HYPOXIA IN SOLID TUMORS

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Summary

Anemia is the main cause of hypoxia in tumor patients. Hemoglobin (Hb) at concentration of 150 g/L, 100% saturated, carries about 200 mL O2/L blood, while Hb 75 g/L carries about 100 mL O2/L. Under normal conditions, O2 extraction ratio (O2ER) is 0.25, meaning that Hb 150 g/L releases 50 mL O2/L in tissues, and Hb 75 g/L releases 25 mL O2/L (hypoxia). In healthy persons, compensatory mechanisms may increase O2ER to the borderline value of 0.50. In tumor patients, Hb concentration should be carefully monitored as their compensatory mechanisms for O2 delivery to cells are disordered. Under anaerobic conditions (without O2), from 1 mol glucose only 5% of necessary energy is released, requiring anemia correction in tumor patients. Hypoxia promotes malignant tumor progression and reduces the sensitivity of tumor cells to radio- and chemotherapy. Despite the fact that some patients survived surgery with Hb 50 g/L, and that, for economic benefits, the aim is to lower a transfusion trigger or erythropoietin Hb < 80 g/L, the verified borderlines of Hb 100 g/L and hematocrit 0.300 are still considered to be safe. It has been known that patients with higher Hb concentration respond better to surgery, chemotherapy and radiotherapy, having a better quality of life and longer survival time.

KEY WORDS: cancer, anemia, hypoxia, oxygen extraction ratio, transfusion trigger

INTRODUCTION

Hypoxia plays an important role in normal physiological processes as well as in tumorigenesis. Hypoxia may develop due to: 1. Low oxygen partial pressure (pO2) in the arterial blood (lung diseases, stay at high altitudes); 2. Blood’s reduced capacity to carry oxygen (anemia, methemoglobin production, carbon monoxide poisoning); 3. Reduced tissue perfusion (generalized or local), 4. Disordered diffuse geometry (abnormal blood flow through the tumor), 5. Incapa-
bility of cells to take up oxygen due to intoxication (various poisonings, by cyanides for example).

Tumor cell expansion requires new blood vessels to supply oxygen and nutrients. Tumor blood vessels are irregular and malformed. Consequently, some tumor areas are not well supplied. Hypoxic tumor areas are less responsive to radiation and chemotherapy. Radiation therapy requires oxygen to form cytotoxic DNA double strand breaks. Chemotherapy drugs require access to proliferating cells to induce cytotoxicity. Hypoxia promotes malignant tumor progression and reduces the sensitivity of the tumor to radioand chemotherapy. Hypoxia increases the expression of glycolytic enzymes which coincides with energy deprivation (1). In tumor tissues, hypoxia develops due to functional and structural abnormalities of immature tumor blood vessels, disordered microcirculation, and tumor or tumor therapy-associated anemia. Hypoxia reduces the sensitivity of tumor cells to radio-and chemotherapy. About 50-60% of locally advanced solid tumors have hypoxic and anoxic areas heterogenously distributed along tumor mass (2, 3). Oxygen deficiency, in general, correlates with a higher grade of tumor malignancy. In normal cells, hypoxia leads to cell death, and in tumor, hypoxia has an opposite effect. The result of hypoxia is that the tumor becomes more aggressive and more difficult to treat. Hypoxia strengthens the tumor. In a hypoxic environment, chemotherapy and radiation therapy have a lesser effect. Under hypoxia, the hypoxia-inducible transcription factor, or HIF-1 is released. It changes the transcriptional repertoire of the cell and plays an important role in hypoxias in cancer, heart diseases, stroke (4). HIF-1 activity is essential for the development of solid tumors (5). Under hypoxic conditions, tumor cells develop a mechanism to protect them against apoptosis. In humans, the critical level of oxygen delivery to tissues, without being hypoxic, has not been defined yet. In older patients under anesthesia, with neuromuscular blockade and mechanical ventilation, the critical level is approximately 5 mL O₂/kg/min (6).

