Cardioprotection in Patients Undergoing Chemo- and/or Radiotherapy for Neoplastic Disease

A Pilot Study

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SUMMARY

Objectives: To assess the cardioprotective efficiency of an antioxidant regimen (vitamins E, C and N-acetylcysteine) in patients receiving high dose chemo- and/or radiotherapy for malignant disease.

Methods: Prospective, placebo controlled, randomized and double blinded pilot study involving 13 patients receiving chemotherapy and 12 patients receiving radiotherapy.

Results: In patients receiving antioxidants, left ventricular ejection fraction did not change (63 ± 4% to 63 ± 4%). In the placebo group, ejection fraction changed from 67 ± 6% to 61 ± 4% (p = 0.03). No patient in the antioxidant group and 6/13 (46%) patients in the placebo group showed a fall of >10% in the left ventricular ejection fraction. In the chemotherapy group, the left ventricular ejection fraction changed from 62% (± 2) to 63% (± 2) in the patients treated with antioxidants (ns) and from 63% (± 5) to 61% (± 5) in patients treated with placebo (ns). No patient showed a significant fall in ejection fraction in the antioxidant group, whereas 2/7 (29%) in the placebo group showed a reduction ≥10%. In the radiotherapy group, left ventricular ejection fraction did not change {64% (± 6) to 64% (± 5)} in patients treated with antioxidants (ns) and changed from 70% (± 8) to 60% (± 4) in patients treated with placebo (p = 0.008). No patient in the antioxidant group, but 4/6 (66%) patients in the placebo group showed a fall of ≥10% in ejection fraction.

Conclusion: The small number of patients in the study precludes a definitive statement. The preliminary results however suggest efficient cardioprotection by this nontoxic and inexpensive antioxidant combination, so larger studies are warranted for confirmation. (Jpn Heart J 1996; 37: 353–359)

Key words: Cardioprotection Antioxidants Cardiotoxicity Chemo-

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This work was supported by grants from the Inselspital (grant nr. 233) and from Hoffmann La Roche (grant nr. 92-1). Vitamins E and C were provided by Hoffmann La Roche Inc, N-acetylcysteine and Placebo by Ipsarazam/Zambon Group.

Received for publication November 17, 1995.

Accepted January 17, 1996.

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BOTH radiotherapy\textsuperscript{1} and chemotherapy, especially adriamycin\textsuperscript{2} are known to be potentially cardiotoxic. The development and extent of cardiotoxicity depends on total radiation or drug dose,\textsuperscript{3} combination therapy,\textsuperscript{4} or preexisting cardiovascular disease.\textsuperscript{5} Chemotherapy mediated cardiotoxicity may be due to the production of free oxygen radicals.\textsuperscript{6} Laboratory\textsuperscript{7,8} and clinical\textsuperscript{9} evidence suggests that cardiotoxicity may be reduced without lessening the antineoplastic effect of the treatment. The aim of this pilot study was to test whether a combination of nontoxic and inexpensive antioxidants (vitamins E, C and N-acetylcysteine) could lead to a reduction in cardiotoxicity, as measured by serial determination of left ventricular ejection fraction using radionuclide ventriculography.\textsuperscript{10}

