsy of the pancreatic head mass confirmed adenocarcinoma. A vascular variant (arc of Buhler) precluded any operative intervention; therefore she received 5 cycles of chemotherapy with gemcitabine (1000 mg/m²) and oxaliplatin (85 mg/m²). Restaging CT scan suggested disease progression, so she began a regimen of gemcitabine (1000 mg/m²) and nab-paclitaxel (125 mg/m²). After her 2nd cycle of chemotherapy, she developed fevers, fatigue, diarrhea and her laboratory evaluation showed new pancytopenia (white blood cell (WBC) count 1.4 K/uL, hemoglobin 7.7 g/dL, platelets 51 K/uL). The peripheral smear revealed 16% circulating blasts. Bone marrow biopsy showed a hypercellular (80%) marrow with trilineage dyspoiesis and 8% blasts. Karyotype was normal female (46, XX). A diagnosis of MDS with excess blasts-2 was made, 10 months from the diagnosis of her primary malignancy.

Chemotherapy was then discontinued and she received supportive care for her MDS. Treatment for her pancreatic cancer was later reinitiated with capecitabine (1000 mg/m2 twice daily) and erlotinib (100 mg daily), a regimen that is not usually associated with hematologic toxicity. She continued this for a total of 12 cycles but died from MDS-related complications around 9 months after her MDS diagnosis.

3. CASE 2
A 69-year-old male with a history of H. pylori gastritis presented with recent onset constipation, early satiety, abdominal distention, and an unintentional weight loss of 4-5 pounds. Computerized tomography (CT) imaging showed extensive gastric wall thickening concerning for a primary gastric malignancy, along with bulky retroperitoneal and mesenteric root adenopathy. Upper endoscopy demonstrated a 7 cm long irregular ulcer in the proximal stomach extending from below the gastroesophageal junction to the fundus, biopsy proven to be moderately differentiated adenocarcinoma.
He began treatment with cisplatin (30 mg/m²) and capecitabine (1000 mg/m²) and restaging scans after 16 cycles demonstrated a new L3 lytic lesion and progressive liver metastases. Treatment was switched to docetaxel (75 mg/m² for 23 cycles) and then to ramucirumab alone (8 mg/kg for 53 cycles).

He developed persistent pancytopenia around 5 years and 8 months after the initial diagnosis of GI malignancy. The patient was diagnosed with myelodysplastic syndrome, in the setting of persistent pancytopenia, despite holding ramucirumab for 10 weeks (WBC count 2.6 K/µL, hemoglobin 10.5 g/dL, platelets 67 K/µL). Bone marrow evaluation revealed erythroid predominance and dyspoiesis, decreased megakaryocytes with small hypolobated forms, no increase in blast forms, and normal male karyotype. A diagnosis of MDS with multi-lineage dysplasia was made. He did not receive any treatment for myelodysplastic syndrome. His ramucirumab was subsequently resumed 3 months after the diagnosis of MDS at 50% of the previous dose (4 mg/kg every 3 week). On his most recent follow up, white cell count was 3.5 K/µL, hemoglobin was 12.4 g/dL and platelet count was 93 K/µL. He was recently switched to pembrolizumab after disease progression.

4. CASE 3
This is a 64-year-old male with a history of alcohol abuse and localized Gleason 3+4 prostate adenocarcinoma (s/p external beam radiation and 6 months of bicalutamide), underwent endoscopic evaluation for progressive dysphagia and was diagnosed with Stage 1A (T1N0) gastric adenocarcinoma invading at least into the muscularis mucosa. Patient declined surgical resection and started 5 weeks of concurrent chemoradiation with capecitabine (1000 mg/m2 twice daily). He developed progressive thrombocytopenia and capecitabine was held for 2 weeks. He had a thymidylate synthase (TYMS) mutation would have put him at an increased risk of toxicity and therefore he was started on ramucirumab maintenance.

Therapy was held after 5 cycles of ramucirumab (6 mg/kg every 3 weeks), as he developed leukopenia (3.7 K/µL) and thrombocytopenia (99 K/µL). Bone marrow biopsy performed at this time (11 months after initial malignancy diagnosis) demonstrated hypercellularity for age with trilineage dyspoietic maturation and no increase in blast forms. This was consistent with MDS with multi-lineage dysplasia. Patient had normal male karyotype.

The diagnosis of MDS was not considered a contraindication for his ongoing treatment for gastric carcinoma. Patient’s cytopenias improved after one month of holding chemotherapy. He did not receive any specific treatment for MDS. On his most recent follow up, his WBC count was 3.3 K/µL, hemoglobin was 10.9 g/dL and platelet count was 91 K/µL.