ANEMIA – THE MAIN CAUSE OF HYPOXIA

Anemia is one of the major causes of hypoxia and a frequent complication in tumor patients. It is especially enhanced after chemotherapy with the myelosuppressive effect. Chemotherapy also reduces the release of endogenous erythropoietin which is important for the production of erythrocytes (7). Cytokines in tumor patients inhibit erythropoiesis in three ways: they damage the mechanism of iron consumption, suppress differentiation of erythroid progenitor cells and reduce the production of erythropoietin. Erythrocytes in anemic tumor patients have a shorter life cycle which cannot be compensated by the production of new cells (8).

Both tumor hemorrhage and tumor-induced coagulopathy also contribute to anemia. Pretreatment anemia prevalence in tumor patients ranges from 5% (prostate cancer) to 90% (multiple myeloma). Anemias are frequent in patients with diseases of the uterine cervix, and those suffering from kidney disorders (9, 10). Anemia lowers the quality of life, reduces the effect of chemo- and radiotherapy and shortens the survival time for patients (11-20). In colorectal carcinoma patients, the incidence of preoperative anemia accounts for 46% (21). During chemo- and radiotherapy, anemia primarily develops due to myelosuppression, but it may also occur due to therapy damage to erythrocytes (22). The chemotherapy agent, cisplatin, impairs the production of erythropoietin and induces anemia. Repeated cycles of such or similar therapy may impair erythropoiesis (23). Cisplatin and etoposide, frequently used in the treatment of non-small-cell lung cancer, induce severe anemias in 16% to 55% of the patients, while the treatment of advanced colorectal cancer with 5-fluorouracil and leucovorin induces severe anemias in only 2%-5% of the patients (24). Irradiation also increases the incidence of anemia. In a randomized study including 600 tumor patients, radiation therapy increased the percentage of anemic patients from pretherapy 41% to posttherapy 54%. In patients with lung and bronchial cancer, radiation therapy increased the prevalence from 55% to 77%, and in colorectal cancer patients, the prevalence grew from 44% to 63% (25). Low preoperative Hb is an independent risk factor for mortality (26). Patients with preoperative hemoglobin level between 100 and 130 g/L require blood transfusions at least three times more than
patients with preoperative hemoglobin level above 140 g/L.\(^{27}\)

**HEMOGLOBIN AND ANEMIA**

Each laboratory has its own reference measurement values for Hb level. Table 1 shows the reference values approved by the World Health Organization for the classification of anemia.

**Table 1. GRADING SYSTEMS FOR ANEMIA**

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>World Health Organization</th>
<th>National Cancer Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 (WNL)</td>
<td>(\geq 110) g/L</td>
<td>WNL</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>95-109</td>
<td>100 - WNL</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>80-94</td>
<td>80-100</td>
</tr>
<tr>
<td>Grade 3 (serious/severe)</td>
<td>65-79</td>
<td>65-79</td>
</tr>
<tr>
<td>Grade 4 (life-threatening)</td>
<td>&lt; 65</td>
<td>&lt; 65</td>
</tr>
</tbody>
</table>

Hemoglobin (Hb) carries oxygen into tissues. Oxygen (O\(_2\)) must be constantly available to the body for the production of energy. Within the cell, at the mitochondrial level, under aerobic conditions (with O\(_2\)) 1 mol glucose generates 36 mols of a highly energetic compound, adenosine three phosphate (ATP), while under anaerobic conditions (without O\(_2\)), 1 mol glucose generates only 2 mols of ATP or 5% of the required energy, showing the importance of anemia correction in tumor patients as a factor for improving quality of life and survival. Blood oxygen levels are determined by Hb concentration, coefficient of oxygen binding to hemoglobin, oxygen partial pressure (pO\(_2\)), hemoglobin saturation by oxygen (SO\(_2\)), concentration of 2,3-diphosphoglycerate (2,3-DPG), quantity of dissolved O\(_2\) in plasma, and quantity of blood the heart pumps into systemic circulation.

