Thrombotic microangiopathies and antineoplastic agents

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THROMBOTIC MICROANGIOPATHIES

- Microangiopathic hemolytic anemia
- Peripheral thrombocytopenia
- Organ failure of variable severity

TTP
- Congenital
- Autoimmune
  - Idiopathic
  - Secondary

HUS
- STEC+
- Complement+

Other entities
- HELLP Sd
- HTA malignes
- Transplantation
- Cancers
- Antineoplastic agts
Epidemiology: burden of patients

Proportion of chemo-associated TTP (from 772 TTP patients)

- Infections: 94 (12%)
- AI diseases: 87 (11.5%)
- Cancer: 71 (9%)
- Pregnancy: 62 (8%)
- Transplantation: 27 (3.5%)
- HIV: 24 (3%)
- Other / several conditions: 18 (2.5%)
- Drugs: 11 (1.5%)

Number of patients (proportion of 772 TTP)

> 100 chemo-associated TMA in the French TMA registry

> 90% of patients have a detectable activity

Most chemo-associated TMA have a detectable ADAMTS13 activity (= not TTP)

Mariotte et al., Lancet Haematol 2016 and unpublished results
Antineoplastic drug-associated TMA

Many have been associated with TMA:

- Mitomycin C
- Gemcitabine

- Anti-VEGF

- Proteasome inhibitors (carfilzomib, bortezomib)

- Yttrium$^{90}$ (> 200 mCi/m$^2$: associated with renal TMA)
  - Anti-CD22 immunotoxin (BL22)

- Tyrosine kinase inhibitors (imatinib mesylate, dasatinib)

- Deoxycoformycin (Nipent®)
  - Cytarabine
  - Daunorubicine
  - Cisplatin

Exceptionally reported...

Medina et al., Curr Op Hematol 2001
Moll et al., Am J Kidney Dis 2001
Yui et al., Am J hematol 2016
Mitomycin C-associated TMA

Medina et al., Curr Op Hematol 2001

TMA in 2% to 15% of patients receiving MMC

Clinical features typically occur 4 to 8 weeks after the last MMC infusion

Usual cumulated dose > 40 mg

Lung involvement is a frequent feature

- Dyspnea
- Lung oedema
- Respiratory distress

Renal failure if cumulated dose > 50-70 mg

ADAMTS13: normal or mildly decreased

Diffuse endothelial lesions induced by the drug

Poor response to plasma exchange ± immunoadsorption

Poor prognosis; death at ~ 4 months

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Table 3. Clinical characteristics of patients with mitomycin C-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome

<table>
<thead>
<tr>
<th>Lesesne [11]*</th>
<th>Snyder [21]*</th>
<th>Sheldon [12]*</th>
<th>Cantrell [17]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>85</td>
<td>55</td>
<td>39</td>
</tr>
<tr>
<td>Chemotherapy regimen included mitomycin C</td>
<td>99</td>
<td>93</td>
<td>82</td>
</tr>
<tr>
<td>Cumulative dose of mitomycin</td>
<td>99</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>C &gt;40 mg</td>
<td>99</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>59</td>
<td>78</td>
<td>44</td>
</tr>
<tr>
<td>Primary site of carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gastric</td>
<td>26</td>
<td>9</td>
<td>44</td>
</tr>
<tr>
<td>breast</td>
<td>18</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td>colorectal</td>
<td>16</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pulmonary</td>
<td>65</td>
<td>NR</td>
<td>49</td>
</tr>
<tr>
<td>neurologic</td>
<td>16</td>
<td>NR</td>
<td>18</td>
</tr>
<tr>
<td>Laboratory features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>microangiopathic hemolytic anemia</td>
<td>100</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>100</td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>renal failure</td>
<td>100</td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>Death</td>
<td>74</td>
<td>55</td>
<td>72</td>
</tr>
</tbody>
</table>

*All values except number of patients are percentages. NR, not recorded.
Gemcitabine-associated TMA

Wasif Saif & McGee, 2005

TMA in ~ 15/100 000 treated patients

Median duration of treatment: 5.8 m

Occurs 1-2 months following the last infusion

TMA syndrome with renal failure and HT

ADAMTS13 detectable or normal

Pathophysiology: unclear+++:
- « Endothelial injury »?
- No clear threshold of toxicity (20 g/m² for some authors); « immunologic » mechanism (IC)?