**Methods**

The study was approved by the institutional ethics committee. Patients undergoing curative chemotherapy and/or radiotherapy for neoplastic disease were randomized to treatment with placebo or vitamin E, vitamin C and N-acetylcysteine. Exclusion criteria were: patients with high cardiac output states (for example due to fever), patients with known or suspected coronary or valvular heart disease, patients with reduced left ventricular function or preexisting regional wall motion abnormalities, patients with obstruction to venous return (mediastinal masses with compression, more than minimal pericardial effusion), and patients on cardioactive drugs. Dosage was 600 mg Vitamin E every day beginning with the first day of therapy, 1 gm vitamin C and 200 mg N-acetylcysteine only on days in which therapy was applied. Patients and medical staff, including the treating oncologist and radiotherapist, as well as nuclear cardiologist were blinded as to treatment received. A total of 32 patients scheduled to receive chemotherapy and radiotherapy were accrued over 1 1/2 years. Two patients refused to participate, 3 began the protocol but refused the post-treatment control, and the condition of 2 patients deteriorated before completion of the study. Randomization occurred before the chemo- or radiotherapy treatment scheme (including total necessary dose) was known. Left ventricular ejection fraction was determined by radionuclide ventriculography before and within 3 weeks of termination of therapy. A fall of \( \geq 10\% \) of the left ventricular ejection fraction was considered to be relevant, thus using a more stringent criterion than recommended.\textsuperscript{11} Calculation of total heart and left ventricle radiation dosage was performed using a computer tomography scan-assisted computerized model. Mediastinal radiotherapy was applied every day, 5 days a week through anterior and posterior ports. Mean total radiation dose was \( 2651 \pm 779 \) Centigray in patients.
receiving antioxidants and $3061 \pm 695$ Centigray in patients receiving placebo ($p = \text{ns}$). Left ventricular radiation dose was $1517 \pm 579$ in patients receiving antioxidants and $2024 \pm 1103$ Centigray in those receiving placebo ($p = \text{ns}$). Chemotherapy included Adriamycin in all patients ($143 \pm 51 \text{ mg/m}^2$ in the antioxidant group and $178 \pm 100 \text{ mg/m}^2$ in the placebo group). The mean doses of the other agents used in chemotherapy (bleomycin, cyclophosphamide, dacarbazine, procarbazine, vincristine, prednisone, etoposid, vinblastine) were similar too, but statistical significance is irrelevant due to widely different chemotherapy treatment protocols. Comparisons between groups for left ventricular ejection fraction were done using the paired t-test, and a $p > 0.05$ was considered to be significant. All values are given as mean ($\pm$ SD).

**RESULTS**

In patients receiving antioxidants (Figure 1), left ventricular ejection fraction did not change ($63 \pm 4\%$ to $63 \pm 4\%$). In the placebo group (Figure 2), ejection fraction changed from $67 \pm 6\%$ to $61 \pm 4\%$ ($p = 0.03$). No patient in the antioxidant group and $6/13$ ($46\%$) patients in the placebo group showed a fall of $>10\%$ in the left ventricular ejection fraction. Considering patients examined after re-

![Figure 1](image)

**Figure 1.** Left ventricular ejection fraction (EF) in patients receiving antioxidants (AO) before and within 3 weeks after chemo- and radiotherapy. The mean change in ejection fraction between both groups was not significant ($p = 0.93$, see Discussion). Age $36 \pm 14$ years, 7 males, 5 patients had Hodgkin-, 5 had Non Hodgkin-Lymphoma, 1 had breast cancer and 1 had lung cancer.
Figure 2. Left ventricular ejection fraction (EF) in patients receiving placebo (P) before and within 3 weeks after chemo- and radiotherapy. The mean change in ejection fraction between both groups was significantly different (p = 0.03). Age 38 ± 19 years, 6 males, 8 patients had Hodgkin-, 3 Non-Hodgkin-Lymphoma and 2 had oesophageal carcinoma.

Receiving chemotherapy, left ventricular ejection fraction changed from 62% (± 2) to 63% (± 2) in patients with antioxidant therapy (p = ns), and from 63% (± 5) to 61% (± 5) in patients in the placebo group (p = ns). No patient in the antioxidant group and 2/7 (29%) patients in the placebo group showed a significant fall of ≥ 10% in ejection fraction. In patients examined after receiving radiotherapy, left ventricular ejection fraction changed from 64% (± 6) to 64% (± 5) in patients with antioxidant therapy (p = ns), and decreased from 70% (± 8) to 60% (± 4) in patients in the placebo group (p = 0.008). No patient in the antioxidant group and 4/6 (66%) patients in the placebo group showed a significant fall of ≥10% in ejection fraction at termination of therapy.

