10. Mauriac L. Chimiothérapie première des cancers du sein opérables. Etude randomisée. *Bull Cancer* 1990, **77** (Suppl. 1), 47s–53s.
11. Bonadonna G, Veronesi U, Brambilla C, *et al.* Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. *J Natl Cancer Inst* 1990, **82**, 1539–1545.
12. Jacquillat C, Weil M, Baillet F, *et al.* Results of neoadjuvant chemotherapy and radiation therapy in breast-conserving treatment of 250 patients with all stages of infiltrative breast cancer. *Cancer* 1990, **66**, 119–129.
13. Spielmann M, Mathieu MC, Le Chavalier T, *et al.* Preliminary results of pre-operative chemotherapy in patients with non-metastatic operable breast cancer of more than 3 cms (abstr.). *Proc Am Soc Clin Oncol* 1990, **9**, 39.
14. Hortobagyi G, Singletary E, McNeese M, *et al.* Breast conservation after neoadjuvant chemotherapy for primary breast cancer (abstr.). *Proc Am Soc Clin Oncol* 1991, **10**, 55.
15. Goldie JH, Coldman AJ. A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep* 1979, **63**, 1727–1733.
16. Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. *Cancer Res* 1983, **43**, 1488–1492.
17. Langlois D. Enquête sur les modalités des traitements conservant le sein dans les centres anticancéreux. *Bull Cancer* 1990, **77**, 793–797.
18. Calle R, Pilleron JP, Schlienger P, Vilcoq JR. Conservative management of operable breast cancer: ten years' experience at the Foundation Curie. *Cancer* 1978, **42**, 2045–2053.
19. Amalric R, Santamaria F, Robert F, *et al.* Radiation therapy with or without primary limited surgery for operable breast cancer: a 20-year experience at the Marseilles Cancer Institute. *Cancer* 1982, **49**, 30–34.
20. Pierquin B, Huart J, Raynal M, *et al.* Conservative treatment for breast cancer. Long-term results (15 years). *Radiother Oncol* 1991, **20**, 16–23.
21. National Surgical Adjuvant Breast Project. Protocol No. B-18. A unified trial to compare short intensive preoperative systemic adriamycin cyclophosphamide therapy with similar therapy administered in conventional post-operative fashion.

Eur J Cancer, Vol. 27, No. 12, pp. 1542–1544, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

New Anthracycline Derivatives: What For?

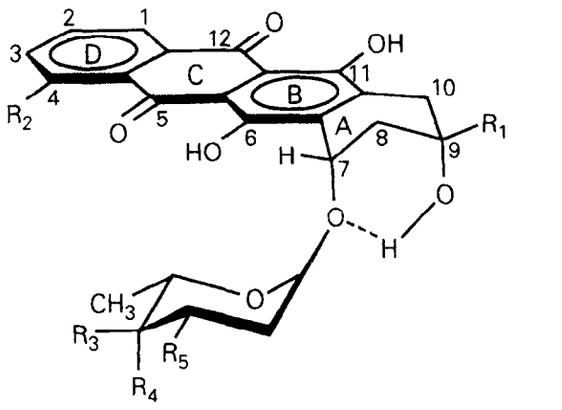
ANTHRACYCLINES ARE probably the most utilised antitumour drug worldwide, and a majority of patients needing systemic treatment for cancer receive either daunorubicin or doxorubicin at some time during their clinical course. There is a difference of only a single hydroxyl group between the chemical structures of daunorubicin and doxorubicin (Fig. 1). Despite only a minor difference in chemical structure, there is a marked difference in their antitumour efficacy. Daunorubicin is one of the major drugs for the treatment of acute leukaemias [1] and doxorubicin is a major drug for the treatment of malignant haematological diseases as well as for the treatment of solid tumours [2, 3]. The clinical success of doxorubicin and this disparity between daunorubicin and doxorubicin in spectrum of antitumour effect resulting from a minor molecular change has been the impetus for a diligent search for other effective or less toxic anthracycline analogues.

