tumors is being evaluated in our hospital. Therefore, beta-emitters such as ^{166}Ho, ^{32}P, ^{90}Y or ^{89}Sr can be used in the treatment of superficial malignant tumors of the skin.

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Clinical Decision Making Based on Radionuclide Determined Ejection Fraction in Oncology Patients

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Decreased left ventricular ejection fraction (LVEF) is a relative contraindication for the use of potentially cardiotoxic chemotherapy. A resting LVEF of 50% is usually used as the lower limit of normal values. The decision to change chemotherapy, however, is complex and is affected by many factors, including ejection fraction. **Methods:** To determine how LVEF data were used by clinical oncologists in clinical decision making, we performed a retrospective analysis of patients referred for ejection fraction measurements from the hematology/oncology divisions of Stanford University from March 1992 through March 1995. The records of 565 patients treated with potentially cardiotoxic chemotherapy were evaluated. **Results:** LVEFs <50% were found in 153 patients. The charts of patients with reduced ejection fractions were reviewed to determine if the radionuclide measurement resulted in either discontinuation of the cardiotoxic agent or substitution of a less cardiotoxic drug or mode of administration. These specific changes in therapy occurred in only 43 of the 153 (28%) patients with ejection fractions below 50%; 24 of the 43 (57%) had ejection fractions ≤40%. Patients with lower ejection fraction values were more likely to have their therapy changed than those with LVEFs close to normal. Patients with ejection fractions ≤30 generally had cardiotoxic agents discontinued. Of patients who had a resting LVEF <50% and whose therapy was not changed, 81% had a normal increase in LVEF with exercise. **Conclusion:** In clinical practice at our institution, ejection fraction <50% is not used as an absolute contraindication to cardiotoxic chemotherapy. When the LVEF is less than 40%, potentially cardiotoxic therapy is most often discontinued or omitted. Radionuclide evidence of cardiac reserve may account for decisions to continue cardiotoxic agents despite ejection fractions <50% in the majority of patients. Further study will be needed to establish standard criteria. Reserve function, as measured by the change in ejection fraction from rest to stress may be an important parameter used by oncologists to help select patients for continued therapy in spite of a reduced ejection fraction. Our results argue that use of fixed criteria may be too restrictive.

Key Words: cardiotoxicity; left ventricle ejection fraction; equilibrium gated radionuclide angiography

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Cardiac toxicity due to chemotherapy with anthracyclines and anthraquinones is a serious adverse effect associated with substantial morbidity in some patients who are fortunate enough to survive their cancer (*1–10*). Recommendations for the "safe" use of anthracyclines have included either not exceeding a defined cumulative dose (e.g., for doxorubicin 400 mg/m^2) or ensuring adequate cardiac function by limiting treatment to patients with ejection fractions >50% (usually defined by quantitative radionuclide angiography). The threshold dose is an unreliable predictor of cardiotoxic risk and, furthermore, varies with the mode of anthracycline administration [i.e., bolus versus continuous infusion (*11*)], as well as the exact drug administered. Pharmacologic advances in cancer chemotherapy have resulted in new ways of safely administering higher cumulative doses of anthracyclines. Dextrazoxane ameliorates anthracycline-induced cardiotoxicity and has recently been approved for use in women with metastatic breast cancer who have received a cumulative dose of doxorubicin of >300 mg/m^2 (*12*). Liposomal doxorubicin preparations have also received recent approval and result in significantly less cardiotoxicity (*13*). A study of endomyocardial biopsies of patients receiving liposomal doxorubicin administered to cumulative doses of up to 860 mg/m^2 revealed no evidence of significant anthracycline specific cardiotoxicity (*14*). Thus, the cumulative dose criteria for establishing safe limits of anthracycline exposure will likely decline in clinical value while objective studies

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TABLE 1
Specific Reasons for Change of Therapy Other Than Causes of LVEF Determination

Patient no.	Sex	Age (yr)	Disease	Specific reason of changed cardiotoxic therapy
1	F	54	Breast cancer	MTTC was stopped due to hemorrhagic cystitis and perirectal abscess.
2	M	56	Lymphoma	Altered from MINE to ESHAP due to progressive disease.
3	M	52	Lymphoma	Stopped cardiotoxic therapy due to complete response.
4	F	32	Lymphoma	Stopped cardiotoxic therapy due to complete response.
5	F	75	Multiple myeloma	Stopped cardiotoxic therapy due to complete response.
6	F	69	Lymphoma	Altered from CHOP to CEPP, second line of progressive lymphoma.
7	M	57	Leukemia	Altered from ara-C/doxorubicin to ara-c alone for consolidate therapy.
8	F	44	Breast cancer	Altered from taxol/doxorubicin to taxol alone for consolidate therapy.
9	F	63	Breast cancer	Stopped cardiotoxic therapy due to complete response.
10	F	63	Breast cancer	Changed from doxorubicin to Taxol as next best drug for breast cancer.
11	M	17	Leukemia	Stopped cardiotoxic therapy due to complete response.
12	F	37	Lymphoma	Stopped cardiotoxic therapy due to complete response.
13	M	81	Prostate cancer	Stopped due to old age.
14	M	49	Adenoid cystic cancer	Stopped cardiotoxic therapy due to personal reason.
15	M	51	Lymphoma	Evaluate for cardiomyopathy.
16	F	46	Lymphoma	Stopped CHOP due to hemorrhagic cystitis and peripheral neuropathy.
17	F	48	Lymphoma	Stopped cardiotoxic therapy due to complete response.

