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 ($\text{Hb} < 121 \text{ g l}^{-1}$). Hb, S-iron and transferrin saturation were lower ($P < 0.01$), and S-ferritin 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 $\leq 400 \mu\text{g l}^{-1}$ ($n = 13$) had longer survival than those with S-ferritin $> 400 \mu\text{g l}^{-1}$ ($n = 18$) ($P = 0.004$).

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 (Østerlind *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 ($1 \text{ g Hb l}^{-1} = 0.062 \text{ mmol Hb l}^{-1}$), 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 $< 121 \text{ g l}^{-1}$ (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 $\leq 20 \mu\text{g l}^{-1}$, and 16 (53%) had values $> 300 \mu\text{g l}^{-1}$ 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)
	134 ^a	11 ^a	28	21 ^a	314 ^a
Discovery (n = 31)	(110–153)	(4–20)	(19–35)	(11–32)	(51–1630)
<i>P</i>	<0.01	<0.05	<0.01	<0.01	<0.01
Death (n = 30)	111 ^a	15 ^b	21 ^a	34	1128 ^a
	(93–129)	(4–38)	(15–32)	(13–94)	(337–2124)
Healthy subjects	♂ 148	19	30	30	♂ 150
(♂ = 55)	(124–171)	(11–30)	(21–36)	(17–50)	(62–725)
(♀ = 48)	♀ 140				♀ 107
	(116–158)				(42–257)

Patients vs healthy subjects. ^a*P* < 0.01; ^b*P* < 0.05.

Figure 1 Changes in serum iron, serum transferrin, transferrin saturation and haemoglobin during course of disease in 31 patients with SCCL (mean ± s.e.m.).

Figure 2 Changes in serum ferritin levels during course of disease in 31 patients with SCCL (mean ± s.e.m.).

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)	No. of patients	
	Discovery n = 31	Death n = 30
≤ 20	0	0
21–40	2	0
41–300	12	1
> 300	17	29

Figure 3 Relation between survival and serum ferritin at discovery in 31 patients with SCCL; regression line: $y = -1.24 \times + 5.56$; $r = -0.63$, $P < 0.0002$.

Figure 4 Survival curves for patients with newly discovered SCCL having serum ferritin $> 400 \mu\text{g l}^{-1}$ (—, $n = 13$), and $\leq 400 \mu\text{g l}^{-1}$ (---, $n = 18$) ($P = 0.004$).

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 produce an impaired release of iron from the storage compartments and a fall in *S-iron* (Lee, 1983; Lipschitz *et al.*, 1971). Chemotherapy 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 compartments (Alfrey *et al.*, 1966).

S-transferrin 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-transferrin* 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-transferrin* 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-transferrin* 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 $\leq 20 \mu\text{g l}^{-1}$ are indicative of 'exhausted', 21–40 $\mu\text{g l}^{-1}$ of 'small', 41–300

$\mu\text{g l}^{-1}$ of 'normal' and $> 300 \mu\text{g l}^{-1}$ of 'increased' iron stores (Milman *et al.*, 1983).

To some extent *S-ferritin* behaves as an acute phase reactant, being inappropriately elevated in infectious, inflammatory and malignant diseases (Gropp *et al.*, 1978; Lee, 1983). *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 (Østerlind *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. Furthermore, there was a pronounced correlation between *S-ferritin* at discovery and survival, which was higher than the correlation between PS and survival. A threshold *S-ferritin* value of $400 \mu\text{g l}^{-1}$ divided the patients in groups with highly significant 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 $600 \mu\text{g l}^{-1}$. Whether *S-ferritin* may be of clinical significance in the future evaluation of the prognosis 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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