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Phase I study using desferrioxamine and iron sorbitol citrate in an attempt to modulate the iron status of tumor cells to enhance doxorubicin activity

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Summary. A novel approach to enhance the activity of doxorubicin is to increase the availability of cellular "chelatable" iron to participate in doxorubicin-mediated free-radical generation. To achieve this, we designed a regimen consisting of desferrioxamine (DFO, 50 mg/kg daily given as an i.v. infusion over 72 h) to increase cellular iron uptake. Thereafter, the combination of iron sorbitol citrate (ISC) and doxorubicin (as a single agent or as part of the CHOP regimen) was given. In a phase I study we investigated the toxicity of this regimen in nine patients with refractory malignant disease. Severe but reversible ocular toxicity (i.e., acute maculopathy) was observed in two patients. As these patients were the only ones who were pretreated with cisplatin, we caution against the use of DFO in cisplatin-pretreated patients. Severe phlebitis was encountered in five of nine patients. A partial remission was observed in two of four patients with refractory Non-Hodgkin's lymphoma who were treated with DFO, ISC, and doxorubicin as part of the CHOP regimen. We conclude that pretreatment with DFO and iron sorbitol citrate may be of benefit in the treatment of malignancies with doxorubicin-containing regimens, but ocular toxicity and severe phlebitis limits the use of DFO in this approach. The attachment of DFO to biocompatible polymers may be a method of overcoming the observed toxicity and warrants further study.

Introduction

Modulation of the cellular iron status is a novel approach to tumor-cell killing [7]. Transferrin-bound iron is internalized by proliferating cells expressing transferrin receptors (TfR). The TfR are up-regulated during the S phase of the cell cycle, reflecting the need for iron. Iron taken up by the cell enters a soluble "chelatable pool". This is iron in transit to more stable compartments with the ability to participate in the catalysis of toxic free radicals. Pretreatment of tumor cells with desferrioxamine (DFO), a potent iron-chelating agent, up-regulates TfR expression, resulting in an increase in iron uptake to replenish intracellular iron and induces cell-cycle synchronization in the G1 phase [3, 32]. It has furthermore been suggested that DFO has prooxidant effects, possibly increasing the susceptibility of cells to oxidant stress [9, 20, 24].

Doxorubicin has a well-documented ability to generate oxygen radicals, a mechanism believed to be mediated by iron [25]. We postulate that when the radical-generating drug doxorubicin is combined with an increased amount of "chelatable" cellular iron, the activity of doxorubicin may be enhanced. To achieve this, we used DFO to limit iron access to cells, aiming at an increase in TfR expression so as to increase the uptake of transferrin-bound iron. DFO infusion was followed by the administration of iron sorbitol citrate (ISC), for rapid saturation of transferrin and doxorubicin. Possible DFO-mediated effects on the cellular antioxidant system may provide additional benefit. Cells in the quiescent state, which exhibit very limited expression of TfR, are less sensitive to this mechanism [29] in comparison with tumor cells with a high proliferation rate.

Abbreviations: PR, partial remission; PD, progressive disease; OT, ocular toxicity; Phl, phlebitis of WHO grade >III; Dox, doxorubicin dose given (whereas CHOP contains 50 mg/m^2 doxorubicin); AC, adenocarcinoma; NHL, Non-Hodgkin's lymphoma; SCLC, small-cell lung cancer; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; COP, cyclophosphamide/vincristine/prednisone; VP16/MTX/Cycl, etoposide/methotrexate/cyclophosphamide; ProMACE-MOPP, prednisone/methotrexate/Adriamycin/cyclophosphamide/etoposide/nitrogen mustard/vincristine/procarbazine/prednisone; FAM(TX), 5-fluorouracil/doxorubicin/mitomycin/methotrexate(TX); CP, cyclophosphamide/cisplatin; CDDP, cisplatin; Mitox, mitoxantrone; CDE, cyclophosphamide/doxorubicin/etoposide; Chl; chlorambucil; E/MTX/C, etoposide/methotrexate/cyclophosphamide

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Table 1. Treatment schedule

Day 1, 5:00 p.m.	DFO at 50 mg/kg given by continuous i.v. infusion over 72 h
Day 4, 5:00 p.m.	Termination of the DFO infusion
Day 4, 11:00 p.m.	100 mg iron sorbitol citrate i.m.
Day 5, 9:00 a.m.	Dox or CHOP chemotherapy
Day 5, 11:00 a.m.	50 mg iron sorbitol citrate i.m.