5. CASE 4
Another case of therapy related MDS has been previously reported by our group [10], where a 55-year-old female with pancreatic adenocarcinoma (Stage pT3N1) was diagnosed with MDS; 8 years after her initial chemotherapy treatment. She received FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin and bevacizumab followed by GEMOX (gemcitabine and oxaliplatin) plus bevacizumab for disease progression. She received further treatment with irinotecan and external beam radiation followed by capecitabine and mitomycin (MIXE). She developed pancytopenia, white blood cell count of 1.7 K/µL, hemoglobin of 8.1 g/dL, and platelet count of 79 K/µL. Bone marrow aspiration and biopsy demonstrated a normocellular marrow (40%) with myelodysplasia and blast count of 6-9%, consistent with refractory anemia with excess blasts-1 (RAEB-1). Cytogenetic evaluation showed a complex karyotype with deletion 5q, 7q, and 12p, losses of one copy of chromosome of chromosomes 21.
17, 18, 21, and 22, and two to three marker chromosomes. She was diagnosed with therapy-related myelodysplastic syndrome. She was enrolled in a clinical trial of decitabine and all-transretinoic acid but rapidly progressed and died of complications of MDS.

6. DISCUSSION

We report four cases of MDS diagnosed in patients with gastrointestinal malignancies; two of these patients had pancreatic cancer and two with gastric cancer. There is scarcity of literature on secondary malignancies in patients with pancreatic cancer as their life expectancy is markedly diminished due to their primary malignancy [10,11]. MDS was diagnosed in the two patients with gastric cancer while they were undergoing anti-vascular endothelial growth factor receptor-2 (VEGF) therapy with ramucirumab, which has not been previously associated with MDS/AML.

In these patients, MDS was diagnosed on evaluation of refractory cytopenias, either during or after chemotherapy treatment for GI malignancies. Persistent cytopenia during ongoing chemotherapy can be easily attributed to the ongoing treatment, necessitating a change in the dose or discontinuation of the offending agent. In fact, preferred chemotherapy combinations used in adjuvant or metastatic setting in pancreatic cancer (such has FOLFIRINOX or gemcitabine-nab paclitaxel) are associated with high rates of hematological toxicity and therapy discontinuation [12,13]. However, blood counts usually recover following dose modification or discontinuation of treatment. Taking into account the poor prognosis associated with advanced gastro-pancreatico-biliary malignancies, secondary malignancies or second primaries are rarely reported in these patients given the lag time usually required between exposure to chemotherapy and onset of treatment-related MDS.

Ramucirumab is a humanized VEGFR2 inhibitor, which is approved for use in metastatic non-small cell lung cancer and gastro-intestinal cancers after progression on or after 1st line therapy [14]. Two of our patients were diagnosed with MDS during ramucirumab maintenance therapy without any antecedent exposure to any alkylating agents or topoisomerase inhibitors. None of these patients had any karyotype abnormalities, which is usually seen in 50-60% of patients with MDS [15]. A thorough literature review could not identify any prior cases of MDS related to ramucirumab use, although ramucirumab-related neutropenia and thrombocytopenia has been frequently seen in clinical trials. When ramucirumab is used in combination with paclitaxel, higher rates of thrombocytopenia (grade > 3: 2-4% vs. grade > 3: 2%) and neutropenia (grade > 3: 41% vs. grade > 3: 19%) were noted compared to paclitaxel alone [14].

In this case series, initial chemotherapy exposure of these patients included anti-metabolites (5-FU, capecitabine), taxes (paclitaxel, docetaxel), platinum agents (cisplatin), nucleoside analog (gemcitabine) and anti-VEGF (ramucirumab). We performed a comprehensive literature search to identify cases of MDS related to these chemotherapy agents on the PUBMED database (Table 2) through a multiple keyword search using generic chemotherapy names, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), therapy-related MDS or AML. All except for cisplatin are only rarely associated with therapy-related MDS/AML [16]. Table 2 shows reported cases of therapy related MDS/AML with non-alkylating/non-topoisomerase inhibitor chemotherapeutic agents. Role of cisplatin in therapy related MDS/AML has been previously reported in two large literature reviews [16,17].
Table 2: Literature review of secondary MDS/AML associated with certain chemotherapy agents.