Anthracyclines are polyfunctional molecules, both chemically and biologically. The current thinking is that these structures have access to multiple mechanisms, which can act in concert, but in varying patterns with structural changes. Unraveling these chemical reactions into those that are desirable (toxicity to the cancer cell) and into those that are not (toxicity to the organism) is an enigma, recently rendered less inscrutable.

A logical site of biochemical action in the anthracycline molecule is the quinone = ring C in Fig. 1, which is known to undergo reduction and reoxidation processes involving one or two electrons. Single-electron redox cycling leads to enhanced production of cytotoxic free radicals, two-electron reduction can lead to quinone methide structures that function as alkylating agents [4, 5]. There is preliminary progress indicating that catalytic redox turnover contributes a significantly greater extent to the host cytotoxicity, rather than to the antitumour activity. Tumour cytotoxicity does not involve any redox event [6]. Furthermore, the present understanding of anthracycline structure–activity relationship does not demand intercalation as a necessary event of the tumour cytotoxicity [7] as it was thought before [8]. As it now stands DNA damage via aerobic degradation, covalent labelling by the quinone methide, or even related to the topoisomerase cleavable complex provide reasonable explanations for the anticancer activity although the exact molecular lesions involved have not been determined exactly up to now.

Analogues of daunorubicin or doxorubicin might be less myelotoxic, less cardiotoxic, less emetogenic, less toxic to the gastrointestinal tract (stomatitis/mucositis), have a broader range of activity, and ideally and clinically important, lack of crossresistance to the parent compound. Of all toxicities mentioned, most attention is called to cardiotoxicity. In the case of curability, it is an important aspect; in case of palliation it is not. Cardiotoxicity is a major problem of anthracycline therapy if the patient can be cured by intensive anthracycline treatment. There is a clear indication that the treatment for a potential fatal childhood cancer (e.g. acute lymphoblastic leukaemia) may cause another serious or fatal disease. A high incidence of late cardiovascular abnormalities in children who received anthracyclines were observed [9]. There has been a growing tendency to associate anthracycline redox cycling and radical production with chronic anthracycline cardiotoxicity [10, 11]. Myocardial alteration due to free radical generation was described in experimental settings [12, 13] and such alterations are similar or even identical to those observed after anthracycline therapy [14], a fact which might be related to the fact that the biochemical equipment to defend the heart cells to free radical attacks by free radical scavengers and by enzyme systems for detoxification (catalase, superoxide dismutase, glutathione) is reduced in heart cells.

Received and accepted 15 Aug. 1991.



DOX	R_1=$COCH_2OH$	R_2=OCH_3	R_3=H	R_4=OH	R_5=NH_2
EPI	R_1=$COCH_2OH$	R_2=OCH_3	R_3=OH	R_4=H	R_5=NH_2
I-DOX	R_1=$COCH_2OH$	R_2=OCH_3	R_3=H	R_4=I	R_5=NH_2
MRA	R_1=$COCH_2OH$	R_2=OCH_3	R_3=H	R_4=OH	R_5=
MRA-MO	R_1=$COCH_2OH$	R_2=OCH_3	R_3=H	R_4=OH	R_5=
MRA-CN	R_1=$COCH_2OH$	R_2=OCH_3	R_3=H	R_4=OH	R_5=
DNR	R_1=$COCH_3$	R_2=OCH_3	R_3=H	R_4=OH	R_5=NH_2
IDA	R_1=$COCH_3$	R_2=H	R_3=H	R_4=OH	R_5=NH_2
RO 31-1215	R_1=CH_3	R_2=H	R_3=H	R_4=OH	R_5=NH_2
MRDnr-CN	R_1=$COCH_3$	R_2=OCH_3	R_3=H	R_4=OH	R_5=

Fig. 1. Chemical structures of C-4, C-9, C-4′ and C-3′ modified anthracyclines. DOX = doxorubicin, EPI = epirubicin, I-DOX = iododoxorubicin, MRA = morpholinyl doxorubicin, MRA-MO = 2-methoxy-morpholinyl doxorubicin, MRA-CN = cyano-morpholinyl doxorubicin, DNR = daunorubicin, IDA = idarubicin, MRDnr-CN = cyano-morpholinyl daunorubicin.