The sequence is repeated every 3–4 weeks. DFO, Desferrioxamine; CHOP chemotherapy, cyclophosphamide (750 mg/m^2, i.v.), doxorubicin (50 mg/m^2, i.v.), vincristine (1.4 mg/m^2, i.v.), prednisone (100 mg p.o. for 5 days)

Although DFO is considered to be safe, ocular, auditory, and pulmonary side effects and an increased susceptibility to infection may occur [5, 15, 26, 31]. In general, the ocular toxicity is reversible after withdrawal of the drug, although irreversible ocular damage has been reported [1]. As compared with patients showing an iron overload, increased toxicity has been suggested for patients whose iron status is normal [28]. We initiated a phase I study to evaluate the toxicity of the sequence of DFO, ISC, and doxorubicin given alone or as combination therapy. This report describes the resultant toxicity and the response of patients to this combination.

Patients and methods

Seven men and two women (mean age, 53 years; range, 30–70 years) with malignant disease were admitted to hospital for sequential treatment with DFO, ISC, and doxorubicin (or a doxorubicin-containing regimen) as detailed in Table 1. The study was approved by the ethics committee of the University Hospital Utrecht. All patients had been heavily pretreated with conventional chemotherapy and experienced progressive disease during prior treatment. The patients' characteristics are presented in Table 2. The sequential scheme was repeated every 3–4 weeks.

The study design included a dose-escalation scheme for doxorubicin, starting with 20 mg/m^2, followed by 50 mg/m^2 (as in the CHOP regimen), 60 mg/m^2, and 70 mg/m^2. At least two patients received doxorubicin at every dose level before proceeding to the next higher dose. If a patient was treated with more than one course, the delivered dose of doxorubicin was not changed. The doses of DFO and ISC remained the same throughout the study. Patients with Non-Hodgkin's lymphoma received the standard CHOP regimen without dose escalation.

In anticipation of the possible ocular toxicity of DFO, we performed an ophthalmological examination, including the registration of visual evoked potentials, prior to and immediately after DFO administration. These measurements were repeated every 6 weeks. Additional ophthalmological tests were performed if abnormalities were observed. Audiograms were obtained every 6 weeks. Microbiological cultures, specifically those for *Yersinia, Salmonella, Staphylococcus aureus, Mucormycosis*, and *Listeria* spp., were performed only when clinical suspicion of infection existed. Doxorubicin cardiotoxicity was monitored by ECG and radionuclide scintigraphy during rest and exercise at cumulative doxorubicin concentrations exceeding 350 mg/m^2. Other toxicity was evaluated according to WHO criteria [23]. Serum iron, iron saturation, serum ferritin and transferrin, and urinary iron excretion were monitored using routine laboratory methods.

Results

In all, 9 patients were treated with the study regimen and received a total of 24 courses. In addition to DFO and ISC, five patients received doxorubicin (in increasing doses) as a single agent, whereas four patients were given doxorubicin as part of the CHOP regimen (Table 2).

Table 2. Patients' characteristics and treatment-related response and toxicity

Patient	Histology	Previous treatment	Dox (mg/m^2)	Response	OT	Phl
A	Gastric AC	FAMTX, FAM	20	–	No	Yes
B	Gastric AC	FAM	20	–	No	No
C	NHL	CHOP, COP, Chl, Mitox E/MTX/C	CHOP	PR	Yes	Yes
D	NHL	CHOP, COP, ProMACE-MOPP, Chl	CHOP	PR	No	Yes
E	NHL	COP, CHOP, MTX, Ara-C, VP16, Chl	CHOP	PD	No	No
F	NHL	COP, CHOP, ProMACE-MOPP	CHOP	PD	No	Yes
G	Bladder carcinoma	CDDP, MTX leucovorin	60	–	Yes	No
H	SCLC	CDE	60	–	No	No
I	Ovarian carcinoma	CP, Gemcytabine	70	–	Yes	Yes

