Oxygenation Gain Factor: A Novel Parameter Characterizing the Association between Hemoglobin Level and the Oxygenation Status of Breast Cancers

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Abstract

Tumor hypoxia has been linked to acquired treatment resistance, tumor progression, and poor prognosis. Because anemia is a major causative factor for the development of hypoxia, the association between blood hemoglobin concentration (cHb) and breast cancer oxygenation was examined in this study. In addition, a novel parameter characterizing the relationship between oxygenation status and rising cHb is introduced: the oxygenation gain factor (OGF). In breast cancer patients, median cHb over the range 8.5–14.7 g/dl correlated positively with the median pO2 (3–15 mm Hg), yielding an average OGF of 2 mm Hg/dl/g. In contrast, in normal tissues (normal breast, subcutis, and skeletal muscle) the median pO2 values were substantially higher (52 mm Hg, 51 mm Hg, and 37 mm Hg, respectively) and remained constant irrespective of the hemoglobin level over the range from 10 to 16 g/dl (OGF = 0 in grade I anemia and nonanemic patients). Moderately lower median pO2 values in subcutis and skeletal muscle were only observed in grade II anemia (8 g/dl < cHb ≤ 10 g/dl), although this would appear to be of no biological relevance. Conversely, in breast cancers, even mild anemia (grade I anemia) is a major causative factor for the development of hypoxia or anoxia.

Introduction

The introduction of the computerized pO2-histography3 system (Eppendorf, Hamburg, Germany) for reliable measurements of tissue oxygen (O2) tensions (pO2) in the clinical setting allowed for the first time the systematic study of the oxygenation status in accessible, locally advanced tumors (1, 2). Over the last decade, assessment of tumor oxygen profiles determined with this O2 microsensor technique repeatedly demonstrated that the presence of tissue hypoxia (i.e., tissue areas with critically reduced oxygen levels) or even anoxia (no measurable O2 levels) are characteristic pathophysiological properties of solid tumors (3–5). In addition, hypoxia proved to be an independent, strong prognostic parameter in these malignancies (3–6). Irrespective of the mode of treatment, patients with hypoxic tumors had a significantly poorer outcome than those with better oxygenated lesions of the same clinical size and stage. More important than its potential impact on the present treatment options are new insights into the fundamental role of tumor hypoxia in tumor propagation, malignant progression, acquired treatment resistance, and poor long-term prognosis (3, 4, 7).

Hypoxia is predominantly caused by structural and functional abnormalities of the newly formed tumor microvessels arising from neovascularization, by a compromised microcirculation, by enlarged diffusion distances, and by tumor-associated and/or therapy-induced anemia (3). The role of anemia in the development of tumor hypoxia as a consequence of a reduced O2-carrying capacity of the blood has been demonstrated in an experimental tumor model (8, 9). These experimental data have provided strong evidence of a relationship between decreased Hb levels and a poor oxygenation status in solid tumors.

Using data from an ongoing prospective study examining the oxygenation status in breast cancers, this investigation is intended to evaluate a possible relationship between Hb levels and pretreatment tumor oxygenation in conscious patients. This is to our knowledge the first study relating blood Hb levels (anemia of grades I and II included, National Cancer Institute system) to the oxygenation status of breast cancers. Results obtained may have important implications for studies identifying inter alia the power of prognostic factors, the requirement of RBC transfusions, and/or the benefit of erythropoietin treatment of anemic patients.

Materials and Methods

The evaluation of intratumoral pO2 distributions in locally advanced breast cancers was conducted at the Department of Obstetrics and Gynecology, University of Leipzig from January 1999 through December 2002. The study design was approved by the Local Human Ethics Committee, and all of the enrolled patients gave informed written consent. Pretreatment pO2 measurements were performed on 37 conscious patients with breast cancer using the pO2 histography system after a standard procedure, which has been described in detail previously (1, 7, 10). All of the pO2 measurements were performed under ultrasound guidance of the O2 sensor. For the description of the oxygenation status of the breast cancers, the median pO2 and the fraction of pO2 readings ≤2.5 mm Hg and ≤5 mm Hg were stated. In all of the patients, cHb was determined by standard procedures in venous blood samples before pO2 measurements.

Results are expressed as means ± SE. Differences between groups were assessed by the Wilcoxon test. The significance level was set at α = 5% for all of the comparisons.

Results and Discussion

Patient and Tumor Characteristics. The age range of the enrolled patients was 42–90 years (median, 65 years). Twelve of the women were premenopausal, and 25 were postmenopausal. Largest tumor diameter ranged from 1.0 to 5.2 cm (median, 2.5 cm). All of the tumors were invasive and were classified according to the Tumor-Node-Metastasis staging system (Unio Internationale Contra Cancerum, 1997), pT-stages were pT1c (n = 10), pT2 (n = 19), pT3 (n = 5), and pT4b (n = 3). According to histopathologic classification, 28 cancers were ducal, 7 lobular, 1 intracystic, and 1 apocrine. Histological grades were G1 (n = 5), G2 (n = 20), and G3 (n = 12). Nodal status was N0 (n = 10), N1 (n = 23), N2 (n = 1), and NX (n = 3). M stage was M0 (n = 8), M1 (n = 2), and MX (n = 27).

Approximately 63% of the breast cancers investigated exhibited hypoxic tissue areas (pO2 ≤ 2.5 mm Hg), which were heterogeneous distributed within the tumor masses. The median pO2 was 6 mm Hg. The fraction of pO2 values ≤2.5 mm Hg was 25%, and 58.5% of the pO2 values were ≤5 mm Hg. When tumors of different
sizes were compared, there was no evidence of a correlation between the median $pO_2$ and the maximum tumor diameter. This implies that the oxygenation in breast cancers and the occurrence of hypoxia and/or anoxia do not correlate with the clinical and pathological stages. In addition, the oxygenation pattern does not correlate with tumor location within the breast, N stage, histological type, and grade, nor with a series of other clinically relevant parameters (e.g., hormone receptor status, parity, and menopausal status).