Response to plasma exchange typically poor; immunoadsorption? Treat HT; dialysis; stop TTT

Mortality ranges from 10% to 70% of cases (variable; role of the underlying disease?)

<table>
<thead>
<tr>
<th>Features</th>
<th>Idiopathic TTP</th>
<th>Gemcitabine-associated TTP</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>3-7/million</td>
<td>150-14 000/million</td>
<td>2</td>
</tr>
<tr>
<td>Sex distribution, F:M</td>
<td>3:1</td>
<td>1:1</td>
<td>18,20-25,34</td>
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<tr>
<td>Hypertension, %</td>
<td>NA</td>
<td>74</td>
<td>18,20-25</td>
</tr>
<tr>
<td>Neurological symptoms, %</td>
<td>50</td>
<td>NA</td>
<td>35</td>
</tr>
<tr>
<td>Pulmonary symptoms, %</td>
<td>NA</td>
<td>60</td>
<td>20,22-24</td>
</tr>
<tr>
<td>Renal insufficiency*, %</td>
<td>45</td>
<td>100</td>
<td>18-23,26,34,36,37</td>
</tr>
<tr>
<td>Schistocytes, %</td>
<td>90</td>
<td>88</td>
<td>18,20,21,24,38</td>
</tr>
<tr>
<td>ADAMTS-13 deficiency†, %</td>
<td>33-100</td>
<td>13</td>
<td>39,40</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>10</td>
<td>13</td>
<td>10,18,20,22-25,41</td>
</tr>
</tbody>
</table>

*Renal insufficiency defined as creatinine ≥ 133 μmol/L. †ADAMTS-13 activity <5%. F=female; M=male. NA=not available. ADAMTS-13=A Disintegrin And Metallproteinase with a Thrombospondin type 1 motif, member 13
Gemcitabine-associated TMA: therapy with complement blockers

Eculizumab therapy for gemcitabine induced hemolytic uremic syndrome: case series and concise review

Omar Al Ustwani, James Lohr, Grace Dy, Charles LeVea, Gregory Connolly, Pradeep Arora, Renuka Iyer

4 patients with gemcitabine-associated TMA:

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Cancer</th>
<th>HT</th>
<th>A13</th>
<th>Creatinine</th>
<th>Eculizumab</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>Stage IV squamous carcinoma of the lung</td>
<td>+++</td>
<td>74%</td>
<td>2.6 mg/dl</td>
<td>Improved</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>Metastatic pancreatic carcinoma</td>
<td>NA</td>
<td>79%</td>
<td>1.82 mg/dl</td>
<td>Improved</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>Metastatic cholangiocarcinoma</td>
<td>NA</td>
<td>NA</td>
<td>3.79 mg/dl</td>
<td>Stabilization; subsequently died</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>Stage IV squamous carcinoma of the lung</td>
<td>NA</td>
<td>&gt;95%</td>
<td>2.79 mg/dl</td>
<td>Improved</td>
</tr>
</tbody>
</table>

Median cumulated dose: 21.2 g/m2

Resolution of TMA features

Improvement of renal function though no recovery
Gemcitabine-associated TMA and eculizumab: the French experience

- Observational, retrospective study including all patients with gemcitabine-induced TMA treated by eculizumab in 4 French centres, between 2011 and 2015
- 6 women, 2 men

Gemcitabine for pancreatic (n=3, 37.5%), ovarian (n=3, 37.5%) and pulmonary (n=2, 25%) cancer

TMA occurred after a median of 5 months (range 1.7-13) following treatment initiation

Median cumulative dose of 27.5 g (range 0.9-48.0)

- Hemolytic anemia (100%), acute renal failure (100%; including 62% stage 3 AKI and 25% dialysis)
- Hypertension (75%)

- Eculizumab was started after a median of 19.5 days (range 6-44) following TMA diagnosis

A median of 4.5 injections of eculizumab was performed (range 3-22)

Grall et al., in preparation
Gemcitabine-associated TMA and eculizumab: the French experience

- Major hematologic response in 6 patients (75%)

  RBC transfusion decreased after 1 injection of eculizumab: median of 2 packed RBC (0-10) vs 0 (0-1)

- Complete recovery of renal function was achieved in 2 patients (25%)

  Partial response in 4 patients (50%) with a median improvement of 15 ml/min/1.73m² (range 7-16) estimated GFR

- Five patients (62.5%) died during follow up despite response (septic and hemorrhagic shock on early stage: 1, cancer evolution after a median of 6 months (range 2-13) following eculizumab initiation: 4)