Ara-C, 1-β-D-arabinofuranosylcytosine

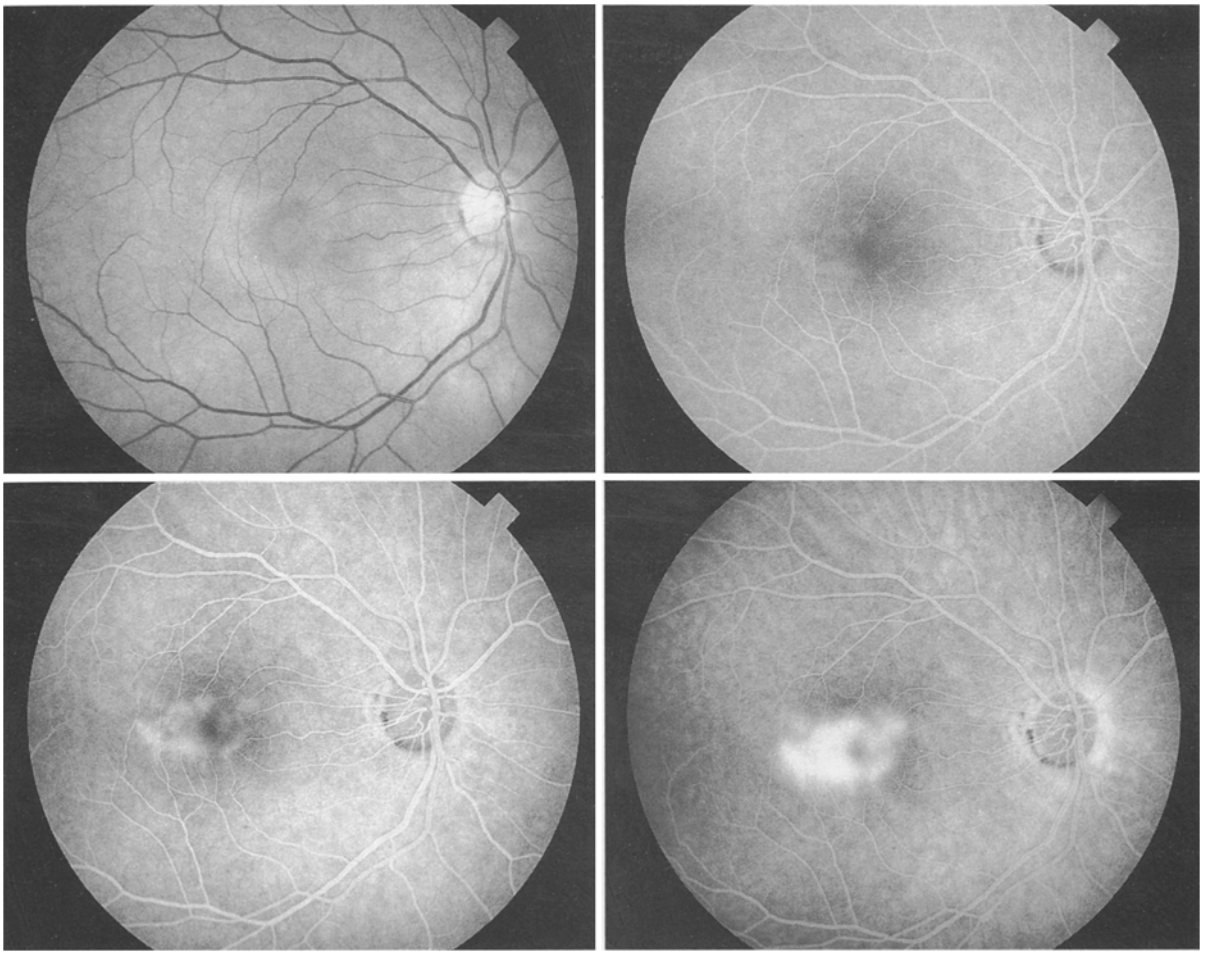

Fig. 1. Acute DFO maculopathy in the right eye of patient G. Red-free fundus picture of the serous detachment in the macula, showing discrete whitening of the RPE (*top, left*). Fluorescein angiogram revealing faint multiple and confluent leakage starting at 36 s after dye injection in the venous phase (*top, right*). An increase in staining finally becomes evident throughout the damaged RPE (*bottom, left and right*)

Toxic effects

Ocular toxicity occurred in the macula in two of nine subjects (patients G and I). Both patients complained of acute decreased visual acuity and xanthopsia within 24 h of the completion of the first course. Visual acuity decreased in both eyes to 0.3 in patient I and to 0.6 in patient G; marked metamorphopsia was noted in both cases on the Amsler grid chart. Funduscopy revealed a similar picture in these two patients: a bilateral serous elevation of the neurosensory retina in the macular area.