CEPP = cyclophosphamide, etoposide, procarbazine, prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; ESHAP = etoposide, solu-medrol, high-dose cisplatin and cystosine arabinoside, prednisone; MINE = mesna, ifosfamide, novantrone, etoposide; MTTC = mitoxantrone, thiotepa, taxol, cyclophosphamide.

of cardiac function may assume a more prominent role in estimating chemotherapy-induced cardiotoxicity.

Similarly, stem cell rescue after high-dose chemotherapy (often consisting of high-dose cyclophosphamide and cytosine arabinoside) and whole-body irradiation [bone marrow transplant (BMT)] is also associated with cardiotoxicity (*15–17*), as is mediastinal irradiation (*16,18*). Patients receiving such treatment have experienced arrhythmias, pericardial effusion and severe congestive heart failure (*15,19,20*).

The decline in ejection fraction due to these drugs is dose-related and can be halted if the drugs are stopped before left ventricular function is severely impaired (*3*). Radionuclide blood-pool imaging at rest, or with exercise, has been used as an accurate means of measuring ejection fraction in these patients (*21–23*). Since some patients can tolerate higher doses of these cardiotoxic drugs without cardiac impairment and may benefit by further control of their tumor, doses should be tailored for each patient. Unfortunately, there is no clear agreement about criteria to determine when these drugs should be discontinued (*3,15,23,24*). Although criteria were proposed, little information is available about how clinicians use this information. As a prelude to designing a trial to address the consequences of treatment with cardiotoxic chemotherapy in patients with ejection fractions <50%, we thought it reasonable to first assess how these values are currently used in clinical decision making at our institution.

MATERIALS AND METHODS

Patients

We performed a retrospective study of all patients referred for LVEF measurement from the oncology/hematology divisions in Stanford University Medical Center from March 1992 through March 1995. During this interval, 565 patients were examined. The records of all studies were reviewed to identify patients whose resting left ventricular ejection fraction (LVEF) values were <50% on equilibrium gated blood-pool scan. The charts of 153 patients (85 men, 68 women; age range 6–83 yr; mean 48.7 yr) were reviewed to determine their condition at the time of measurement and define how the requesting oncologist used this information in the management of therapy. The primary neoplasm was lymphoma in 65, leukemia in 31, breast cancer in 24, prostate cancer in 13, multiple myeloma in 10, lung cancer in 4 and other tumors in 6 patients. Because of generalized debility or musculoskeletal problems in patients with malignancies, 25 of 153 (16%) patients did not undergo exercise testing. Fifty-one patients were evaluated for BMT. Results of both rest and exercise LVEF were available in 50 of 51 patients in this group.

Patients selected for BMT were studied in anticipation of the use of high-dose chemotherapy and whole-body irradiation. In the non-BMT group, patients were generally studied after several doses of potentially cardiotoxic drugs including doxorubicin, idarubicin, daunorubicin and mitoxantrone.

Therapy was considered to be changed by the radionuclide measurement when: (a) a specific note was present indicating that therapy was changed as a result of the LVEF determination; (b) patients were refused BMT because of their cardiac status; or (c) when cardiotoxic agents were deleted or a less cardiotoxic drug or mode of administration was selected. Patients who had progressive cancer requiring changes of therapy or complete response requiring no further therapy (Table 1) were not considered to have changed their therapy as a result of the radionuclide measurement. Patients with multiple studies were also evaluated to see the reproducibility and the outcome after cardiotoxic or noncardiotoxic treatment.

