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 O_2/L blood, while Hb 75 g/L carries about 100 mL O_2/L. Under normal conditions, O_2 extraction ratio (O_2ER) is 0.25, meaning that Hb 150 g/L releases 50 mL O_2/L in tissues, and Hb 75 g/L releases 25 mL O_2/L (hypoxia). In healthy persons, compensatory mechanisms may increase O_2ER to the borderline value of 0.50. In tumor patients, Hb concentration should be carefully monitored as their compensatory mechanisms for O_2 delivery to cells are disordered. Under anaerobic conditions (without O_2), 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*

HIPOKSIJA U BOLESNIKA SA SOLIDNIM TUMORIMA

Sažetak

Anemija je glavni uzrok hipoksije u tumorskih bolesnika.Hemoglobin (Hb) u koncentraciji od 150 g/L, zasićen 100%, prenosi oko 200 mL O_2/L krvi, dok Hb 75 g/L prenosi oko 100 mL O_2/L. U normalnim uvjetima O_2 ekstrakcija u tkiva (O_2ER) je 0.25, što znači da Hb 150 g/L ostavlja tkivu 50 mL O_2/L, a Hb 75 g/L ostavlja 25 mL O_2/L - hipoksija. U zdravih osoba kompenzatornim mehanizmima O_2ER se može povisiti do graničnih 0.50. U tumorskih bolesnika vrlo je važno paziti na Hb koncentraciju, jer su kompenzatorni mehanizmi dovoda O_2 u stanicu poremećeni. U anaerobnim uvjetima (bez O_2) iz 1 mola glukoze oslobađa se samo 5% potrebne energije, stoga je jako važna korekcija anemije u tumorskih bolesnika. Hipoksija potiče malignu progresiju tumora i smanjuje osjetljivost tumora na radiokemoterapiju. Iako su neki ljudi preživljeli operacije s Hb 50 g/L, iako se iz ekonomskih razloga «trigger» transfuzije ili eritropoietina nastoji spustiti na Hb < 80 g/L, još uvijek se provjerenom granicom smatra Hb 100 g/L i hematokrit 0.300. Zna se da ljudi s višom koncentracjom Hb povoljnije reagiraju na operaciju, kemoterapiju i radioterapiju, da imaju bolju kvalitetu života i duže preživljenje.

KLJUČNE RIJEČI: *rak, anemija, hipoksija, ekstrakcija kisika, transfuzijski «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 radio- and 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 trasncriptional 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 O_2/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 erythropoesis in three ways: they damage the machanism 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 eythrocytes (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.

Table1.

GRADING SYSTEMS FOR ANEMIA

SEVERITY	World Health Organization	National Cancer Institute
Grade 0 (WNL)	≥ 110 g/L	WNL
Grade 1 (mild)	95-109	100 - WNL
Grade 2 (moderate)	80-94	80-100
Grade 3 (serious/severe)	65-79	65-79
Grade 4 (life-threatening)	< 65	< 65

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 hemoblobin, 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 = oxygen partial pressure

$pO_2 = pAtm \times O_2\ \%$

$pO_2 = 760$ mmHg x 0.21

$pO_2 = 160$ mmHg (dry air)

As dry air enters the respiratory system, it moistens in combination with water vapor, with both the portion of O_2 and pO_2 in such air being lower.

pO_2 = oxygen partial pressure

$= (pAtm - pH_2O) \times 0.21$

$= (760$ mmHg $- 47$ mmHg$) \times 0.21$

$= 150$ mmHg (moist air)

Alveolar pO_2 equals arterial pO_2 and reads 100 mmHg. Venous pO_2 is 40 mmHg.

O_2 content

$= (Hb\ g/L \times 1.34 \times saturation\ \%) + (pO_2 \times 0.03)$

O_2 supply

$=$ cardiac output x O_2 content $_{arterial}$

$= 5\ L/min \times (150 \times 1.34 \times 100\%) + (100 \times 0.03)$

$= 5\ L/min \times 201 + 3$

$= 5\ L/min \times 204$

$= 1020\ mL\ O_2/min$

Table 2.