Fluorescein angiography was performed promptly in patient G, revealing increased leakage of dye across the retinal pigment epithelium (RPE), which started during the early venous phase (see Fig. 1). No delayed choroidal perfusion was noted. The fluorescence pattern of the optic disc, retinal vessels, and retinal periphery was normal. In both patients, progressive pigmentary changes appeared in the macula at 3–4 weeks after the onset of symptoms with the gradual disappearance of the serous elevation.

In patient I we performed color-vision tests, electroretinography (ERG), electro-oculography (EOG), and tests for visual evoked potentials (VEPs) at 1 h after the onset of the maculopathy. In spite of the xanthopsia, all color-vision tests were within normal limits (Ishihara plate test and Lanthony 15-hue desaturated caps test). Additional color-vision tests were refused. The ERG and EOG were normal; the VEPs demonstrated subnormal amplitudes with normal latencies.

A third individual (patient C) experienced a short period (4 h) of xanthopsia at 2 days after the termination of the regimen, but by the time he was studied the symptoms had disappeared and no abnormalities could be detected. Subsequent courses were not complicated by ocular toxicity in this patient.

Phlebitis was a severe and debilitating complication in five of nine patients, requiring new peripheral intravenous devices more than once a day. Phlebitis was not related to doxorubicin treatment, since it occurred within 24 h of the initiation of the DFO infusion. Diluting DFO in large volumes of saline did not prevent this side effect.

Auditory functions were not impaired. Hematological toxicity was not observed. The WBC differential revealed monocytosis after the DFO infusion (range, 14%–36%) in four patients. No episode of arrhythmia or angina pectoris was encountered. The left ventricular ejection fractions determined during rest and exercise remained normal. Hair loss was seen in all patients. Nausea and vomiting were

Table 3. Pretreatment evaluation of the patients' iron status and response to DFO infusion as measured by urinary iron excretion and saturation of serum transferrin with iron

Patient	Ferritin (μg/l)	Tf (g/l)	Sat_b (%)	Sat_a (%)	Fe_s (μM)	Fe_u (μM/72 h)
A	12	2.32	18	22	10	–
B	474	2.27	14	10	7	433
C	809	2.28	26	12	12	41
D	452	2.16	37	18	24	112
E	732	1.33	41	36	14	578
F	93	2.24	21	13	10	222
G	872	1.95	–	–	–	–
H	664	1.88	5	10	1.8	2
I	340	2.18	24	14	12	440

Tf, Transferrin; Sat_b, transferrin saturation with iron before DFO treatment; Sat_a, transferrin saturation with iron after DFO treatment; Fe_s, serum iron concentration; Fe_u, cumulative urinary iron excretion during the 72-h DFO infusion

mild. Diarrhea was not observed. Therapy-related infections did not occur.

Response to treatment

Four patients with Non-Hodgkin's lymphoma were evaluable for response. All four patients had previously received CHOP chemotherapy, and all initially responded to this treatment except patient C, who had progressive disease from the onset. Patients C and D, who received seven and six courses of DFO/ISC/CHOP, respectively, achieved a partial remission; the duration of response was 5 months in patient C. Patient D reached a cumulative doxorubicin dose of 800 mg/m^2 without showing signs of cardiac toxicity or tumor progression and proceeded to alternative chemotherapy with bone marrow transplantation. Patients E and F developed progressive disease.

Iron status

The pretreatment evaluation of the patients' iron status is presented in Table 3. Although serum ferritin levels were high, as commonly seen in malignant diseases, none of the patients was considered to have an iron overload. DFO treatment resulted in a small decrease in serum latent iron-binding capacity (47 ± 19 before vs 35 ± 8 after DFO) and iron saturation ($23\% \pm 12\%$ before vs $17\% \pm 9\%$ after DFO). Urinary iron excretion during DFO infusion varied substantially. After administration of ISC, iron saturation ranged from 58% to 89%, whereas the average latent iron-binding capacity was 11 ± 7 (range, 4–22). Serum iron content is the sum of transferrin-bound iron and small-molecular-weight iron complexes. It must be noted that after ISC administration, serum ISC complexes may have been included in the determination of serum iron content. The observed increase in transferrin-saturation measurements may therefore have reflected the serum content of absorbed ISC and transferrin-bound iron.