No patient complained of side effects ascribed to antioxidant treatment or placebo.

**Discussion**

ICRF-187 (Dexrazoxane) has recently been approved for reduction of anthracycline-induced cardiotoxicity in the United States. Although ICRF - 187 has been found to be very useful in permitting greater doses of doxorubicin to be
administered in patients with breast cancer\textsuperscript{14)}, the drug may have relevant adverse reactions, although their incidence did not differ significantly from placebo (Ref. 14, producer’s product information). In view of the potential toxicity and the producer’s advice not to use the drug with chemotherapy regimens not containing anthracyclines, we looked for an alternative antioxidant regimen as a potential cardioprotector in patients subjected to combined chemo- and radiotherapy. Vitamins E, C and N-acetylcysteine were chosen because of a potentially synergistic action of the combination\textsuperscript{12,13}, good patient acceptability as “natural substances”, absence of side effects with the chosen dosage and oral route of administration. In addition they are readily available and inexpensive.

Due to the small patient numbers and the inhomogeneous clinical characteristics of the patients, both groups not being age, sex and therapy-matched, the statistical significance is only formal and allows for both alpha or beta type bias. This fact is amply acknowledged in the analysis of the study. However, even if patients received different therapeutic regimens (randomization occurred before allocation to treatment, thus these errors are truly “random”), the obvious fall in individual systolic ventricular performance in the placebo subgroup shows the need for cardioprotective therapy.

Three patients receiving antioxidants and 4 patients receiving placebo showed a rise in left ventricular ejection fraction after treatment completion (Figures 1 and 2). Except for 2 patients in the antioxidant group, the rise was less than 5\% and can thus be fully accounted for by the inherent divergence described when performing repeated assessment of ventricular function using radionuclide ventriculography in healthy individuals\textsuperscript{11}. There was no noticeable change in the clinical or laboratory parameters (fever etc.) of the 2 patients with a rise of 6\% and 7\% in ejection fraction, so that a different cardiac loading status must be postulated, enhancing the methodological variability, to explain the rise in ejection fraction. If the results are recalculated so that all ejection fractions showing an increase are assumed to have remained stationary, then the mean ejection fraction of the group receiving antioxidants will decrease significantly ($p = 0.01$). The decrease in ejection fraction of the placebo group will increase in statistical significance to $p = 0.004$. These changes may be formally significant, yet they lack clinical meaning, as no individual patient in the antioxidant group showed a clinically significant decrease in ejection fraction of \textgreater 5\% (Figure 1). It is for this reason that a cut off value of 10\% reduction in ejection fraction was chosen in our study to be clinically significant, thus ensuring that only very obvious worsening of systolic function was accredited to cardiotoxicity.

Because a span of 1 1/2 years was allowed for the study (financial constraints, availability of study participants, etc.), it could not be extended until a larger number of patients could be included. The study has focused on reduction
of short term deterioration of left ventricular ejection fraction. The more important question of whether antioxidant therapy can reduce long term cardiotoxic effects was not addressed. Because of the individually tailored chemotherapy regimens, dosage comparisons yield only limited information as to their potential cardiotoxicity. Although radiotherapy doses to the heart and left ventricle did not differ significantly between the two groups, the results may still be biased in favor of antioxidant therapy because of the large SD and small number of patients. Additionally, 2 patients randomized to the placebo group suffered from esophageal malignancy, and therefore received higher radiation doses than average.

CONCLUSIONS

The antioxidant combination featuring vitamin E and C as well as N-acetylcysteine may provide efficient cardioprotection in patients receiving high dose chemo- or radiotherapy. Although the small number of patients precludes more than cautious interpretation of any statistical significance, the encouraging results of this double blind study warrant confirmation by larger ones.

REFERENCES

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