OXYGEN PARTIAL PRESSURE, OXYGEN SATURATION, HEMOGLOBIN CONCENTRATION

pO_2 mmHg	SO_2 %	O_2 mL/L (Hb 150 g/L)	O_2 mL/L (Hb 120 g/L)	O_2 mL/L (Hb 100 g/L)	O_2 mL/L (Hb 90 g/L)	O_2 mL/L (Hb 80 g/L)	O_2 mL/L (Hb 75 g/L)
100 artery	100	204	164	137	124	110	103
99,6	97,5	199	160	134	121	107	100
74,2	95	193	155	129	117	104	97
57,8	90	183	147	123	111	98	92
44,5	80	161	130	108	98	87	81
40 vein	75	152	122	101	92	81	76
36,9	70	142	114	95	86	76	71
26.6 critical	50	101	81	68	61	54	51
22.8	40	81	65	55	49	44	41
19.2	30	61	49	41	37	33	31
10.3	10	20	16	13	12	11	10

O_2 consumption
= cardiac output x (O_2 content $_{arterial}$ - O_2 content $_{venous}$)
= 5 L/min x (204 mL O_2/L - 152 mL O_2/L)
= 5 L/min x 52 mL O_2/L
= 260 mL O_2 /min

O_2 extraction ratio (O_2ER)
= O_2 consumption / O_2 supply
= 260/1020
= 0.25

If arterial oxygen saturation (SaO_2) = 100%, and venous oxygen saturation (SvO_2) = 75%, 25% of O_2 (O_2ER = 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 O_2/L blood, 36 mL O_2/L and 29 mL O_2/L blood, respectively. Tissue hypoxia develops at pO_2 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%.

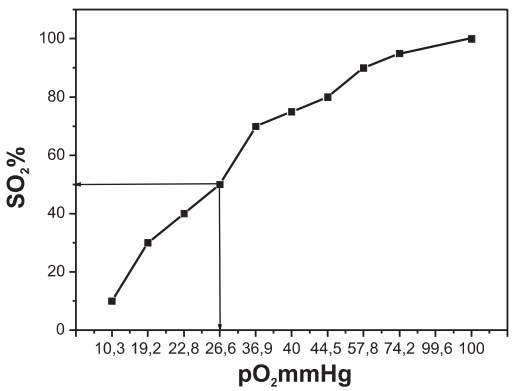

Figure 1. Oxyhemoglobin curve. Hemoglobin saturation = 50%; pO_2 = 26.6 mmHg.

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 (O_2) 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 pO_2. Therefore, stopping smoking during radiotherapy and chemotherapy is very worthwile, as it reduces tissue oxygenation.

Table 3.
CAUSES OF DISPLACEMENT OF THE OXYHEMOGLOBIN CURVE

Left displacement	Right displacement
Decrease in hydrogen ion (increse in pH)	Increase hydrogen ion (decrease in pH)
Decrease in temperature	Increase in temperature
Decrease in pCO_2	Increase in pCO_2
Decrease of 2,3-DPG in red blood cells	Increase of 2.3-DPG in red blood cells
Decrease of ATP in red blood cells	Increase of ATP in red blood cells
Increase in carboxyhemoglobin	Decrease of zinc in red blood cells
Increase in methemoglobin	Abnormal hemoglobins
Abnormal hemoglobins	

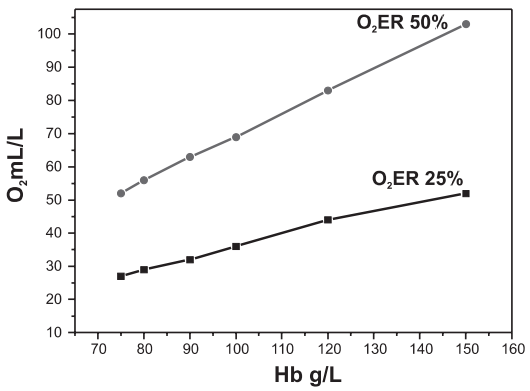

Figure 2. Oxygen extraction O_2ER 25% - normal; O_2ER 50% - critical.

When O_2ER 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 O_2ER 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 consumtion. 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 O_2 to cells. Isovolemic hemodilution down to an arterial oxygen content of 100 O_2mL/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 O_2ER.

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 respsiratory system delivery of O_2. 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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