Discussion

The present study investigated the toxicity of treatment with DFO, ISC, and doxorubicin-containing chemotherapy in nine patients. The results obtained in two of four patients with heavily pretreated Non-Hodgkin's lymphoma indicate efficacy. One subject (patient C) responded to treatment despite initial resistance to CHOP chemotherapy.

Several observations formed the basis of the present approach. Transferrin receptor (TfR) expression has been related to the proliferative potential of malignancies [12, 21]. Non-Hodgkin's lymphoma exhibits variable TfR expression, and an increase in TfR expression has been suggested to correlate with a better response to treatment [17]. DFO has been demonstrated to up-regulate TfR expression and increase iron uptake [3, 33].

The mechanism of action of anthracyclines partly involves the generation of oxygen radicals in the presence of an iron catalyst [25]. Delivering an increased amount of circulating transferrin-bound iron (by the inclusion of ISC in the present regimen) to tumor cells with the ability to increase iron uptake by means of an increase in TfR expression may result in a more favorable radical-generating "chelatable" iron/doxorubicin ratio. A reduction in the cellular antioxidant defense has been demonstrated to enhance the in vitro effectivity of doxorubicin [13]. Alkylating agents such as those included in the CHOP regimen reduce the cellular antioxidant status [14] and may have an additional toxic effect.

Several in vitro studies have indicated a possible prooxidant effect of DFO [9, 20, 24] and have cautioned against the use of DFO under conditions of elevated oxidative stress. Via a mechanism that is incompletely understood, DFO changes the cellular antioxidant defense system in vitro and in vivo toward a possibly increased susceptibility to oxidative stress [34]. Combining DFO with cytostatic, radical-generating drugs such as anthracyclines imposes such oxidative stress on cells. In agreement with this approach is the previous observation that DFO enhances the activity of doxorubicin in neuroblastoma cells [2]. It has been demonstrated that DFO induces cell-cycle synchronization [3]. This effect may be advantageous when DFO is used in combination with drugs that are active in a specific phase of the cell cycle (e.g., doxorubicin). In vitro studies have shown that DFO-induced cell-cycle synchronization and cytotoxicity occur when cells are cultured in growth medium supplemented with fetal bovine serum [33]. Fetal bovine serum contains bovine transferrin, which has a low affinity for human TfR, if any. No effect on the distribution of cells in the various cell-cycle phases was observed in the presence of human pooled serum containing human transferrin. This indicates that cell-cycle synchronization may not be relevant at DFO concentrations that are achievable in humans.

It should be noted that the responses to the present treatment were observed in patients who received doxorubicin as part of the CHOP regimen rather than as a single agent. Therefore, we cannot rule out the possibility of DFO- and ISC-mediated tumor sensitization to cyclophosphamide, vincristine, or prednisone.

Although we observed responses to the treatment, ocular toxicity and severe phlebitis posed a significant problem. The ocular toxicity clearly occurred at the macular RPE level. Fluorescein angiography in patient G revealed the initial damage and its disturbing sequelae. A light microscopy study has also documented RPE changes in the entire retina following high-dose DFO treatment [30]. That the EOG (representing RPE function in general) was normal in patient I might be explained by the selective localization of the RPE damage. The EOG reflects the response of the entire retina, whereas in our patients, only the macular area was affected. The xanthopsia pointed to sudden changes in the macular area, evoking an imbalance of color perception [22] with a predilection for short-wavelength-sensitive cones. The Amsler grid chart was a sensitive indicator of acute DFO maculopathy. The benefits of screening by EOG seem to be limited in the revelation of acute ocular side effects of DFO. The mechanism of DFO-induced acute ocular toxicity remains to be elucidated. These data suggest that the ocular toxicity of DFO seems to be related to the underlying disease and/or concomitant treatment rather than to the prescribed DFO dose.

DFO is widely used in the treatment of iron-overload disease and aluminum intoxication in chronic renal failure. For these indications, only a low incidence of DFO-related ocular toxicity has been reported [4, 6, 10, 22]. DFO-related ocular toxicity has been observed in studies involving patients with rheumatoid disease [27] and in a leukemia patient treated with DFO and cytosine arabinoside [19]. On the other hand, treatment of nine neuroblastoma patients with a single course of high-dose DFO did not result in ocular side effects [11]. Similar results have been obtained using low doses of DFO in Alzheimer's disease [8] and at doses comparable with ours in adults with asymptomatic *Plasmodium falciparum* parasitemia [16]. Ocular toxicity is generally reversible after DFO withdrawal, although irreversible damage has been reported [1].