Another argument for a different mechanism of cardiotoxicity and anticancer activity is the fact that use of the bisperazinedione ICRF 187, a chelator, ameliorates the cardiotoxic effects but does not reduce the anticancer effect [15]. This is in line with the statement that free radical formation plays no major role in anticancer activity [16]. Analogue research focussing on reduced carditoxicity while keeping the anticancer efficacy is worthwhile. Nevertheless, the prominent new analogues epirubicin and idarubicin, both with minor structural changes [17], introduced as the successors of doxorubicin and daunorubicin, respectively with reduced cardiotoxicity and similar or even better anticancer efficacy have not fulfilled expectations. The drugs are less cardiotoxic, in the case of epirubicin shown using the most sensitive method with cardiac biopsies in humans [18], the pharmacokinetics and metabolism is different [19], but the spectrum of anticancer activity is not broader or different [20]. There is no cancer cell that can be treated better with epirubicin than with doxorubicin. Cardiotoxicity of epirubicin is only reduced if equimolar doses are compared, then it can be administered repetitively for slightly longer. In case of equipotent or equimyelosuppresive doses this difference becomes insignificant. In the case of idarubicin data from large trials are missing. I have no doubt that it is only a matter of time before oncologists are aware that idarubicin is not a great step forward. These new anthracyclines are slightly better than the parent drugs but is such a minor improvement enough? The spectrum of activity has not become broader or different and there is nearly complete crossresistance to the parent drugs. Launching such drugs depends on several aspects of commercial interests.

During the last years the anticancer drug resistance problem has become a major focus in research [21]. All natural anticancer drugs like anticancer antibiotics (anthracyclines, mitomycin, dactinomycin), vinca alcaloids and podophyllotoxins are affected by the multidrug resistance (MDR) phenomenon [22]. The development of analogues which are at best not or not completely crossresistant to their parent drugs is an important issue to overcome resistant cancer cells.

My point of view is that we need anthracyclines with different features because we need an anthracycline: (1) with less cardiotoxicity but the same antitumour activity (curative intention); (2) with a broader and/or different spectrum of activity (for the treatment of lung cancer, colon cancer, pancreatic cancer); (3) that can be successfully used after an anthracycline treatment failure (no crossresistance to doxorubicin or daunorubicin, respectively, epirubicin and idarubicin, MDR problem); (4) with the possibility of oral administration with good bioavailability; and (5) with less acute side-effects. Alopecia, nausea/vomiting and unpleasant mucositis are distressing side-effects, particularly with palliative treatment. These desirable demands will not be realised with the development of only one anthracycline. Search for such analogues is going on, critical events to the molecule seemed to be the 9-alkyl substitution as a distinct molecular feature in anthracycline, an incorporation of which leads to a marked decrease in resistance factor in human MDR cell lines [23]. Changes at the adjacent 3′- 4′-position of the sugar can also confer activity against MDR cells. Iododoxorubicin and morpholinyl anthracyclines are such compounds [24–27]. The morpholinyl anthracyclines especially have features like another or additional mechanism of action, specific inhibition of RNA polymerase and/or covalent strand crosslinking of DNA which are novel in the anthracycline series [28].

It would be indeed fortuitous if, out of all the anthracyclines known, the most effective anthracyclines were the first two discovered, daunorubicin and doxorubicin. It takes a lot of patients, time, and monetary resources for the medical oncologists to determine the value of each anthracycline analogue. There might be some oncologists who feel that we could spend our efforts and resources looking for compounds with new structures and/or new mechanisms of action. I count myself not with those who feel that way: we need both, a better doxorubicin as well as a better daunorubicin *and* new drugs. How say you?

