A Comparative Study on the Two Different Doses of Dexrazoxane

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Many chemotherapy agents have been associated with cardiotoxicity.\(^1\)\(^,\)\(^2\) Anthracyclines and related compounds (doxorubicin, daunorubicin, and epirubicin, etc) are used alone or in combination with other chemotherapeutic agents.\(^3\) They are important treatment options for many cancer types. Their clinical utility, however, was limited by cardiotoxicity such as MI (myocardiac infaction), CHF (congestive heart failure), and decreasing LVEF (left ventricular ejection fraction). These cardiac toxicities are progressive and irreversible with each subsequent dose of anthracyclines.\(^4\) The incidence of this cardiac toxicity is related to the cumulative dose of anthracycline administered.\(^5\) Chemotherapy is not a short term therapy, so it limits for some of cancer patients to get their entire treatment.

Since the late of 1990s, studies have shown dexrazoxane is effective for preventing cardiotoxicity caused by use of anthracyclines.\(^6\)\(^,\)\(^7\) The mechanism of cardioprotection is thought to be through chelation of iron. Since dexrazoxane is a hydrosoluble nonpolar substance, it easily reaches the cytoplasm of the cardiac cell where it hydrolyzed in the shape of open rings, acquiring a strong iron-chelating property by which it prevents the uptake of iron.\(^8\)\(^,\)\(^9\)

- Key words - dexrazoxane, cardioprotection, doxorubicin, anthracycline
production of the iron-doxorubicin compound involved in the formation of the free radicals that cause cardiac injury. Therefore, dexrazoxane became a worldwide used medication. By giving dexrazoxane prior to each doxorubicin dose, the risk of cardiotoxicity has been decreased. Compared with those receiving anthracycline alone, patients treated with dexrazoxane experienced significantly fewer cardiac events (39% vs 13%, P < 0.001) and a lower and less severe incidence of CHF (11% vs 1%, P < 0.05).

Nevertheless, dosage of dexrazoxane was not consistent between in Europe and US. This difference gives many health care providers confusion. This is also an important thing that we should consider. Dexrazoxane (brand name of dexrazoxane in Europe and Korea: cardioxane®, brand name of dexrazoxane in America; zinecard®) was approved in Europe first. The dosage was a 20:1 dexrazoxane:doxorubicin dose ratio in Europe. Korea also uses the same dose as European countries do. However, FDA approved dexrazoxane:doxorubicin dose ratio as 10:1 (zinecard®). Dexrazoxane is relatively a high-priced medication, and it could have toxicity. Thus it is important to compare the toxicity and efficacy associated with the different dosing regimens.

The purpose of this paper is to compare the efficacy and toxicity of two different doses.

**METHOD**

PubMed were searched from inception for periods from 1990 to 2010. Clinical trials published in English language were sought that compared protective effectiveness of dexrazoxane for cardiotoxicity caused by anthracyclines; included all age treated for cancer with anthracyclines; and used patient-based primary outcomes of mortality, heart failure, arrhythmia or measures of cardiac performance.

Keyword used was dexrazoxane limited by clinical trial, human, English and free full text. The results showed 11 journals. There was one article about continuous infusion versus bolus administration of dexrazoxane, and five articles about other indication of dexrazoxane such as extravasation. These were excluded, and 5 articles were left. (Searched on 2010. 5. 1)

**RESULTS**

**Quantity and quality of research**

The results showed 11 journals. There was one article about continuous infusion vs bolus administration of dexrazoxane, and five articles about other indication of dexrazoxane such as extravasation. These were excluded, and 5 articles were left (Frances 1993, Steven 2004, Marty 2006, Ranulfo 2006, and Albert 2007).

**ASSESSMENT OF EFFECTIVENESS**


In Frances 1993 study, a cardiologist examined each patient before each dose of anthracycline was given and about a month after the last treatment. Two children (40%) in the control group (no dexrazoxane group) developed symptomatic congestive heart failure and one died. There were no children in treatment group developed cardiac failure or left ventricular dysfunction.

The difference in change in shortening fraction and ejection fraction between groups after treatment was statistically significant ($P=0.04$, student’s $t$ test). This was a small study, but it seemed dexrazoxane provided an effective cardioprotection to the children with end-stage malignancy.

