Iron status markers in patients with small cell carcinoma of the lung. Relation to survival

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Summary A longitudinal study of iron status markers (haemoglobin (Hb), serum (S-) iron, S-transferrin, transferrin saturation, S-ferritin) was performed in 31 chemotherapy treated patients with small cell lung cancer. At discovery, eight patients were anaemic (Hb < 121 g l−1). Hb, S-iron and transferrin saturation were lower (P < 0.01), and S-ferritin was higher (P < 0.01) than in healthy subjects. Chemotherapy induced an immediate fall in Hb (P < 0.003), increase in S-iron (P < 0.003) and transferrin saturation (P < 0.001). Later in the disease a fall in S-transferrin (P < 0.006) and an increase in S-ferritin (P < 0.02) occurred. Thirty patients died during the 2 years observation. S-ferritin at discovery was correlated to performance status score (r = 0.57, P = 0.01) and to survival (r = −0.63, P < 0.0002). Patients with S-ferritin ≤ 400 µg l−1 (n = 13) had longer survival than those with S-ferritin > 400 µg l−1 (n = 18) (P = 0.004).

Patients with untreated malignant disease demonstrate characteristic changes in iron metabolism with anaemia, low serum (S-) iron and S-transferrin together with inappropriately elevated S-ferritin (Groop et al., 1978; Lee, 1983). In general, the administration of cytotoxic agents induces a further fall in haemoglobin (Hb), and an increase in S-iron levels (Alfrey et al., 1966; Doll et al., 1983; Grau et al., 1985; Pollera et al., 1987). The pathophysiological mechanisms of these changes in iron kinetics are unclariﬁed.

The aim of the present investigation was to study changes in iron status markers in patients with small cell carcinoma of the lung (SCCL), and to evaluate their relation to survival.

Material and methods

The material comprised 34 consecutive patients with SCCL; two were excluded due to short survival < 1 month, and one due to porphyria cutanea tarda with iron overload. Median age in the included 31 patients (24 males, seven females) was 64 years (range 39–76). Prior to treatment, bone marrow and liver biopsies were performed to evaluate the stage of disease; 19 patients had limited disease, i.e. conﬁned to one hemithorax including bilateral supraclavicular lymph nodes. Twelve patients had extensive disease, four of these had bone marrow involvement. Performance status score (PS) was assessed according to WHO criteria (WHO, 1979). All patients received combination chemotherapy consisting of lomustine, cyclophosphamide, methotrexate, vincristin, etoposide and doxorubicin in limited disease (Østerlund et al., 1991), and of lomustine, cyclophosphamide, vincristin and etoposide in extensive disease.

None took iron supplementation. Blood transfusions were registered. Blood samples (non-fasting) were taken prior to chemotherapy, and every 4th week until death. Hb was measured on Coulter-S (1 g Hb l−1 = 0.062 mmol Hb l−1), S-iron by spectrophotometry (Iron Test Roche® on Kobas Bio®), S-transferrin by immunoelectrophoresis, and S-ferritin by radioimmunoassay (Ferritin RIA Amersham®). Biochemical liver tests (S-aspartate aminotransferase and S-alkaline phosphatase) were measured by standard methods. The control material consisted of 103 healthy 65-year-old subjects (55 males, 48 females) recruited through a population study in Copenhagen County (Milman et al., GEN-MONICA study, unpublished results). Iron status markers were measured by the same methods as in the present study.

In the statistical analysis, Wilcoxon's rank sum test for paired values was employed to evaluate the significance of differences, and correlations were assessed with Pearson's coefficient of correlation. Cumulative survival rates were calculated by the Kaplan-Meier method and compared statistically by the log rank test.

Results

One male patient survived for more than 2 years. Median survival in the other 30 patients was 337 days (range 86–576). Neither Hb nor iron status indicators displayed any significant sex difference in the SCCL patients, and due to the small number of females, values in both sexes were pooled (Table I, Figures 1–2).

Haemoglobin

Eight patients (26%) had Hb values < 121 g l−1 (7.5 mmol l−1) at discovery, vs 12 (40%) at the last measurement before death. There was a marked decline in Hb levels during the disease, the major fall occurring 1 month after initiation of chemotherapy (Table I, Figure 1).

Iron status markers

S-iron showed a significant increase from discovery to death. The major increase was observed within 1 month after initiation of chemotherapy. S-transferrin demonstrated a decline occurring gradually and being significant from the third month of survival. Transferrin saturation showed a significant increase, being most pronounced in the first 3–4 months after initiation of chemotherapy. None of the patients displayed values < 15%. High values > 60% were observed in 5 (17%) patients shortly before death. S-ferritin demonstrated a significant rise, which occurred late in the disease, after 10–11 months of survival (Figure 2). The distributions of S-ferritin values are shown in Table II. None of the patients had values ≤ 20 µg l−1, and 16 (53%) had values > 300 µg l−1 at discovery compared to 29 (97%) at death.

Blood transfusions

The long term survivor received 42 transfusions, while 22 patients had a median of four transfusions (range 2–12).
Table I  Haemoglobin and iron status markers (median and 5–95 percentile) in patients with SCCL and in healthy subjects

| Patients | Hb (g l⁻¹) | S-iron (μmol l⁻¹) | S-transferrin (μmol l⁻¹) | Transferrin saturation (%) | S-ferritin (μg l⁻¹) |
|----------|------------|-------------------|--------------------------|---------------------------|-------------------|
| Discovery (n = 31) | 134⁺ | 11⁺ | 28 | 21⁺ | 314⁺ |
| (110–153) | (4–20) | (19–35) | (11–32) | (51–1630) |
| P | <0.01 | <0.05 | <0.01 | <0.01 | <0.01 |
| Death (n = 30) | 11itung | 15ৎ | 21ৎ | 34 | 1128ৎ |
| (93–129) | (4–38) | (15–32) | (13–94) | (337–2124) |
| Healthy subjects (n = 55) | 148 | 19 | 30 | 30 | 150 |
| (124–171) | (11–30) | (21–36) | (17–50) | (62–725) |
| (n = 48) | 140 | 34 | 20 | 107 | 150 |
| (116–158) | |

Patients vs healthy subjects. *P < 0.01; **P < 0.05.