We employed a relatively low dose of DFO and encountered ocular toxicity in two patients. These patients were the only ones in our study with a history of cisplatin treatment. Cisplatin has been reported to cause retinal toxicity in the form of cone dysfunction [36]. The cumulative cisplatin dose was considered to be an important factor, and symptoms persisted for up to 16 months in some patients. The cumulative cisplatin doses in patients G and I were relatively low (240 and 150 mg/m^2, respectively). The interval between cisplatin treatment and DFO infusion was about 16 months. We suggest that previous treatment with cisplatin may have enhanced DFO-related ocular toxicity in the present study. Therefore, we caution against the use of DFO in cisplatin-pretreated patients.

Unexplained, severe phlebitis was frequently observed following DFO infusions. This side effect has not been reported when DFO is given to treat iron overload disease. Although pulmonary toxic effects of DFO have been described [31, 35], no manifestation of lung injury was encountered in the current study. As mentioned earlier, proliferating cells such as tumor cells, bone-marrow progenitor cells, and intestinal epithelial lining are considered to be most affected by this regimen. Although we observed a regression of the tumor volume in two patients, this response was not accompanied by hematological toxicity or gastrointestinal symptoms. This finding may indicate an organ-specific response to the regimen.

We conclude that the hypothesis that our regimen of DFO, ISC, and doxorubicin exerts enhanced activity may be true as judged from the responses observed in patients with refractory Non-Hodgkin's lymphoma. However, ocular toxicity (i.e., acute maculopathy) and severe phlebitis limit the use of DFO on this schedule. A history of cisplatin treatment may enhance DFO-induced maculopathy. Serial ophthalmic examination of these patients is imperative. Modulation of the toxicity of DFO by covalent attachment to biocompatible polymers [18] may be a method for overcoming the observed toxicity in the future and warrants further study.

References

1. Bene C, Manzler A, Bene D, Kranias G (1989) Irreversible ocular toxicity from a single "challenge" dose of deferoxamine. Clin Nephrol 31: 45
2. Blatt J, Huntley D (1989) Enhancement of in vitro activity against neuroblastoma by doxorubicin and deferoxamine. J Natl Cancer Inst 81: 866
3. Bomford A, Isaac J, Roberts S, Edwards A, Young S, Williams R (1986) The effect of desferrioxamine on transferrin receptors, the cell cycle and growth rates of human leukaemic cells. Biochem J 236: 243
4. Borgna-Pignatti C, De Stefano P, Broglia AM (1984) Visual loss in patients on high dose subcutaneous desferrioxamine. Lancet I: 681
5. Brock JH, Ng J (1983) The effect of desferrioxamine on the growth of *Staphylococcus aureus, Yersinia enterocolitica* and *Streptococcus faecalis* in human serum: uptake of transferrin bound iron. FEMS Microbiol Lett 20: 439
6. Cases A, Kelly J, Sabater F, et al (1990) Ocular and auditory toxicity in haemodialyzed patients receiving desferrioxamine. Nephron 56: 19
7. Cazzola M, Bergamaschi G, Dezza L, Arosio P (1990) Manipulations of cellular iron metabolism for modulating normal and malignant cell proliferation: achievements and prospects. Blood 75: 1903
8. Crapper McLachlan DR, Dalton AJ, Kruck TPA, et al. (1991) Intramuscular desferrioxamine in patients with Alzheimer's disease. Lancet 337: 1304
9. Davies MJ, Donkor R, Dunster CA, Gee CA, Jonas S, Willson RL (1987) Desferrioxamine (Desferal) and superoxide free radicals. Biochem J 246: 725
10. Davies SC, Hungerford JL, Arden GB, Marcus RE, Miller MH, Huehns ER (1983) Ocular toxicity of high dose intravenous desferrioxamine. Lancet II: 181
11. Donfrancesco A, Deb G, Dominici C, Pileggi D, Castello MA, Helson L (1990) Effects of single course of deferoxamine in neuroblastoma patients. Cancer Res 50: 4929
12. Faulk PW, Hsi B-L, Stevens PJ (1980) Transferrin and transferrin receptors in carcinoma of the breast. Lancet II: 390
13. Ford JM, Yang J-M, Hait WN (1991) Effect of buthionine sulfoximine on toxicity of verapamil and doxorubicin to multidrug resistant cells and to mice. Cancer Res 51: 67
14. Frisher H, Ahmad T (1977) Severe generalised glutathione reductase deficiency after antitumour chemotherapy with BCNU. J Lab Clin Med 89: 1080
15. Gallant T, Boyden MH, Gallant LA, Carley H, Freedman M (1987) Serial studies of auditory neurotoxicity in patients receiving deferoxamine therapy. Am J Med 83: 1085
16. Gordeuk VR, Thuma PE, Brittenham GM, et al (1992) Iron chelation with desferrioxamine B in adults with asymptomatic *Plasmodium falciparum* parasitemia. Blood 79: 308