Steven study used cardiac troponin T instead of echocardiographic measurements as an indicator of myocardial injury because of poor sensitivity and specificity of echocardiography in identifying subclinical abnormalities of left ventricular structure and function in children with cancer who are receiving doxorubicin. Significantly fewer patients in the group given dexrazoxane and doxorubicin had any elevation in cardiac troponin T (21% vs 50%, $P <0.001$), any extreme elevations in cardiac troponin T (10% vs 32%, $P<0.001$), or multiple elevations in cardiac troponin T (12% vs 37%, $P <0.001$). Differences between the groups in the percentage of
patients with at least one elevated cardiac troponin T level began to emerge between 61 and 120 days after the start of therapy, and these differences persisted throughout the rest of the treatment period, becoming significant during the interval between 121 and 180 days. \( P < 0.001 \). The median follow-up was 2.7 years.

Marty study evaluated cardiac events those are defined as the rate reduction in LVEF, or the appearance of clinical symptoms of cardiac insufficiency (graded according to the NYHA classification of cardiac status). \(^{13}\) Significantly fewer cardiac events \( (P < 0.001, \text{relative risk reduction of } 68\%) \) and cases of CHF \( (P = 0.015, \text{relative risk reduction of } 88\%) \) occurred in the dexrazoxane group compared with the control group. The CHF severity (compared with NYHA standard grade) is also lower than control group (one patient in the treatment group; NYHA grade 2 vs eight patients in the control group; one NYHA grade 2, three NYHA grade 3 and four NYHA grade 4).

Ranulfo study showed a significant difference \( (P = 0.029) \) between the average of shortening fraction percentage at both groups in evaluation two, three, and four. This trial suggested some level of myocardial protection granted by dexrazoxane. This is corroborated by the fact that doxorubicin induced cardiac toxicity is dose-dependent, and between each one of these evaluations, group II received a cumulative mean dose approximately 15\% greater than group I, a statistically significant difference \( (P < 0.001) \). This result showed that patients who got dexrazoxane prior to anthracycline based chemotherapy can receive more cycle they needed.

In Albert study, patients treated with doxorubicin alone were more likely than who received dexrazoxane to have elevated troponin T samples during therapy (50\% versus 21\%; \( P < 0.001 \)). The results also described dexrazoxane had a preventive effect for the acute cardiac injury.

Tumor effect of doxorubicin with or without dexrazoxane (Steven 2004, Marty 2006, and Albert 2007)

In Steven study, the rate of event-free survival at 2.5 years was 83\% in both groups \( (P = 0.87 \text{ by the log-rank test}) \). In Marty study, overall response rates (complete response(CR) + partial response(PR)) were similar in both groups (35\% observed in both groups). There was also no statistically significant difference in either progression–free survival or overall survival. In Albert study, the 5-year event free survival for patients randomized to receive doxorubicin with dexrazoxane was 76\%±4\%, compared with 77\%±4\% for those randomized to receive doxorubicin alone \( (P = 0.99) \).

Adverse drug reaction of dexrazoxane (Marty 2006)

Marty study discusses that the adverse events such as alopecia, nausea, neutropenia, vomiting, leukopenia and anemia were more frequent (28\% in control group vs 36\% in the dexrazoxane group) in the dexrazoxane group. Administration of dexrazoxane produces a slight increase (16\% versus 11\%, respectively) in the incidence of anemia and aggravation of febrile neutropenia.

Cardioprotective effects of dexrazoxane for other anthracyclines except for doxorubicin (Marty 2006)

In Marty study, patients treated with epirubicin or doxorubicin based combination treatment were assigned either to receive or not receive concomitant dexrazoxane therapy. \(^{13}\) Dexrazoxane was infused intravenously over fifteen minutes at 10:1 dexrazoxane: epirubicin dose ratio, thirty minutes before infusion of epirubicin based chemotherapy.

DISCUSSION

Three studies (Steven 2004, Frances 1993, and Albert 2007) showed that 10:1 ratio of dexrazoxane: doxorubicin has enough effects as a cardioprotectant of anthracycline. In Albert 2007, ninety two patients from 10 to 18 years were included. After people are 10 years, body surface area (BSA) would be similar to adults. \(^{18}\) The dose of doxorubicin is determined by BSA not body weight. In Marty 2006, we also saw that dexrazoxane possibly has adverse effects such as febrile neutropenia \(^{13}\) at 20:1 dose ratio of dexrazoxane: doxorubicin. According to these findings, 10:1 dose ratio of dexrazoxane: doxorubic-
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Dexrazoxane can be recommended for adult and children as a cardiac protectant caused by anthracyclines.

