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덱스라족산의 두 가지 다른 용량의 비교 연구

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A Comparative Study on the Two Different Doses of Dexrazoxane

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본 연구에서는 anthracyclines의 심장 독성을 예방하기 위해 사용되는 dexrazoxane의 가장 적절하고 안전한 용량을 평가하고자 했다. 이 약물은 같은 적응증에도 불구하고 미국과 유럽에서 두 배 차이가 나는 용량으로 허가 받아 사용되고 있다. 그러므로 dexrazoxane의 anthracycline로 인한 심독성의 예방에 관한 논문을 찾아 dexrazoxane : doxorubicin = 20: 1의 비율로 사용했을 경우와 10:1로 사용했을 때의 효과와 부작용을 비교 하였다. 이 두 가지 용량으로 진행된 모든 임상 연구에서 dexrazoxane이 doxorubicin의 심독성 예방에 통계적으로 유효한 효과가 있다고 결론 내렸다. 또한 dexrazoxane의 추가 요법으로 인해 Tumor effect의 차이를 비교 분석한 결과, 두 가지 용량 모두에서 dexrazoxane이 doxorubicin의 항암 효과에 영향을 미치지 않는 것으로 분석되었다. 대부분의 연구에서 dexrazoxane의 약물 자체의 부작용은 분석하지 않았지만, dexrazoxane:doxorubicin을 20:1의 비율로 사용했던 한 연구에서 dexrazoxane군에서 부작용이 있음이 평가되었다. 반면, dexrazoxane의 용량을 doxorubicin 용량에 비해 10:1로 사용한 모든 연구는, 대상 환자군이 18세 이하의 소아 청소년으로 이 용량을 성인에게도 적용할 수 있는지에 대한 추가 연구가 필요하다. 그러나 항암제의 경우, 대부분 환자의 체표면적(BSA)을 기준으로 약용량을 결정하며, 이는 일반적으로 10세 이상이 되면 어른의 체표면적의 70% 정도가 된다. 그러므로, 본 연구에서는 통계적으로 충분한 수의 10세 이상의 소아, 청소년에게 doxorubicin으로 인한 심독성 예방 효과가 입증되었던 dexrazoxane: doxorubicin을 10:1의 용량으로 사용하여도 임상적인 효과를 기대 할 수 있으며, 이 용량은 dexrazoxane 자체의 유해반응도 감소시킬 수 있을 것이라고 결론 맺는다.

□ Key words - dexrazoxane, cardioprotection, doxorubicin, anthracycline

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 is hydrolyzed in the shape of open rings, acquiring a strong iron-chelating property by which it prevents the

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production of the iron-doxorubicin compound involved in the formation of the free radicals that cause cardiac injury.[8] Therefore, dexrazoxane became a worldwide used medication. By giving dexrazoxane prior to each doxorubicin dose, the risk of cardiotoxicity has been decreased.[9] 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%, $P < 0.05$).[12]

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.[10] Korea also uses the same dose as European countries do. However, FDA approved dexrazoxane:doxorubicin dose ratio as 10:1 (zinecard®).[11] 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[11], Steven 2004[12], Marty 2006[13], Ranulfo 2006[14], and Albert 2007[15]).

ASSESSMENT OF EFFECTIVENESS

Doxorubicin therapy with or without dexrazoxane (Frances 1993, Steven 2004, Marty 2006, Ranulfo 2006, and Albert 2007))

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.[17, 18] 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, relative risk reduction of 68%) and cases of CHF (P=0.015, 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 grade4).

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 anthracycine 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 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: doxorubi-

cin 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/m^2 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.

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Table 1. Comparison the design, regimens, results of the studies

Author & Date	Study design	No. of enrolled patients	Inclusion criteria	Exclusion Criteria	Study duration & location
Marty 2006	Multiple, international, open-label, randomized, controlled phase III study	Total 164 pts (dexrazoxane group = 85, control group = 79)	1.Older than 18years 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 :18pts (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 February2001
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 : 11months: control : 9.8 months: dexrazoxane group
Albert 2007	Prospective Randomized	Total:491pts HR:205pts doxorubicin:100pts dexrazoxane:105pts	1. newly diagnosed ALL 2. WBC count 50×10^9/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 consensent(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)

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

Table 1. Comparison the design, regimens, results of the studies (Continued)

Author & Date	Method of measurement for cardiac protection	Outcomes variables measured	Major Finding (result)
Marty 2006	Physical examination Multiple-gated acquisition(MUGA) scan Echocardiography Blood pressure measurements ECG Chest X-rays	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	1. significantly fewer events occurred in the dexrazoxane group compared with the control group (P<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
Ranulfo 2006	Echocar diography	Any changes in echocardiogram 1. Left ventricular shortening fraction (%) 2. Changes in the left ventricular systolic function 3. Systolic dysfunction	1.Mean of cumulative dos was 15 % grater in Group II , as compared group II, in evaluations two, three, and four(P<0.0001) 2. Significant different between the mean of shortening fraction %age in both groups in evaluations 2,3, and 4.
Steven 2004	Cardiac troponin T	Cardiac troponin T elevation Timing of elevations in cardiac troponin T	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
Frances 1993	Echocar diography	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 (%)	No cardiac dysfunction in the dexrazoxane group Two CCF(congestive cardiac failure), one reduced shortening fraction reported in control group
Albert 2007	Cardiac troponin T	Cardiac troponin T elevation	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<0.001) Dexrazoxane prevent acute cardiac injury caused by anthracyclines.