Klaus Mross
University Clinic Eppendorf
Department Oncology and Hematology
Martinistr. 52
D-2000 Hamburg 20
Germany

1. Gale RP, Foon KA. Therapy of acute myelogenous leukemia. *Sem Hematol* 1987, **24**, 40–54.
2. Zuckermann KS, LoBuglio AF, Reeves JA. Chemotherapy of intermediate- and high-grade non-Hodgkin's lymphomas with a high-dose doxorubicin-containing regimen. *J Clin Oncol* 1990, **8**, 248–256.
3. Gianni L, Corden BJ, Meyers E. The biochemical basis of anthracycline toxicity and antitumor activity. In: Hodgson E, Bend JR, Philpot RM, eds. *Reviews in Biochemical Toxicology*. New York, Elsevier Biomedical, 1983, 1–82.
4. Lown JW. The mechanism of action of quinone antibiotics. *Mol Cell Biochem* 1983, **55**, 17–40.
5. Moore HW. Bioactivation as a model for drug design. *Biored Alk Sci* 1977, **197**, 527–538.
6. Kennedy KA, Siegfried JM, Sartorelli AC, Tritton TR. Effects of anthracyclines on oxygenated and hypoxic tumor cells. *Cancer Res* 1983, **43**, 55–59.
7. Abdella BRJ, Fisher J. A chemical perspective on the anthracycline antitumor antibiotic. *Environ Health Perspect* 1985, **64**, 3–18.

8. Arcamone F. Antitumor anthracyclines: recent developments. *Med Res Rev* 1984, **4**, 153–188.
9. Lipshutz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991, **324**, 808–815.
10. Davies KJA, Doroshow JH. Redox cycling of anthracyclines by cardiac mitochondria. *J Biol Chem* 1986, **261**, 3060–3067.
11. Doroshow JH, Davies KJA. Redox cycling of anthracyclines by cardiac mitochondria. *J Biol Chem* 1986, **261**, 3068–3074.
12. Burton KP, McCord JM, Ghai G. Myocardial alterations due to free-radical generation. *Am J Physiol* 1984, **246**, H776–H783.
13. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med* 1985, **312**, 159–163.
14. Billingham ME, Bristow MR. Evaluation of anthracycline cardiotoxicity: Predictive ability and functional correlation of endomyocardial biopsy. *Cancer Treat Symp* 1984, **3**, 71–76.
15. Speyer JL, Green MD, Kramer E, *et al.* Protective effect of the bispiperrazineedione ICRF-187 against doxorubicin-induced cardiac toxicity in women with advanced breast cancer. *N Engl J Med* 1988, **319**, 745–752.
16. Keizer HG, Pinedo HM, Schuurhuis GJ, Joenje H. Doxorubicin: a critical review of free radical-dependant mechanisms of cytotoxicity. *Pharmacol Ther* 1990, **47**, 219–231.
17. Weiss RB, Sarosy G, Clagett-Carr K, Russo M, Leyland-Jones B. Anthracycline analogs: the past, present, and future. *Cancer Chemother Pharmacol* 1986, **18**, 185–197.
18. Torti FM, Bristow MM, Lum BL, *et al.* Cardiotoxicity of epirubicin and doxorubicin: assessment by endomyocardial biopsy. *Cancer Res* 1986, **46**, 3722–3727.
19. Mross K, Maessen P, van der Vijgh WJF, Gall H, Boven E, Pinedo HM. Pharmacokinetics and metabolism of epidoxorubicin and doxorubicin in humans. *J Clin Oncol* 1988, **6**, 517–526.
20. Cersosimo RJ, Hong WK. Epirubicin: a review of the pharmacology, clinical activity, and adverse effects of an anthracycline analogue. *J Clin Oncol* 1986, **4**, 425–439.
21. De Vita V. The problem of resistance; keynote address. In: Mihich E, Cibbey J, eds. *Drug Resistance: Mechanisms and Reversal.* Roma 1990, 7–27.
22. Pastan I, Gottesman M. Multiple-drug resistance in human cancer. *N Engl J Med* 1987, **316**, 1388–1393.
23. Coley HM, Twentyman PR, Workman P. Identification of anthracyclines and related agents that retain preferential activity over adriamycin in multidrug-resistant cell lines, and further resistance modification by verapamil and cyclosporin. *Cancer Chemother Pharmacol* 1989, **24**, 284–290.
24. Mross K, Mayer U, Langenbuch T, Hamm K, Burk K, Hossfeld DK. Toxicity, Pharmacokinetics and metabolism of iododoxorubicin in cancer patients. *Eur J Cancer* 1990, **26**, 1156–1162.
25. Acton EM, Tong GL, Mosher CW, Wolgemuth RL. Intensely potent morpholinyl anthracyclines. *J Med Chem* 1984, **27**, 638–645.
26. Sikic BI, Ehsan MN, Harker WG, *et al.* Dissociation of antitumor potency from anthracycline cardiotoxicity in a doxorubicin analog. *Science* 1985, **228**, 1544–1546.
27. Coley HM, Twentyman PR, Workman P. 9-alkyl, morpholinyl anthracyclines in the circumvention of multidrug resistance. *Eur J Cancer* 1990, **26**, 665–667.
28. Acton EM, Wasserman K, Newman A. Morpholinyl anthracyclines. In: Lown JW, ed. *Anthracycline and Anthracenedione-Based Anticancer Agents.* Elsevier, Amsterdam, 1988, 55–101.