\[
pO_2 = \text{oxygen partial pressure} = \text{pAtm} - \text{pH}_2\text{O} \times 0.21 = (760 \text{ mmHg} - 47 \text{ mmHg}) \times 0.21 = 150 \text{ mmHg (moist air)}
\]

Alveolar pO\(_2\) equals arterial pO\(_2\) and reads 100 mmHg. Venous pO\(_2\) is 40 mmHg.

\[
\text{O}_2\text{ content} = (\text{Hb g/L} \times 1.34 \times \text{saturation %}) + (\text{pO}_2 \times 0.03)
\]

\[
\text{O}_2\text{ supply} = \text{cardiac output} \times \text{O}_2\text{ content arterial} = 5 \text{ L/min} \times (150 \times 1.34 \times 100\%) + (100 \times 0.03) = 5 \text{ L/min} \times 201 + 3 = 5 \text{ L/min} \times 204 = 1020 \text{ mL O}_2/\text{min}
\]

**Table 2. OXYGEN PARTIAL PRESSURE, OXYGEN SATURATION, HEMOGLOBIN CONCENTRATION**

<table>
<thead>
<tr>
<th>pO(_2) mmHg</th>
<th>SO(_2)</th>
<th>O(_2) mL/L (Hb 150 g/L)</th>
<th>O(_2) mL/L (Hb 120 g/L)</th>
<th>O(_2) mL/L (Hb 100 g/L)</th>
<th>O(_2) mL/L (Hb 90 g/L)</th>
<th>O(_2) mL/L (Hb 80 g/L)</th>
<th>O(_2) mL/L (Hb 75 g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 artery</td>
<td>100</td>
<td>204</td>
<td>164</td>
<td>137</td>
<td>124</td>
<td>110</td>
<td>103</td>
</tr>
<tr>
<td>99.6</td>
<td>97.5</td>
<td>199</td>
<td>160</td>
<td>134</td>
<td>121</td>
<td>107</td>
<td>100</td>
</tr>
<tr>
<td>74.2</td>
<td>95</td>
<td>193</td>
<td>155</td>
<td>129</td>
<td>117</td>
<td>104</td>
<td>97</td>
</tr>
<tr>
<td>57.8</td>
<td>90</td>
<td>183</td>
<td>147</td>
<td>123</td>
<td>111</td>
<td>98</td>
<td>92</td>
</tr>
<tr>
<td>44.5</td>
<td>80</td>
<td>161</td>
<td>130</td>
<td>108</td>
<td>98</td>
<td>87</td>
<td>81</td>
</tr>
<tr>
<td>40 vein</td>
<td>75</td>
<td>152</td>
<td>122</td>
<td>101</td>
<td>92</td>
<td>81</td>
<td>76</td>
</tr>
<tr>
<td>36.9</td>
<td>70</td>
<td>142</td>
<td>114</td>
<td>95</td>
<td>86</td>
<td>76</td>
<td>71</td>
</tr>
<tr>
<td>26.6 critical</td>
<td>50</td>
<td>101</td>
<td>81</td>
<td>68</td>
<td>61</td>
<td>54</td>
<td>51</td>
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<td>22.8</td>
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<td>65</td>
<td>55</td>
<td>49</td>
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<td>41</td>
</tr>
<tr>
<td>19.2</td>
<td>30</td>
<td>61</td>
<td>49</td>
<td>41</td>
<td>37</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>10.3</td>
<td>10</td>
<td>20</td>
<td>16</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>
O₂ consumption
= cardiac output x (O₂ content arterial - O₂ content venous)
= 5 L/min x (204 mL O₂/L - 152 mL O₂/L)
= 5 L/min x 52 mL O₂/L
= 260 mL O₂ /min

O₂ extraction ratio (O₂ER)
= O₂ consumption / O₂ supply
= 260/1020
= 0.25

If arterial oxygen saturation (SaO₂) = 100%, and venous oxygen saturation (SvO₂) = 75%, 25% of O₂ (O₂ER = 0.25) is released in tissues. In patients with Hb 150 g/L, Hb 100 g/L and Hb 80 g/L it accounts for 52 mL O₂/L blood, 36 mL O₂/L and 29 mL O₂/L blood, respectively. Tissue hypoxia develops at pO₂ of arterial blood < 40 mmHg or at oxygen saturation of arterial blood < 75%, and at the partial pressure of oxygen in venous blood < 26.6 mmHg or oxygen saturation of venous blood < 50%.

