Cardiotoxicity of Interferon*  
A Review of 44 Cases  
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Cardiovascular complications have occurred in clinical trials of interferon. We review herein experience to date of cardiotoxicity with all types of interferons in cancer patients. The most common presentations of cardiotoxicity were cardiac arrhythmia, dilated cardiomyopathy, and symptoms of ischemic heart disease, including myocardial infarction and sudden death. The cardiac effects were not related to the daily dose, cumulative total dose, or period of therapy. Some of the patients in whom interferon has caused cardiovascular sequelae have had a history of coronary heart disease or have previously been given chemotherapy with drugs known to be cardiotoxic. In most of the patients, cardiac toxicity was reversible following the cessation of the drug therapy.

Clinical trials with interferon have been carried out in recent years in patients with various malignant diseases, but principally in patients with advanced nontreatable cancer.1 The most common side effect is a flulike syndrome. Various systems have been reported to be affected, including the central nervous, gastrointestinal, hematopoietic, musculoskeletal, and endocrine systems. Skin, adnexa and renal function are also affected. That interferon might be cardiotoxic in humans was first suggested following four deaths due to myocardial infarction in patients treated with that agent. Since that report, there have been a few additional reports concerning the possible cardiotoxic effects of interferon. Different manifestations of interferon-induced cardiotoxicity have been reported in some of the patients and were related to the febrile reaction induced by first exposure to interferon. It was also suggested that cardiovascular complications are superimposed on hearts with limited coronary or myocardial reserve. The purpose of the present report is to review the literature on interferon-related cardiotoxicity, to describe the various manifestations of cardiotoxicity, and to determine the risk factors possibly associated with interferon effects on the heart.

DATA ON REPORTED CASES

There have been 15 reports on 44 patients with interferon-induced cardiotoxicity.4,5,6 Table 1 summarizes the type of toxicity, the daily and cumulative total dose, the period of treatment, and the coexistence of underlying heart disease.

Sex and Age

The sex and the age of 11 patients were reported. There was no correlation between cardiotoxicity and age or sex (Table 1).

Type of Interferon

Most patients with interferon-related cardiotoxicity received recombinant interferon alpha. The subtype recombinant interferon alpha-2 was used by 12 patients. Recombinant interferon gamma was used by eight patients. None of the patients received interferon beta.

Doses and Duration of Treatment

Low daily doses (<9 x 10^6 U/d) of interferon were administered in only seven patients, while ten of the patients were treated with high doses (>35 x 10^6 U/d). The cardiotoxic effect of interferon was not related to the total amount of interferon nor to the duration of treatment. Toxic effects were documented from doses as low as 0.1 x 10^6 U/d and sometimes after a period of only one day. On the other hand, some of the patients did not show signs of toxicity until after a period of treatment of more than six months, with a cumulative dose of 8,400 x 10^6 U, and in one patient after the cumulative dose exceeded 8,400 x 10^6 U (Table 1).

Underlying Heart Disease

At least 12 of the patients had some evidence of preexisting heart disease; a few had known coronary heart disease. However, while in almost all of those with known heart disease the manifestations of interferon-induced cardiotoxicity were either arrhythmia or myocardial infarction, none of the patients with cardiomyopathy induced by interferon had known previous heart disease (Table 1).

Doxorubicin Treatment

Previous as well as concurrent treatment with doxorubicin (Adriamycin) was reported in at least eight of the patients. None of these patients had shown any evidence of cardiotoxic effects during the period of doxorubicin therapy (Table 1).

Manifestations of Toxicity

Table 2 summarizes the various ways in which interferon-induced cardiotoxicity presented. Most of the patients suffered from arrhythmia. Ten suffered a myocardial infarction or sudden death, and cardiomyopathy occurred in five patients. In nine patients the cardiotoxic effect of interferon was the direct cause of their death.4,7 The various manifestations of the cardiotoxicity were not related to the duration of treatment, to the single daily dose, or to the total amount of interferon.

Arrhythmia: Supraventricular and ventricular arrhythmias, which were the most common manifestations of cardiotoxicity, were reported in 25 patients.4,7,9,11,18,34 Most had underlying heart disease. Atrial arrhythmias did not represent life-threatening events. Three patients with supraventricular arrhythmia continued treatment without further arrhythmia while receiving treatment with antiarrhythmic drugs.11 One patient had fatal ventricular fibrillation11 and

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## Table 1—Summary of Reported Cardiotoxicity of Interferon*