Pretreatment median cHb measured in our patient cohort was 13.0 g/dl (range, 8.0–15.3 g/dl). Larger tumors or higher stages tended to correlate with lower cHb values (12.95 g/dl in patients with tumors <2.5 cm diameter versus 12.05 g/dl in patients with cancers ≥2.5 cm). At presentation, 27% of our breast cancer patients were anemic. This value is in line with data published earlier (e.g., 28.7%; Ref. 11).

Association between Hb Levels and Breast Cancer Oxygenation. In patients with normal Hb levels (cHb ≥12 g/dl) the median $pO_2$ was significantly higher than in anemic patients ($P = 0.015$). Additionally, analysis of the oxygenation status as a function of baseline cHb was performed by dividing the patients into five groups based on “high” (above median cHb; median cHb of age-matched healthy women = 14.0 g/dl; Ref. 12), “intermediate” cHb values (13.0 g/dl ≤ cHb ≤14.0 g/dl), “lower-normal” cHb values (12.0 g/dl ≤ cHb ≤13.0 g/dl), mild anemia (grade I, 10.0 g/dl < cHb <12.0 g/dl), and moderate anemia (grade II, 8.0 g/dl < cHb ≤10.0 g/dl).

On the basis of this separation, a correlation between Hb levels and median $pO_2$ values as shown in Fig. 1 was obtained. In moderately anemic patients all of the median $pO_2$ values were <6 mm Hg. At a mean Hb level of 8.5 ± 0.2 g/dl, the median $pO_2$ was 3 mm Hg. With increasing cHb values the median $pO_2$ exponentially increased (log $pO_2 = 0.114 \text{cHb} - 0.472; r^2 = 0.985$) reaching a maximum

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* Unpublished observations.
pO2 of 15 mm Hg in the cHb range above the median (mean cHb = 14.7 ± 0.2 g/dl). The difference in the oxygenation status of breast cancer in moderately anemic patients and women with cHb values above the median (“high” cHb group) was statistically significant (P = 0.005; see Fig. 1). Accordingly, the hypoxic fraction of pO2 values ≤5 mm Hg increased significantly from 53% ± 6% to 77% ± 7% (P = 0.020) when breast cancers of nonanemic patients (cHb = 13.6 ± 0.2 g/dl) were compared with anemic patients (cHb = 9.4 ± 0.5 g/dl).

Association between Hb Levels and Normal Tissue Oxygenation. pO2 measurements performed in normal breast tissue, in the fatty tissue of the subcutis in skeletal muscle (sternocleidomastoid muscle; Ref. 13) provided substantially different data (see Fig. 1). In normal breast tissue, the median pO2 was 52 mm Hg over the cHb range from 8.4 to 14.8 g/dl with no cHb-related differences in pO2 being evident. In the subcutis, the median pO2 was 51 mm Hg in the cHb range from 10 to 16 g/dl with no differences in pO2 being seen over this range. Only cHb values <10 g/dl (grade II anemia) were associated with decreased median tissue pO2 values (P < 0.001). The relative decrease in the median pO2 was only 23% compared with 80% in breast cancers. At a cHb of 9.5 g/dl, the median pO2 was ~40 mm Hg, which can still be considered as a “physiological” O2 level and would not be expected to compromise the cellular energy status in any way (3). In skeletal muscle, the median pO2 was 37 mm Hg in the cHb range from 10 to 17 g/dl. Here again, no pO2 differences were observed between nonanemic and mildly anemic (grade I anemia) patients. As was the case with the subcutis, only cHb values <10 g/dl (moderate anemia, grade II anemia) coincided with a slightly lower muscle oxygenation status reaching a median pO2 of 34 mm Hg at a cHb range of 9.4 g/dl corresponding to a relative decrease in the median pO2 of 9%. This latter O2 status must also still be considered as being within the “physiological range.”

OGF. To characterize the association between cHb levels and the oxygenation status of primary breast cancers, we suggest a novel parameter, the tumor OGF, which is defined as follows:

\[
OGF = \frac{\Delta pO_2 (\text{mmHg})}{\Delta cHb (\text{g/dL})}
\]

The ∆s represent differences used to express a differential quotient and, thus, OGF is the approximation of the derivation of pO2 by cHb. Hence, the calculation of OGF is based on a smooth nonlinear correlation function derived from individual values.

In breast cancer of anemic patients, OGF equals 1.5 mm Hg/dl/g. This indicates that the median pO2 in anemic breast cancer patients should rise by ~1.5 mm Hg for every 1 g/dl increment in cHb (see Table 1). Surprisingly, an even greater gain in tumor oxygenation (~3 mm Hg per 1 g/dl rise in cHb) was seen over the normal cHb range (cHb ≥12 g/dl). A similar dependency was observed when improvement in overall QoL was assessed as a function of Hb levels. In 7724 patients QoL improved slightly in the anemic range, whereas at Hb levels ≥12 g/dl there was a more pronounced improvement in QoL (14–16).

In contrast, in normal tissues OGF is zero at cHb values ≥10 g/dl, i.e., in mildly anemic patients (10 g/dl ≤ cHb ≤ 12 g/dl) the reduced O2 carrying capacity of the blood is fully compensated by a rise in local blood flow (and a possible increase in the O2 extraction from the blood). In locally advanced solid tumors these two adaptive (compensatory) mechanisms may not work because flow regulation is limited, if not impossible, and O2 extraction ratios are already high at physiological Hb levels (17).

References


7637

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