Eur J Cancer, Vol. 27, No. 12, pp. 1544–1545, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Lung Cancer Therapy in the Elderly

SHOULD ELDERLY patients with small cell lung cancer be treated differently than younger patients? Of the population in the western world, 10–15% is over the age of 70. The life expectancy of this population is on average 15 years for women and 8–10 years for men. A substantial and increasing percentage of the new malignancies will occur in this age group. Up till now patients over the age of 70 with lung cancer were frequently excluded from clinical trials for different reasons, such as the disease's supposed more indolent behaviour, the impaired bone marrow tolerance of the elderly, the presence of a compromised renal and liver function interfering with drug clearance, concomitant chronic disease, the diminished life expectancy and their attitude towards intensive treatment.

Age is not a recognised independent negative prognostic factor in patients with lung cancer. Extent of disease, initial performance status and weight loss are such dominant prognostic factors, that, in retrospective studies in particular, it is impossible to determine the effect of age. A less extensive presentation, with a possible impact on prognosis, is not uncommon in the described patient population [1]. With advancing age drug metabolism may be altered due to an increase in the volume of distribution, a decrease in hepatic drug metabolism and in renal clearance. Negative interactions of cytostatic drugs with medication taken because of concomitant chronic disease, has not proven a major problem but warrants careful consideration when dealing with this patient population. Clinicians are becoming more and more aware that the conception that older patients with lung cancer should not be treated may be wrong. Furthermore, patients have been treated and cured with chemotherapy [2]; this is recognised and also reflected in a joint EORTC/National Cancer Institute meeting recently held in Venice, Italy to discuss the need for studies in the elderly and to determine age criteria [3].

There are retrospective studies on the effect of treatment of elderly patients with small cell lung cancer, as by Clamon *et al.* [4] and by Findlay *et al.* (p. 1597–1601). Although the results may be interesting, these studies can not solve the question how to treat lung cancer in the elderly. These studies have many drawbacks. Not stated is why patients were selected to be treated and others not. Treatment was not uniform. Dose schedules were not always optimal. The considerations leading to full dose or gentle chemotherapy are not clear.

These studies only show that chemotherapy can be given to a selected group of elderly patients, but reveal no guidelines how to treat which patients. In phase II studies both with single drugs [5, 6] and with combination chemotherapy [7, 8] it has been demonstrated that treatment is feasible. They do not answer the question if aggressive, conventional or gentle treatment for elderly patients is effective.

Time has passed for drawing conclusions from retrospective studies on the treatment of patients over 70 years. There is an under-representation of patients aged 75 years and older among patients with lung cancer seen at comprehensive cancer centres

Received and accepted 3 Sep. 1991.