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Ref. No.</th>
<th>Sex/Age (yr)</th>
<th>Previous Cardiac Disease</th>
<th>Type of Interferon</th>
<th>Single Interferon Dose (U)</th>
<th>Total Interferon Dose (Period)</th>
<th>Interferon-induced Cardiotoxicity</th>
<th>Comments</th>
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<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>ND</td>
<td>None</td>
<td>NR alpha</td>
<td>$15 \times 10^6$</td>
<td>$75 \times 10^6$</td>
<td>Fatal VF</td>
<td>(1 wk)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>ND</td>
<td>Arrhythmia</td>
<td>R alpha-2</td>
<td>ND</td>
<td>ND</td>
<td>Atrial arrhythmia</td>
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<td>8</td>
<td>ND</td>
<td>None</td>
<td>R alpha</td>
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<td>$(1 \text{ wk})$</td>
<td>VF</td>
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</tr>
<tr>
<td>2</td>
<td>8</td>
<td>ND</td>
<td>None</td>
<td>R alpha</td>
<td>$50 \times 10^6$</td>
<td>$50 \times 10^6$</td>
<td>VPBs</td>
<td></td>
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<td>1</td>
<td>11</td>
<td>F/67</td>
<td>Left axis</td>
<td>R alpha-2</td>
<td>$30 \times 10^6/m^3$</td>
<td>$150 \times 10^6/m^3$</td>
<td>SVT</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>F/67</td>
<td>1°-AVB</td>
<td>R alpha-2</td>
<td>$50 \times 10^6/m^3$</td>
<td>$1000 \times 10^6/m^3$</td>
<td>AF</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>ND</td>
<td>None</td>
<td>R gamma</td>
<td>$0.6-20 \times 10^6/m^3$</td>
<td>ND</td>
<td>AFI and VPBs</td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>ND</td>
<td>1°-AVB</td>
<td>R gamma</td>
<td>ND</td>
<td>ND</td>
<td>AFI</td>
<td></td>
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<tr>
<td>1</td>
<td>16</td>
<td>ND</td>
<td>None</td>
<td>R gamma</td>
<td>$0.1 \times 10^6/m^3$</td>
<td>ND</td>
<td>APBs</td>
<td></td>
</tr>
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<td>F/64</td>
<td>AF</td>
<td>R alpha-2</td>
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<td>$300 \times 10^6/m^3$</td>
<td>AF</td>
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<tr>
<td>1</td>
<td>11</td>
<td>M/71</td>
<td>None</td>
<td>R alpha-2</td>
<td>$10 \times 10^6/m^3$</td>
<td>$60 \times 10^6/m^3$</td>
<td>AF</td>
<td>Doxorubicin</td>
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<tr>
<td>4</td>
<td>2</td>
<td>ND</td>
<td>Alpha</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ISCHEMIA</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>ND</td>
<td>MI</td>
<td>R alpha</td>
<td>ND</td>
<td>ND</td>
<td>Fatal MI</td>
<td></td>
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<tr>
<td>1</td>
<td>6</td>
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<td>IHD</td>
<td>R alpha</td>
<td>$50 \times 10^6/m^3$</td>
<td>$(1 \text{ d})$</td>
<td>Fatal MI</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>ND</td>
<td>AP</td>
<td>R alpha</td>
<td>$50 \times 10^6/m^3$</td>
<td>$50 \times 10^6/m^3$</td>
<td>MI</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>ND</td>
<td>IHD</td>
<td>R alpha-2</td>
<td>$5 \times 10^6/m^3$</td>
<td>$65 \times 10^6/m^3$</td>
<td>MI</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>ND</td>
<td>AP</td>
<td>R gamma</td>
<td>$1 \times 10^6/m^3$</td>
<td>$2 \times 10^6/m^3$</td>
<td>Ischemia</td>
<td></td>
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<tr>
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<td>None</td>
<td>NR alpha</td>
<td>$3 \times 10^6$</td>
<td>$3 \times 10^6$</td>
<td>Cardiac arrest</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>ND</td>
<td>None</td>
<td>R alpha-2</td>
<td>$10 \times 10^6/m^3$</td>
<td>ND</td>
<td>Left heart failure</td>
<td>Concurrent doxorubicin therapy</td>
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<tr>
<td>1</td>
<td>9</td>
<td>ND</td>
<td>LVH</td>
<td>R alpha-2</td>
<td>$1 \times 10^6/m^3$</td>
<td>$6 \times 10^6/m^3$</td>
<td>Sudden death</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>ND</td>
<td>ND</td>
<td>R gamma</td>
<td>ND</td>
<td>ND</td>
<td>1°-AVB</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>M/58</td>
<td>None</td>
<td>R alpha-2</td>
<td>$30 \times 10^6/m^3$</td>
<td>$300 \times 10^6/m^3$</td>
<td>HR 168/m</td>
<td>Doxorubicin</td>
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<td>12</td>
<td>F/62</td>
<td>None</td>
<td>R alpha-2</td>
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<td>$27 \times 10^6$</td>
<td>Cardiomyopathy</td>
<td></td>
</tr>
<tr>
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<td>13</td>
<td>M/42</td>
<td>None</td>
<td>R alpha</td>
<td>$3-35 \times 10^6$</td>
<td>$5,500 \times 10^6/m^3$</td>
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<td>R alpha</td>
<td>$35 \times 10^6$</td>
<td>$2,700 \times 10^6/m^3$</td>
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<td>M/37</td>
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<td>R alpha</td>
<td>$11.8 \times 10^6$</td>
<td>$8,400 \times 10^6/m^3$</td>
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<tr>
<td>1</td>
<td>14</td>
<td>M/74</td>
<td>None</td>
<td>R alpha-2</td>
<td>$3 \times 10^6$</td>
<td>$540 \times 10^6$</td>
<td>Cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>