17. Habeshaw JA, Lister TA, Stansfield AG (1983) Correlation of transferrin receptor expression with histological class and outcome in non-Hodgkin's lymphoma. Lancet I: 498
18. Hallaway PE, Eaton JW, Panter SS, Hedlund BE (1989) Modulation of deferoxamine toxicity and clearance by covalent attachment to biocompatible polymers. Proc Natl Acad Sci USA 86: 10108
19. Kaplinsky C, Stark B, Goshen Y, Yaniv I, Bashara S, Zaizov R (1988) Deferoxamine (Desferal)-induced ocular toxicity. Pediatr Hematol Oncol 5: 293
20. Klebanoff SJ, Waltresdorph AM, Michel BR, Rosen H (1989) Oxygen-based free radical generation by ferrous ions and deferoxamine. J Biol Chem 264: 19765
21. Kozlowski R, Reilly IAG, Sowter D, Robins RA, Russel NH (1988) Transferrin receptor expression on AML blasts is related to their proliferative potential. Br J Haematol 69: 275
22. Lakhanpal V, Schocket SS, Jiji R (1984) Deferoxamine (Desferal)-induced toxic retinal pigmentary degeneration and presumed optic neuropathy. Ophthalmology 91: 443
23. Miller AB, Hoogstraten B, Staquet M, et al (1981) Reporting results of cancer treatment. Cancer 47: 207
24. Mordente A, Meucci E, Miggiano GAD, Martorana GE (1990) Prooxidant action of desferrioxamine: enhancement of alkaline phosphatase inactivation by interaction with ascorbate system. Arch Biochem Biophys 277: 234
25. Muindi JRF, Sinha BK, Gianni L, Myers CE (1984) Hydroxyl radical production and DNA damage induced by anthracycline-iron complex. FEBS Lett 172: 226
26. Olivieri NF, Buncic JR, Chew E, et al (1986) Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. N Engl J Med 314: 869
27. Pall H, Blake DR, Winyard P, et al (1989) Ocular toxicity of desferrioxamine – an example of copper promoted autooxidative damage? Br J Ophthalmol 73: 42
28. Polson RJ, Jawed A, Bomford A, Berry H, Williams R (1985) Treatment of rheumatoid arthritis with desferrioxamine: relation between stores of iron before treatment and side effects. Br Med J 291: 448
29. Poot M, Rabinovitch PS, Hoehn H (1989) Free radical mediated cytotoxicity of desferrioxamine. Free Radical Res Commun 6: 323
30. Rahi AHS, Hungerford JL, Ahmed AI (1986) Ocular toxicity of desferrioxamine: light microscopic histochemical and ultrastructural findings. Br J Ophthalmol 70: 373
31. Tenenbein M, Kowalski S, Sienko A, Bowden DH, Adamson IYR (1992) Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. Lancet 339: 699
32. Theil EC (1990) Regulation of ferritin and transferrin receptor mRNAs. J Biol Chem 265: 4771
33. Voest EE, Rooth H, Neijt JP, Asbeck BS van, Marx JJM (1992) The in vitro response of human tumor cells to desferrioxamine is growth medium dependent. Cell Prolif (in press)
34. Voest EE, Dalen JJW van, Asbeck BS van, Marx JJM (1992) Desferrioxamine alters the antioxidant status of rat organs. Proceedings, International Meeting on Porphyrin and Iron Metabolism, Papendal, 1992
35. Weitman SD, Buchanan GR, Kaman BA (1991) Pulmonary toxicity of deferoxamine in children with advanced cancer. J Natl Cancer Inst 83: 1834
36. Wilding G, Caruso R, Lawrence TS, et al (1985) Retinal toxicity after high-dose cisplatin therapy. J Clin Oncol 3: 1683