There was no correlation between the number of transfusions and iron status markers at death.

Biochemical liver tests

At discovery 16 (52%) patients had elevated S-transaminase and/or S-alkaline phosphatase. Iron status markers in patients with abnormal biochemical liver tests were not significantly different from those in patients with normal liver tests.

Stage of disease

There was no significant difference in iron status markers between patients with limited and extensive disease.

Correlation between iron status markers

At discovery, correlations existed between S-ferritin vs S-transferrin (r = -0.48, P < 0.01), Hb vs S-iron (r = 0.58, P < 0.0005), and Hb vs S-transferrin (r = 0.42, P < 0.02).

Survival

PS was correlated to survival (r = -0.37, P = 0.05). S-transferrin at discovery was correlated to survival (r = 0.44, P < 0.02), but closer analysis showed that this relation was of no clinical relevance. S-ferritin at discovery showed a negative correlation to survival (log vs log values, r = -0.63, P < 0.0002, Figure 3). Analysis of survival rates revealed that a threshold ferritin value of 400 μg l⁻¹ yielded the best discrimination between the two survival groups (Figure 4). Furthermore S-ferritin at discovery was correlated to PS (r = 0.57, P = 0.01). Iron status markers at death showed no correlation to survival.

Discussion

Iron status in patients with SCCL was profoundly influenced by disease and chemotherapy. Prior to treatment, Hb values were low and many patients were anaemic. Chemotherapy was immediately followed by a decrease in Hb levels due to inhibition of erythropoiesis (Alfrey et al., 1966); the addi-

Table II  Distribution of serum ferritin values in patients with SCCL at discovery and prior to death

| S-ferritin (μg l⁻¹) | Discovery n = 31 | Death n = 30 |
|---------------------|-----------------|-------------|
| ≤ 20                | 0               | 0           |
| 21–40               | 2               | 0           |
| 41–300              | 12              | 1           |
| > 300               | 17              | 29          |
tional fall prior to death was probably caused by metastatic marrow invasion.

Before chemotherapy, the patients were hyposideraemic, consistent with the fact that malignant disease produces an impaired release of iron from the storage compartments and a fall in S-iron (Lee, 1983; Lipschitz et al., 1971). Chemo-
terapy induced a rise in S-iron levels, as described in other investigations (Grau et al., 1985; Pollera et al., 1987). The rise begins already 24–48 h after initiation of therapy (Pollera et al., 1987). Throughout the remaining period of disease, S-iron remained elevated. The reasons for these changes in S-iron are unknown. Haemolysis can be excluded according to previous studies (Doll et al., 1983; Pollera et al., 1987), and increased iron absorption or decreased excretion are unlikely to give these rapid fluctuations. A decreased Hb synthesis per se induces a moderate rise in S-iron, as erythropoiesis modulates the release of iron from storage compart-
ments (Alfrey et al., 1966).

S-transferin values at discovery were of the same order as in healthy subjects, but declined after 3–4 months of disease. Malignancies are known to reduce S-transferin levels, probably due to decreased synthesis combined with increased catabolism (Hughes et al., 1972; Lee, 1983).

The increase in transferrin saturation was a consequence of the rise in S-iron, combined with an almost constant S-
transferin level. None of the patients had values <15%, indicating insufficient iron delivery to the erythron. Later in the disease, there was a rise in saturation due to declining S-transferin and a further increase in S-iron.

In healthy subjects, the S-ferritin concentration reflects mobilisable iron stores, mainly located in the liver, spleen and bone marrow (Walters et al., 1973); values $\leq 20 \mu g \ l^{-1}$ are indicative of 'exhausted', $21–40 \mu g \ l^{-1}$ of 'small', $41–300 \mu g \ l^{-1}$ of 'normal' and $> 300 \mu g \ l^{-1}$ of 'increased' iron stores (Milman et al., 1983).

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S-ferritin was elevated at discovery and remained relatively constant until late in the disease, where a marked rise was observed at 10–11 months, probably reflecting an increased tumour mass. The present ferritin assay uses antibodies against basic spleen ferritin, and thus underestimates the presence of acidic ferritin often produced in malignant tumours (Hazard et al., 1977).

Prognostic indicators of survival are of importance to the clinician in the decision for treatment. In a study comprising 778 patients with SCCL (Österlind et al., 1986), a number of clinical and biochemical variables (not including iron status markers) were tested against survival. PS at the time of diagnosis appeared to be the most weighty single factor. In the present study, PS also correlated to survival. Further-
more, there was a pronounced correlation between S-ferritin at discovery and survival, which was higher than the correla-
tion between PS and survival. A threshold S-ferritin value of $400 \mu g \ l^{-1}$ divided the patients in groups with highly signifi-
cant differences in survival, i.e. high ferritin levels were related to a short survival. Cox et al. (1986) also found a relation between S-ferritin and survival in SCCL, using a discriminative value of $600 \mu g \ l^{-1}$. Whether S-ferritin may be of clinical significance in the future evaluation of the prog-
osis in patients with SCCL should be investigated in more comprehensive studies.

The study was supported by The Danish Cancer Society (grant no. 86-033).

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