Anthracycline cardiotoxicity and acute myelogenous leukaemia

The cardiotoxicity of the anthracycline antibiotic daunorubicin (DNR) and its 14-hydroxylated analogue Doxorubicin (DXR) limits their use in cancer treatment.[1] The cardiotoxicity manifests itself as sudden heart failure which may progress rapidly to death.[2] The most frequent electrocardiographic abnormality is low voltage of the QRS complex, but monitoring the ECG does not appear to be helpful in predicting toxicity,[3] and this was so in our patients who all received a total dose of more than the recommended maximum of 550 mg/m².[4]

Patients, methods, and results

Twenty patients with acute myeloblastic leukaemia (AML) who received DNR or DXR, or both, in a total dose of more than 550 mg/m² were studied (table). All patients except one had no evidence of cardiac disease before treatment. Eighteen patients had received repeated induction courses consisting of single injections of DNR (1·5 mg/kg) and cytosine arabinoside (CA) (1 mg/kg intravenously 12-hourly for five days). Two patients had had their first induction with CA and thioguanine, but required the anthracycline drugs for reinduction when they relapsed. Patients were then randomised to receive either maintenance chemotherapy alone or chemotherapy together with immunotherapy. Nine patients had chemotherapy only as maintenance, while eleven patients had additional immunotherapy. Maintenance chemotherapy was given every four weeks and consisted of a single dose of DNR (1·5 mg/kg) or DXR (1 mg/kg intravenously) and CA (1 mg/kg) given intravenously in normal saline over eight hours. Immunotherapy with intravenous BCG (Glaxo Ltd) was given 14 days after the completion of maintenance chemotherapy and alternating with chemotherapy every two weeks.[5] Patients who were still in remission after receiving a total dose of anthracycline antibiotics of 550 mg/m² were transferred to CA and thioguanine. Patients who had relapsed usually received re-induction treatment with anthracycline antibiotics and CA. All patients had their chest *x*-ray examination and ECG carefully assessed before each anthracycline infusion.

Of the 20 patients in the study, only two developed cardiomyopathy. The first patient (patient 12, table) received a total dose of 1006 mg/m² of the anthracycline antibiotics (709 mg/m² of DNR and 297 mg/m² of DXR), the last dose of DXR about six weeks before the onset of heart failure. Congestive heart failure developed rapidly, with the sudden onset of breathlessness and ankle oedema. A third heart sound was easily heard and the chest *x*-ray film showed a large heart. The ECG, which was normal initially, now showed low voltage complexes with flattened and inverted T-waves. Prompt treatment with digoxin and diuretics reversed her congestive cardiac failure and she again became ambulant without symptoms.

The second patient (patient 14, table), received a total dose of 825·8 mg/m² of DNR, the last dose two weeks before symptoms of heart failure developed. Chest *x*-ray examination showed an enlarged heart with evidence of pulmonary oedema and bilateral pleural effusions. The ECG showed low voltage in the frontal plane leads with flattened T-waves in these leads and in the lateral precordial leads. She responded to anti-heart-failure measures and the ECG changes disappeared. The patient died 15 weeks later with a relapse of her acute leukaemia. In both patients there had been no changes on the chest *x*-ray film or ECG before heart failure was clinically evident.

One patient (patient 20, table) had had a posterior myocardial infarct two years previously. He suffered no unexpected side effects from treatment, his ECG was unchanged throughout, and subsequent post-mortem examination showed an old posterior myocardial infarct. Repeated chest *x*-ray films and ECGs in the remaining 17 patients were normal throughout.

Discussion

Most patients were given DNR initially, changing later to DXR (see table), and the recommended total dose was exceeded because many patients with AML in relapse had become resistant to other cytotoxic drugs. Only two of our patients developed heart failure: predictably the two who received the largest total doses. Furthermore, both responded to anti-failure treatment and in neither patient was heart failure the cause of death.

In view of the low incidence of DXR/DNR congestive cardiac failure in our patients (9%), and of the satisfactory response to treatment, we consider that these drugs should not be withheld from patients who have malignant disease with a poor prognosis and who have become resistant to other cytotoxic agents, but who have already received the maximum recommended total dose. The potential benefit in terms of further remission outweighs the risk of toxicity. Other reports have suggested that congestive heart failure may be controlled in children, particularly if diagnosed early,[2] and our experience has shown that this is also possible in adults. We would therefore recommend reintroduction of anthracycline drugs for these patients while being aware of the increased risk of heart failure.

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Successful treatment of longstanding biliary atresia

Biliary atresia is generally believed to have a poor prognosis, untreated patients usually surviving only one to two years.[1] Even when surgery is technically possible there is a high mortality from operation, ascending cholangitis, and the effects of secondary biliary cirrhosis.

We describe a patient with remarkably longstanding biliary atresia who obtained benefit from surgery at the age of 19 years.

Case report

The patient, aged 19, was born at home after an uncomplicated pregnancy. At 5 months he underwent laparotomy for obstructive jaundice. The hepatic,

Doxorubicin and daunorubicin dosage details in 20 patients receiving a total dosage of over 550 mg/m²

Patient	Age	Sex	Surface Area (m²)	Total dose of DNR (mg)	Total dose of DXR (mg)	Dose of DNR/m² (mg)	Dose of DXR/m² (mg)	Total dose of DNR + DXR/m² (mg)
1	20	M	1·6	610	520	381·25	325	706·25
2	63	M	1·65	640	390	387·87	236·36	624·24
3	27	F	1·4	560	330	400	235·71	635·71
4	58	M	2	1120	370	560	185	745
5	40	F	1·55	635	350	409·67	225·80	635·47
6	60	M	1·72	810	540	470·93	313·95	784·88
7	73	M	1·75	740	410	422·85	234·28	657·03
8	21	M	1·7	870	680	511·76	400	911·76
9	44	M	2	960	390	480	195	675
10	64	F	1·5	600	360	400	240	640
11	42	F	1·63	1100	—	674·8	—	674·8
12	56	F	1·65	1170	490	709	297	1006
13	35	F	1·48	1000	135	675·67	91·21	766·88
14	27	F	1·55	1280	—	825·8	—	825·8
15	44	F	1·75	930	50	531·42	28·57	560
16	69	M	1·65	900	380	545·4	230·3	775·7
17	45	M	1·7	630	480	370·58	282·35	652·9
18	59	M	1·6	710	520	443·7	325	768·7
19	40	F	1·5	1000	—	666	—	666
20	58	M	1·75	610	440	398·5	251·4	600