Acceptable indication in gemcitabine-associated TMA provided a reasonable underlying oncologic prognosis

Grall et al., in preparation
Possible role of complement in gemcitabine-induced TMA

Immunostaining with anti-C5b9 (MAC)

Patients (N=3)  Control

Positive staining in glomerular and tubular membrane and also in the capillary wall

Grall et al., in preparation
TMA and anti-VEGF agents
VEGF inhibition leads to TMA

6 patients treated with bevacizumab developed a TMA syndrome (proteinuria, hypertension, TMA)

VEGF has a role in vascular homeostasis

Question: is VEGF inhibition sufficient to induce a TMA?

Murine model of TMA by VEGF inhibition: VEGF KO tissue (podocyte)-specific and Dox+ inducible

VEGF has a major role in vascular homeostasis

Lumens of glomerular capillaries are collapsed or obliterated (b)

Endothelial cells swollen (d); dense subendothelial deposits (f)

Intracapillary thrombi (e)

Schistocytes on blood smear

IHC positive for fibrin

Anti-VEGF agents and pre-eclampsia-like syndrome

22 patients – Renal biopsy 16.2 ± 10.6 months > anti-VEGF (MoAb, TKI and VEGF-Trap) initiation for proteinuria or renal failure

<table>
<thead>
<tr>
<th>No. of patient</th>
<th>Sex</th>
<th>Age</th>
<th>Cancer localization</th>
<th>Anti-angiogenic drug</th>
<th>RAS blocker</th>
<th>Serum creatinine (μmol/L)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>56</td>
<td>Rectum</td>
<td>Bevacizumab</td>
<td>ACEI</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>71</td>
<td>Liver</td>
<td>Brivanib then naxavar</td>
<td>ARB</td>
<td>153</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>40</td>
<td>Breast</td>
<td>Bevacizumab</td>
<td>ACEI</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>52</td>
<td>Breast</td>
<td>Bevacizumab</td>
<td>ARB</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>64</td>
<td>Kidney</td>
<td>Sotalenib then sunitinib</td>
<td>ACEI</td>
<td>177</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>48</td>
<td>Kidney</td>
<td>Bevacizumab</td>
<td>ARB + ACEI</td>
<td>124</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>75</td>
<td>Liver</td>
<td>Sotalenib or brivarib</td>
<td>ARB</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>70</td>
<td>Kidney</td>
<td>Sunitinib</td>
<td>ARB</td>
<td>400</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>71</td>
<td>Rectum, liver and lung metastasis</td>
<td>Bevacizumab</td>
<td>ACEI</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>64</td>
<td>Lung</td>
<td>Aflibercept</td>
<td>ARB</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>57</td>
<td>Liver</td>
<td>Brivanib</td>
<td>ACEI</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>60</td>
<td>Caeacum</td>
<td>Bevacizumab</td>
<td>ACEI</td>
<td>92</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>56</td>
<td>Pancreas</td>
<td>Sunitinib</td>
<td>ACEI</td>
<td>290</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>46</td>
<td>Breast</td>
<td>Bevacizumab</td>
<td>ACEI</td>
<td>69</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>47</td>
<td>Breast</td>
<td>Bevacizumab</td>
<td>ACEI</td>
<td>64</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>61</td>
<td>Gliblastoma</td>
<td>Bevacizumab</td>
<td>ACEI</td>
<td>62</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>43</td>
<td>Breast</td>
<td>Bevacizumab</td>
<td>ACEI</td>
<td>62</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>80</td>
<td>GIST</td>
<td>Sunitinib</td>
<td>ARB + DRI</td>
<td>220</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>47</td>
<td>Breast</td>
<td>Bevacizumab</td>
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<td>60</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>64</td>
<td>Pleura</td>
<td>Bevacizumab</td>
<td>ACE-I</td>
<td>135</td>
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<td>21</td>
<td>F</td>
<td>68</td>
<td>Breast</td>
<td>Bevacizumab</td>
<td>ACE-I</td>
<td>80</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>55</td>
<td>Gliblastoma</td>
<td>Bevacizumab</td>
<td>No</td>
<td>72</td>
</tr>
</tbody>
</table>

Hypertension in ~ all cases – Mean proteinuria 2.97 ± 2.0 g/day - No or mild signs of TMA
Renal failure variable (normal creatinine level to 400 mcm.L⁻¹/anuria)