CONCLUSION

Dexrazoxane could be considered for the patients who have received as a cumulative dose a more than 300 mg/m² of doxorubicin. The dose ratio of dexrazoxane and doxorubicin should be recommended 10:1. For the patient who has received epirubicin could be applied. Dexrazoxane could be used for both children and adult. Dexrazoxane could be considered for the cancer patients who had received anthracycline regardless cancer types.

REFERENCES

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Study design</th>
<th>No. of enrolled patients</th>
<th>Inclusion criteria</th>
<th>Exclusion Criteria</th>
<th>Study duration &amp; location</th>
</tr>
</thead>
</table>
| Marty 2006   | Multiple, international, open-label, randomized, controlled phase III study | Total 164 pts (dexrazoxane group = 85, control group = 79) | 1. Older than 18 years  
2. Confirmed advanced metastatic breast cancer  
3. History of prior anthracycline exposure  
4. Have progressive disease  
5. Anthracycline-free for at least six months prior to the start of the study  
6. Normal LVEF or lower limit of the normal range | 1. Experienced a MI in the previous year  
2. History of uncontrolled angina pectoris,  
3. History of CHF  
4. History of symptomatic valvular heart disease | Thirty six centers  
In the Czech Republic, France, Germany, Poland, South Africa and Spain  
Between December 2000 and September 2003 (34 months) |
| Ranulfo 2006 | Prospective Non-randomized | 55 patients  
Group I : 37 pts (control)  
Group II : 18 pts (dexrazoxane) | 1. Recently diagnosed with highly malignant osteosarcoma not induced by radiation, confirmed by biopsy and not previously treated  
2. Osteosarcoma at any site with or without metastasis  
3. Under age of 21  
4. No evidence of cardiovascular disease, current or previous, based on clinical history, physical examination, electrocardiogram, chest X-ray and echocardiogram  
5. Normal kidney and liver function | No exclusion criteria noted | Three centers in Brazil  
From May 1996 to February 2001 |
| Steven 2004  | Prospective, randomized, Open label | Total 206 patients  
(101 pts: dexrazoxane group, 105 pts: control) | 1. Under 18 years of age  
2. Newly diagnosed and previously untreated high-risk ALL | Mature B-cell ALL | Single center in the US (Boston)  
Between January 1996 and September 2000 |
| Frances 1993 | Retrospective, non-randomized | Total 10  
dexrazoxane: 5 pts  
Control: 5 pts | 1. Have recurrence of malignant disease  
2. Was re-treated with chemotherapy containing anthracycline drugs | No exclusion criteria noted | Single center in England  
Mean time to death or latest follow up: 11 months: control  
9.8 months: dexrazoxane group |
| Albert 2007  | Prospective Randomized | Total: 491 pts  
HR: 205 pts doxorubicin: 100 pts  
dexrazoxane: 105 pts | 1. Newly diagnosed ALL  
2. WBC count 50x10^9/L or higher or 3. Age younger than 1.00 years or 10.00 yrs older or 4. Presence of leukemia blast in cytocentrifuged cerebrospinal cerebrospinal fluid specimen regardless CSF WBC count or 5. Radiographic evidence of a mediastinal mass or 6. T-cell immunophenotype. (Philadelphia chromosome) | Mature B-cell ALL Incorrect diagnosis Pretreatment with corticosteroid Infection with HIV-1 Incorrect consent (consented for SR therapy but treated as HR pt) | Between January 1996 and September 2000  
10 multi-centers in Canada and US |
### Table 1. Comparison the design, regimens, results of the studies (Continued)