Scintigraphic Technique

Rest gated blood-pool scans were recorded in the anterior and the 30°–50° left anterior oblique projections with the patient supine. The radiopharmaceutical was 20 mCi ^{99m}Tc-labeled human serum albumin or in vivo labeled red blood cells. The studies before October 1994 were performed using an Ohio Nuclear Series 120 portable gamma camera interfaced to an Informatek Simis 4 computer. From October 1994 to March 1995, data were recorded using a Siemens low-energy mobile gamma camera with a high-resolution collimator linked to a Siemens Icon computer. The exercise study recorded data in the LAO 45° position for the last 2 min of each stage of a graded exercise protocol while the patient exercised on a Collins electronic bicycle ergometer. The work load was increased at 3-min intervals. The endpoints for exercise were

TABLE 2
Parameters from EGNA in Different Groups of Patients

	Age (yr)	Resting EF	Ex-Rest EF	Maximal load
BMT (n = 51)	39.2 ± 14.0*	43.4 ± 4.2†	12.9 ± 9.1	350.0 ± 174.4
Changed (n = 3)	47.3 ± 4.7	38.3 ± 9.9	−1.7 ± 5.5	250.0 ± 173.0
Unchanged (n = 48)	38.7 ± 14.2	43.7 ± 3.6	13.8 ± 8.6	356.4 ± 174.3
Non-BMT (n = 102)	53.4 ± 16.3*	41.1 ± 7.0†	10.3 ± 8.2	313.8 ± 154.0
Changed (n = 40)	57.5 ± 15.4	38.0 ± 7.3*	7.5 ± 7.3†	291.2 ± 136.6
Unchanged (n = 37)	50.8 ± 15.2	44.9 ± 3.9*	12.9 ± 8.9†	284.6 ± 134.7
Other (n = 25)	50.6 ± 18.5	39.4 ± 8.3	11.3 ± 7.4	375.0 ± 192.7

*$p < 0.01$ from non-BMT group.
†$p < 0.05$.

dyspnea, fatigue, attainment of 85% of the maximal predicted heart rate or the development of ventricular arrhythmias. The LVEF was determined from the gated studies using a count-based approach.

Exercise ejection fraction was considered abnormal if the rest ejection was <65% and the LVEF failed to rise by more than 5% from the resting value during maximum exercise (*23,25*).

Statistical Analysis

Statistical analysis was performed using the unpaired Student's t-test. Data were expressed as mean ± s.d. A p value <0.05 was considered as statistical significance.

RESULTS

Of the 153 patients with resting LVEFs <50%, specific changes in therapy that met the reviewers criteria for inclusion were documented in the medical record in 43 (29%) patients. Of these 43 patients, 24 (57%) had resting LVEFs <40%.

Twenty-five patients who stopped cardiotoxic therapy after radionuclide angiography were excluded from analysis. In 17 patients, the reviewers thought that the change was made for other reasons not related to the ejection fraction result (Table 1). Another eight patients were excluded from further analysis since they were on experimental protocols that did not include cytotoxic chemotherapy.

Therapy was changed in 3 of 51 (6%) patients in the BMT group and 40 of 77 (52%) of the non-BMT group (Table 2). The oncologists' response to minimize further cardiotoxicity in the non-BMT patients included cessation of cardiotoxic drugs (n = 37), dose reduction (n = 1) or a continuous infusion over 48 hr rather than bolus injection (n = 2). The resting LVEF and the LVEF response to exercise in 40 patients whose therapy was changed differed significantly from those with unchanged treatment ($p < 0.01$ and $p < 0.05$, respectively) (Table 2). Patients with lower LVEF values were more likely to have their medication changed than those with near normal values (Table 3). The treatment protocol was changed in 85% (23 of 27) of patients whose LVEF was <40% in the non-BMT group. Diminished left ventricular functional reserve was seen in 17 of 32 (53%) patients who experienced a change in protocol compared to 5 of 26 (19%) patients in whom therapy was not altered (Table 4). All ineligible candidates for BMT had reduced LVEF responses to exercise.

TABLE 4
Difference of EF Value Response to Exercise in the Non-BMT Group

	(Stress-rest) EF ≤ 5	(Stress-rest) EF > 5
Changed (n = 32)	17 (53.1%)	15 (46.9%)
Unchanged (n = 26)	5 (19.2%)	21 (80.8%)

DISCUSSION

The incidence of clinical cardiotoxicity in patients treated with doxorubicin may be reduced by monitoring the cumulative dose received and monitoring LVEF (*3,26*). Criteria were developed that utilize the baseline ejection fraction and reductions in ejection fraction seen on serial studies as indications to discontinue cardiotoxic chemotherapy. Several new anthracycline derivatives with less cardiotoxicity have been developed (*27–29*), and the technique of slow infusion of doxorubicin has been described to reduce cardiotoxicity (*24,30–33*). Furthermore, oncologists seem to have a higher tolerance for minor cardiac impairment, if they believe continued therapy or BMT may offer a cure for the underlying cancer. In our 153 patients, one-third of the radionuclide ejection fraction studies were done in the course of work-up for BMT, 20 were done while patients were treated with other anthracycline derivatives like idarubicin or daunorubicin and 24 were during mitoxantrone therapy.