Double contours+thrombi of capillaries, duplication of the glomerular basement membranes, widening of the subendothelial spaces, endothelial swelling, consistent with features of TMA

Vigneau et al., Nephrol Dial Transplant 2014; Izzedine et al., Medicine 2014
Down-regulation of podocyte proteins with anti-VEGF agents

Nephrin, podocin, synaptopodin are down-regulated, as a possible consequence of VEGF inhibition and may lead to features of pre-eclampsia

Vigneau et al., Nephrol Dial Transplant 2014
Role of VEGF pathway in vascular homeostasis: a general theme in TMA

MoAb anti-VEGF

ITK anti-VEGFR

sVEGF-R (sFlt1) (preeclampsia, HELLP syndrome)

- VEGF/VEGFR (/AKT/mTOR/eNOS) pathway has a major role in vascular homeostasis (kidney, placenta)
- VEGF induces the formation of fenestrations in endothelium; loss of VEGF = microvascular injury & TMA

Robinson et al., Semin Nephrol 2010
Proteasome inhibitor-associated TMA

Bortezomib n=3
Carfilzomib n=8

Variable timing
ADAMTS13 detectable
5/11: dialysed/CNS rare
Liver/digestive tract+++  

TPE: n=4; eculizumab: n=3

9/11: resolution of TMA; 2/11: stabilization of MAHA

1 patient: recurrence of TMA after PI reintroduction

3 deaths, including 1 responder

Strong level of evidence that PI can cause TMA

Yui et al., Am J hematol 2016
How to distinguish antineoplastic drug-associated TMA from paraneoplastic TMA?
## Cancer-associated TMA: clinical features

**Table 1. Clinical findings**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Type of cancer</th>
<th>Metastasis</th>
<th>Symptom duration before TMA diagnosis</th>
<th>Weakness associated with weight loss and anorexia</th>
<th>Fever</th>
<th>Bone pain</th>
<th>Dyspnea</th>
<th>Abdominal pain</th>
<th>Thoracic pain</th>
<th>CNS involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>74</td>
<td>Lung</td>
<td>Bone</td>
<td>30 days</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>54</td>
<td>Colon</td>
<td>Bone, bone marrow; lymph nodes</td>
<td>30 days</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>70</td>
<td>Breast</td>
<td>Bone, bone marrow</td>
<td>3 days</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>55</td>
<td>Breast</td>
<td>Liver, pleural; bone</td>
<td>6 days</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>65</td>
<td>Breast</td>
<td>Liver, bone marrow</td>
<td>30 days</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>51</td>
<td>Breast</td>
<td>Bone marrow</td>
<td>10 days</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>38</td>
<td>Stomach</td>
<td>Bone marrow; lymph nodes</td>
<td>30 days</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<td>8</td>
<td>F</td>
<td>75</td>
<td>Breast</td>
<td>Lung</td>
<td>30 days</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>52</td>
<td>Stomach</td>
<td>Bone, bone marrow; liver</td>
<td>15 days</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>51</td>
<td>Stomach</td>
<td>Bone, lung</td>
<td>15 days</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>11</td>
<td>F</td>
<td>59</td>
<td>Stomach</td>
<td>Pleura; bone</td>
<td>5 days</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>12</td>
<td>M</td>
<td>79</td>
<td>ACUP</td>
<td>Bone, bone marrow; lymph nodes</td>
<td>30 days</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>60</td>
<td>Liver</td>
<td>Lymph nodes; bone marrow</td>
<td>190 days</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>69</td>
<td>Prostate</td>
<td>Bone</td>
<td>1 day</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>53</td>
<td>Lung</td>
<td>Liver</td>
<td>7 days</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>16</td>
<td>M</td>
<td>74</td>
<td>Liver</td>
<td>Bone, bone marrow; lymph nodes</td>
<td>180 days</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>65</td>
<td>Prostate</td>
<td>Bone, lung; meninges</td>
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<td>Y</td>
<td>N</td>
<td>N</td>
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<tr>
<td>18</td>
<td>F</td>
<td>64</td>
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<td>Bone, liver</td>
<td>60 days</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>38</td>
<td>Breast</td>
<td>Bone, bone marrow</td>
<td>85 days</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<td>N</td>
<td>N</td>
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</tr>
<tr>
<td>20</td>
<td>M</td>
<td>66</td>
<td>Lung</td>
<td>Brain</td>
<td>19 days</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