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Dose ratio</th>
<th>Malignancy types</th>
<th>Age of patient</th>
<th>Evaluation of the tumor effect</th>
<th>Toxicity of dexrazoxane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marty 2006</td>
<td>20:1</td>
<td>advanced/metastatic breast cancer</td>
<td>Median age: 52 years (30-76 years)</td>
<td>Overall response rate was used (CR + PR)</td>
<td>Table shows dexrazoxane group had more anemia, febrile neutropenia, and leukemia.</td>
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<tr>
<td></td>
<td>10:1</td>
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<tr>
<td>Ranulfo 2006</td>
<td>20:1</td>
<td>osteosarcoma</td>
<td>Group I: average age: 15.4 yrs Group II: average age: 15.1 yrs</td>
<td>No tumor effect evaluated</td>
<td>No toxicity evaluated</td>
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<tr>
<td></td>
<td>(dexrazoxane: Doxorubicin)</td>
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<tr>
<td>Steven 2004</td>
<td>10:1</td>
<td>ALL (acute lymphoblastic leukemia)</td>
<td>Median age at diagnosis: 7.3 yrs control group 7.5 yrs dexrazoxane group</td>
<td>Event free survival</td>
<td>No toxicity evaluated</td>
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<tr>
<td></td>
<td>(dexrazoxane: Doxorubicin)</td>
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<tr>
<td>Frances 1993</td>
<td>10:1</td>
<td>Osteosarcoma(2), bone metastasizing renal tumor(1), AML relapse(2), neuroblastoma(3), rhabdomyosarcoma(1), Hodgkin’s relapse(1)</td>
<td>Mean of receiving dexrazoxane group: 10.9 yrs Mean of control group: 9.9 yrs</td>
<td>No tumor effect evaluated</td>
<td>No toxicity evaluated</td>
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<td></td>
<td>(dexrazoxane: Doxorubicin)</td>
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<tr>
<td>Albert 2007</td>
<td>10:1</td>
<td>ALL (acute lymphoblastic leukemia)</td>
<td>Younger than 1.00 yr: 14 pts 1.00-9.99 yrs: 385 pts 10.00 and 18.00: 92 pts</td>
<td>5 year event free survival</td>
<td>No toxicity evaluated</td>
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<td>(dexrazoxane: Doxorubicin)</td>
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</tbody>
</table>
Table 1. Comparison the design, regimens, results of the studies (Continued)

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Method of measurement for cardiac protection</th>
<th>Outcomes variables measured</th>
<th>Major Finding (result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marty 2006</td>
<td>Physical examination</td>
<td>Primary efficacy parameter: incidence of cardiac events Cardiac events: 1. reduction in LVEF by 10% absolute %age points or more as measured by MUGA scan or more as measured by echocardiography 2. reduction in absolute LVEF as measured by MUGA or echocardiography 3. appearance of clinical signs of cardiac insufficiency</td>
<td>1. significantly fewer events occurred in the dexrazoxane group compared with the control group (P&lt;0.001) 2. significantly fewer cases of CHF occurred in the dexrazoxane group compared with the control group (P=0.015), and these cases were less severe than control group cases</td>
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<td>Ranulfo 2006</td>
<td>Echocardiography</td>
<td>Any changes in echocardiogram 1. Left ventricular shortening fraction (%) 2. Changes in the left ventricular systolic function 3. Systolic dysfunction</td>
<td>1. Mean of cumulative dos was 15 % grater in Group II, as compared group II, in evaluations two, three, and four(P&lt;0.0001) 2. Significant different between the mean of shortening fraction %age in both groups in evaluations 2, 3, and 4.</td>
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<tr>
<td>Steven 2004</td>
<td>Cardiac troponin T</td>
<td>Cardiac troponin T elevation Timing of elevations in cardiac troponin T</td>
<td>1. Significantly fewer patients in the given dexrazoxane and doxorubicin had any elevation in cardiac troponin T compared with control group. 2. time goes by, the differences between the group in the %age of patients with at least one elevated cardiac troponin T level was persisted</td>
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<tr>
<td>Frances 1993</td>
<td>Echocardiography</td>
<td>Any changes in echocardiogram 1. Left ventricular diastolic diameter 2. Left ventricular systolic diameter 3. Systolic LV posterior wall thickness 4. Shortening fraction (%) 5. Ejection fraction (%)</td>
<td>No cardiac dysfunction in the dexrazoxane group Two CCF(congestive cardiac failure), one reduced shortening fraction reported in control group</td>
</tr>
<tr>
<td>Albert 2007</td>
<td>Cardiac troponin T</td>
<td>Cardiac troponin T elevation</td>
<td>High risk patients(defined above) treated with doxorubicin alone were more likely than those received dexrazoxane to have elevated troponin T samples during therapy (50% vs 21% ; p&lt;0.001) Dexrazoxane prevent acute cardiac injury caused by anthracyclines.</td>
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