The oxyhemoglobin curve will depend not only on hemoglobin concentration but on other factors, too (Table 2). A shift in the curve to the left shows reduced oxygenation, while a shift to the right shows increased tissue oxygenation. Carbon monoxide (CO) binds 240 times more than oxygen (O₂) to hemoglobin in carboxyhemoglobin, with the effect of shifting the hemoglobin saturation curve to the left. Increased CO levels may result in severe hypoxemia, despite of normal pO₂. Therefore, stopping smoking during radiotherapy and chemotherapy is very worthwhile, as it reduces tissue oxygenation.

When O₂ER approaches 50%, lactate production in the left heart ventricle is significantly increased, generally a sign of oxygen deficiency and anaerobic metabolism initiation (28,29). The critical value of O₂ER may be a useful guideline for blood transfusion (30).

CRITICAL HEMOGLOBIN CONCENTRATIONS - INDIVIDUAL VALUE

Anesthesia, neuromuscular blockade and mechanical ventilation reduce oxygen consumption, and thus the critical borderline oxygen requirements. Thus determined critical borderline of oxygen requirement cannot apply to the person whilst awake. The normal human organism
have a variety of mechanisms for compensation of acute and chronic anemia, for example heart rate acceleration, increase of heart-minute volume, increase in 2-3-DPG. Compensatory mechanisms may be blocked in the ill. There are different opinions on the critical level of hemoglobin ranging from 11 to 5 g/L, or hematocrit from 0.330 to 0.150. However, non-Hb components also play a role in the oxygen supply to tissues. Therefore, critical hemoglobin or hematocrit is an individual value and a generally valid transfusion trigger does not exist. Silent myocardial ischemia is a decisive factor for the tolerance of anemia. Clinical evidence shows that patients over age 40 should not be subjected to Hb < 100 g/L or hematocrit 0.300, without prior exclusion of silent myocardial ischemia (31). Septic shock leads to increased oxygen consumption. It leads to the release of a variety of mediators, activation of leukocytes, endothelial damage, interstitial edema and potential multiple organ damage. Limiting erythrocyte flow in the microcirculation and arterial hypotension can reduce the delivery of O2 to cells. Isovolemic hemodilution down to an arterial oxygen content of 100 gO2/mL/L, corresponding to Hb 75 g/L (Table 2) or a hematocrit value of 0.225, is a tolerable value for healthy individuals. In patients with lung disorders or coronary and cerebral sclerosis, however, hemoglobin levels should be higher. Compensation of anemia is regulated by an increase in stroke volume, an increase in heart frequency, and an increase in venous utilization (32). With hematocrit restricted by isovolemic hemodilution, compensatory mechanisms are activated to produce an increased cardiac output, redistribution of blood flow to vital organs (heart, brain) and an increase of O2ER.

CONCLUSION

About 50% of cancer patients develop anemia (Hb<120 g/L). Anemia leads to hypoxia which is an especially undesirable condition in cancer patients. It brings surgery into question and reduces the effect of chemo- and radiotherapy. The patient’s quality of life is lowered and, most importantly, the survival is significantly reduced. Anemia, or sufficient oxygen supply to tissues, should be corrected by erythrocyte transfusion, artificial blood, recombinant human erythropoietin, iron supplements and increased respiratoriy system delivery of O2. A generally valid transfusion trigger does not exist, and each case should be evaluated individually. Minimal transfusion trigger should be about Hb 100 g/L, Hct 0.300. Hemoglobin levels should be higher in patients over 40 years of age, patients with miocardial ischemia, septic shock, multiple organ damage, lung disorders, and coronary and cerebral sclerosis.

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