The incidence and severity of cardiotoxicity is variable (*4,26*), as is the maximal tolerated cumulative dose of doxorubicin (*34*). Several guidelines set the point beyond which further therapy would result in cardiotoxicity. Schwartz et al. (*3*) described guidelines based on LVEF measurements from serial radionuclide angiograms recorded at rest during the course of doxorubicin therapy. A baseline level of resting LVEF less than 50% identified high-risk patients, and it is recommended that doxorubicin should not be administered with baseline LVEF <30%. They also suggested that empiric dose limitations of doxorubicin are unnecessary in patients with baseline LVEFs above 30%. Others, however, suggest cutoffs at higher values of LVEF. Somlo et al. (*35*) recommended a decrease of LVEF below 50% as an important determination. Alexander et al. (*26*) observed that LVEF <30% correlated with irreversible and often fatal clinical congestive heart failure and advocated discontinuation of doxorubicin when LVEF was <45%, in similar fashion to Druck et al. (*36*). Other investigators proposed different lower limits of resting LVEF (*15,23–25*).

This study found that clinical use of radionuclide LVEF seems to vary with the clinical situation. However, patients with resting LVEF <30% were not treated with cardiotoxic agents, in accord with the recommendation of Schwartz. We found that resting LVEF is regarded as a useful tool to evaluate the cardiotoxicity of planned chemotherapy. In the non-BMT group more than one-half (52%) of the therapy protocols were influenced by the resting LVEF result, especially when the resting LVEF was <40% (85%). The resting LVEF and the difference of LVEF response to exercise in 40 changed therapy

TABLE 3
Cumulative Number of Patients in Each Group Using Different Criteria in the Non-BMT Group

	EF (%) cutoff value								
Rx	<50	≤45	<45	≤40	<40	≤35	<35	≤30	<30
Changed (n =)	40	33	32	23	21	14	12	4	3
Unchanged (n =)	37	17	14	4	3	1	1	0	0
Percent changed	52	66	70	85	88	93	92	100	100

patients differed significantly from those without changed therapy ($p < 0.01$ and $p < 0.05$, respectively).

Limited left ventricular functional reserve was also helpful in identifying patients who should limit their cardiotoxic chemotherapy. Compensatory responses are often able to maintain myocardial function in the normal range in spite of myocardial damage until a certain threshold is crossed (*36*). Evidence of cardiac reserve may account for decisions to continue cardiotoxic agents despite LVEFs < 50% in the majority of patients. Due to the difficulty exercising debilitated oncology patients, only 58 of the 77 patients in the non-BMT group had exercise studies. Most of the patients (81%) who increased their LVEF by more than 5% in response to exercise did not have their therapy changed. In patients with resting ejection fractions <50%, this finding suggested that despite impaired baseline function, there is still significant reserve.

Patients in the BMT group were highly selected. For example, the average age and resting LVEF in the BMT group differed significantly from the non-BMT group in this study ($p < 0.01$ and 0.05, respectively). More patients underwent exercise test (98% versus 77%) in BMT group versus non-BMT (Table 3). The LVEF response to exercise and maximal load of exercise of the BMT group is also relatively higher than those of the non-BMT group. In this study, we found the criteria of decision making in these two groups were different. A surprisingly low incidence of cardiac toxicity has been reported for BMT (*15,37,38*). Cardiotoxicity was observed in only 7 of 126 cases (6%) by Bearman et al. (*38*). Hertenstein et al. (*15*) found cardiotoxicity in 8 of 170 patients (5%) after BMT and decided to stop the routine evaluation of myocardial function by radionuclide angiography before BMT in patients without evidence of cardiac disease. They suggest patients with subclinical impairment of cardiac function should not be excluded from BMT. Therefore, diminished cardiac function is not considered an absolute contraindication for BMT unless LVEFs were severely impaired. In the three ineligible BMT patients, one had a resting LVEF of 27% with an increase of LVEF after exercise of less than 5%. The other two patients, even with LVEFs of 43% and 45%, had decreased LVEF responses to exercise. It appears that the resting LVEF <50% was not used in a majority of the patients in the BMT group as a tool to alter therapy. It may be reasonable to lower the LVEF cutoff point in the evaluation of BMT candidates.

CONCLUSION

This study suggests that oncologists use a resting LVEF threshold of about 40% to consider withholding cardiotoxic chemotherapy. In addition, a diminished response to exercise was associated with a higher incidence of changed therapy, suggesting oncologists also consider this information in their decision making. Further study will be required to establish standard criteria for the use of ejection fraction measurements in patients treated with cardiotoxic drugs, especially in this era of safer analogs or modes of administration.

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