- **Breast:** 7 cases
- **Stomach:** 4 cases
- **Lung:** 3 cases
- **Liver:** 2 cases
- **Colon:** 1 case
- **Prostate:** 2 cases
- **Indetermined:** 1 case
- **Wasting, weight loss:** 75%
- **Multimetastatic cancer**
- **Bone pain:** ~ 50%
Cancer-associated TMA: clinical features

Table 2. Biological findings

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>ADAMTS13 activity (%)</th>
<th>ADAMTS13 inhibitor</th>
<th>Hemoglobin level (g/dl)</th>
<th>Reticulocyte count ($10^6$/mm$^3$)</th>
<th>Schistocytes</th>
<th>LDH (×N)</th>
<th>Platelet count ($10^5$/µl)</th>
<th>Prothrombin rate (%)</th>
<th>Fibrinogen level (g/l)</th>
<th>D-dimers (µg/ml)</th>
<th>Creatinine level (µM)</th>
<th>Estimated GFR (ml/minute)</th>
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<td>70</td>
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<tr>
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<td>120</td>
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</table>

| 39%         | (0–70)                | 8.3                | (6.9–9.3)               | 193                | (143–259) | 4.5           | (3.2–8.9)              | 48                | (21–73)               | 74             | (68–102)            | 70             | (48–82)              |

ADAMTS13 normal/detectable (82% of cases)

DIC common (Fg < 2 g/L in 40% of cases)

Renal involvement usually mild

Peripheral erythroblasts (85% of cases)
Bone marrow exploration

### Table 3. Bone marrow aspiration and/or biopsy findings

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Results of bone marrow exploration</th>
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<tbody>
<tr>
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<td>Erythroblastic hyperplasia</td>
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<tr>
<td>2</td>
<td>Metastatic cells; fibrosis</td>
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<tr>
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</tr>
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<td>Erythroblastic hyperplasia</td>
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<td>Erythroblastic hyperplasia</td>
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<td>15</td>
<td>NA</td>
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<tr>
<td>16</td>
<td>Metastatic cells</td>
</tr>
<tr>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>18</td>
<td>NA</td>
</tr>
<tr>
<td>19</td>
<td>Metastatic cells</td>
</tr>
<tr>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

 Bone marrow metastasis in 12/15 patients explored

 Bone marrow fibrosis in 4 patients

Oberic et al., Oncologist 2009

[Images of bone marrow pathology showing tear drop cells, Schistocytes, and Erythroblasts]
# How to distinguish antineoplastic drug-associated TMA from cancer-associated TMA

<table>
<thead>
<tr>
<th></th>
<th>Antineoplastic drug-associated TMA</th>
<th>Cancer-associated TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasting, weight loss, bone pain</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary symptoms</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>ADAMTS13</td>
<td>Normal/detectable</td>
<td>Normal/detectable</td>
</tr>
<tr>
<td>Tear drop cells</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Erythroblasts</td>
<td>0</td>
<td></td>
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<tr>
<td>DIC</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Treatment</td>
<td>Stop chemo</td>
<td>Start chemo</td>
</tr>
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</table>
**Conclusion**

- Significant understanding in anti-VEGF agents-associated TMA:
  - The direct targeting of VEGF is sufficient to induce vascular injury and TMA; class effect
  - Role of VEGF in the structure and homeostasis of the slit diaphragm in humans

- Anti-VEGF agents-associated TMA: may lead to intraglomerular TMA, kidney limited
  - sometimes only proteinuria/HT: need to be assessed!

- Recovery of kidney function is more frequently seen (e.g., less severe course) after anti-VEGF interruption than in other chemo-induced TMA
Conclusion

- Complement blockage: a therapeutic perspective in gemcitabine-associated TMA; requires evaluation

  Complement abnormalities need to be investigated in this context

- Cancer-associated TMA and chemo-associated TMA need to be distinguished on the basis of clinical evaluation:
  - Disseminated intravascular coagulopathy | Cancer-associated TMA
  - Circulating erythroblasts | Chemo-associated TMA
  - Hypertension, renal insufficiency | Chemo-associated TMA
Antineoplastic agents-associated TMA: an extension of HUS spectrum?

Infections

Complement

VEGF/VEGFR pathway

Post-infectious

STEC+

Complement-related

Gemcitabine?

Preeclampsia
HELPP syndrome

VEGF/VEGFR/eNOS-related

DGKE?

Anti-VEGF/R

Rapamycin?