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Primary Malignancy</th>
<th>Age</th>
<th>MDS/AML</th>
<th>Karyotyping</th>
<th>Time to MDS/AML (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-metabolites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon cancer [20]</td>
<td>60</td>
<td>AML</td>
<td>MDS/AML</td>
<td>t(5;21)(q23;q22)</td>
<td>39</td>
</tr>
<tr>
<td>Gastric cancer [21]</td>
<td>49</td>
<td>AML</td>
<td>NA</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Colon cancer [22]</td>
<td>68</td>
<td>AML</td>
<td>MDS</td>
<td>Monosomy 7</td>
<td>30</td>
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<tr>
<td>Colon cancer [23]</td>
<td>74</td>
<td>AML</td>
<td>MDS</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Colon cancer [24]</td>
<td>56</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Rectal cancer [25]</td>
<td>71</td>
<td>MDS</td>
<td>MDS/AML</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Colorectal cancer [26]</td>
<td>74</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Gastric cancer [26]</td>
<td>68</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>Colon [27]</td>
<td>68</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>~60</td>
</tr>
<tr>
<td><strong>Oxaliplatin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer (2 cases) [28]</td>
<td>57 &amp; 55</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>22 &amp; 17</td>
</tr>
<tr>
<td>Ovarian cancer [29]</td>
<td>73</td>
<td>MDS/AML</td>
<td>MDS/AML</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Endometrial cancer [31]</td>
<td>63</td>
<td>MDS/AML</td>
<td>MDS/AML</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Ovarian cancer [32]</td>
<td>75</td>
<td>MDS</td>
<td>MDS/AML</td>
<td></td>
<td>106</td>
</tr>
<tr>
<td>Ovarian cancer [33]</td>
<td>52</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>~30</td>
</tr>
<tr>
<td>Breast [34]</td>
<td>62</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>44</td>
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<tr>
<td><strong>Taxanes (Paclitaxel, docetaxel, sub-paclitaxel)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal cancer [35]</td>
<td>48 &amp; 51</td>
<td>MAML</td>
<td>MDS/AML</td>
<td></td>
<td>55 &amp; 50</td>
</tr>
<tr>
<td>Laryngeal cancer [16]</td>
<td>64</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Esophageal cancer [36]</td>
<td>70</td>
<td>AML</td>
<td>MDS/AML</td>
<td></td>
<td>32</td>
</tr>
</tbody>
</table>

Two of our patients (case 1 and 3) developed hematopoietic dysplasia within a year of their initial cancer diagnosis but lacked any karyotype changes associated with therapy-related MDS. None of above patients above had any exposure to alkylating agents or topoisomerase inhibitors. This could possibly suggest a de novo diagnosis of MDS. It is possible that use of chemotherapy accentuated the already present bone marrow injury and maturation arrest of the disease clone, leading to refractory cytopenia. It can be difficult to make a diagnosis of MDS in patients who are receiving chemotherapy and/or growth factors. We acknowledge that the diagnosis of MDS in these patients should be made cautiously. Our patients had normal karyotype. The use of next generation sequencing may support the diagnosis of MDS. However, since there is no single diagnostic test to confirm the diagnosis of MDS, heightened awareness in these patients may help in the diagnosis and treatment planning.

Diagnosis of MDS poses a challenge to further therapy and limits therapeutic options for management of an active malignancy. As the field of targeted therapy expands, it is possible that it will assume the role of maintenance therapy for GI malignancies. Also, consideration can be made for regimen such as gemcitabine and erlotinib, which has minimal hematologic toxicity and can provide palliative disease control [18]. This case-series of MDS suggests that
continuing treatment in these patients may involve sequential chemotherapy to minimize the additive hematological toxicity from multiple chemotherapeutic agents, especially when used for a non-curative intent [19].

With improving survival and advancement in cancer therapeutics bringing forth multiple lines of anti-neoplastic therapies, we expect to see an increase in patients with secondary hematological malignancies. In patients who receive chemotherapy for non-curative intent, secondary malignancies could contribute to a poor quality of life, affect primary treatment outcomes, and raise mortality. The patients we report presented with prolonged cytopenias following chemotherapy and had evidence of multi-lineage dysplasia. For such patients, a diagnosis of MDS should be considered and diagnostic workup including bone marrow evaluation should be done in patients who develop refractory cytopenia despite modification or discontinuation of chemotherapy.

7. CONCLUSION
In conclusion, patients with GI malignancies can develop either de novo or therapy-related MDS following treatment of their primary disease. Persistent cytopenias despite discontinuation of treatment should be further investigated to rule out any underlying bone marrow injury. Hematological toxicity can occur with ramucirumab, but no cases of MDS have been reported previously and therefore, prospective studies are needed to further delineate the magnitude of this risk.

REFERENCES