*Ref = reference; ND = no data; R = recombinant; NR = nonrecombinant; VF = ventricular fibrillation; VPBs = ventricular premature beats; SVT = supraventricular tachycardia; 1°-AVB = 1st-degree atrioventricular block; AF = atrial fibrillation; AFI = atrial flutter; APBs = atrial premature beats; MI = myocardial infarction; AF = angina pectoris; IHD = ischemic heart disease; CHF = congestive heart failure; LVH = left ventricular hypertrophy; HR = heart rate.
another experienced ventricular tachycardia, both without a history of heart disease. The ventricular tachycardia resolved after the dose of interferon was reduced.

Ischemia: Myocardial infarction was reported in eight patients, six of whom died. One additional patient had development of chest pain associated with ST segment elevation on electrocardiogram that was complicated by pulmonary edema. All five patients who were questioned concerning previous heart disease indeed had underlying coronary artery disease. Three of the five experienced the ischemic event within the first two days of interferon therapy. Therapy was restarted in one patient after the single dose was reduced significantly, without further cardiac toxicity.

Cardiomyopathy: The first case of interferon-induced cardiomyopathy was reported in 1988 by Cohen et al. Since then cardiomyopathy has been described in another four patients who were treated with interferon. In four of the five patients, myocardial dysfunction significantly improved after interferon therapy was suspended. All four patients were treated for a relatively long period, but the average daily dose appeared to be high in only one of the four. Two of the patients were retreated with lower doses of interferon but did not demonstrate a change in the ejection fraction during the rechallenge.

**DISCUSSION**

Three different types of cardiovascular sequelae attributed to interferon treatment have been reported: arrhythmia, manifestations of ischemic heart disease, and cardiomyopathy. In most of the cases, the cardiotoxic effect of interferon consisted primarily of arrhythmias. In one study, however, 20 patients receiving recombinant DNA gene interferon were prospectively assessed for cardiac rhythm disturbances; no significant changes in average heart rate and in the frequency of ventricular or supraventricular ectopic beats were documented when comparing monitoring at baseline and during therapy. It seems, therefore, that even arrhythmia is a very uncommon side effect of interferon administration. Moreover, from 15 phase I trials involving a total of 432 patients, most of whom were given recombinant interferon alpha or interferon gamma, and a few interferon beta, no significant cardiotoxic adverse effects of interferon were reported. In some of these studies, however, acute effects of interferon in the cardiovascular system consisted mainly of tachycardia, hypertension, and distal cyanosis. Since these side effects were described during the first exposure to interferon, it was suggested that they were related to the flulike reaction.

Predisposing factors for interferon-related cardiotoxicity are not clear. It appears that in most of the cases, toxicity was not necessarily related to a long period of interferon therapy. Of those on whom data were available, cardiotoxicity occurred in 18 of 24 within five weeks. Similarly, cardiotoxicity occurred in patients receiving low and high daily doses and in patients receiving accumulating doses. Some of the patients died of a cardiac event following the administration of a very low total dose and within one to seven days of initiating the drug treatment. Toxicity was also not related to age. The only possible risk factor for cardiotoxicity was previous cardiac disease, as reported in 12 of the patients. An interesting finding is that none of the patients with toxic cardiomyopathy had known previous heart disease. It seems, therefore, that the presence of underlying heart disease can be considered a risk factor for interferon-induced arrhythmia or ischemic manifestations. The importance of previous or concurrent administration of doxorubicin is also not clear. One might speculate that some of the cases of interferon-induced cardiotoxicity were not reported because the toxicity was ascribed to the administration of doxorubicin. More data on cardiotoxicity in patients receiving treatment with interferon who had been previously treated with doxorubicin might clarify the importance of doxorubicin as a contributing risk factor for interferon-induced cardiotoxicity.

Although some of the adverse effects of the different types of interferon might differ from one another, they are, in general, similar. Most of the patients with interferon-related cardiotoxicity received recombinant interferon alpha or recombinant interferon alpha-2. A few received recombinant interferon gamma, while none received interferon beta. Since a great majority of trials with interferon therapy were carried out with the recombinant alpha type, we have to assume that this is the reason that most reports on interferon-related cardiotoxicity were from patients who had been treated with recombinant interferon alpha.

The various presentations of interferon-related cardiotoxicity as shown in the present review indicate more than one mechanism. The most common dose-limiting toxicity of interferon is a flulike syndrome. Febrile responses are generally noted in all patients and always most severely after the first dose. Increased oxygen demand caused by fever, chills, and tachycardia may therefore precipitate infarction or arrhythmia in compromised myocardium. Another possibility is that interferon induced coronary spasm in these patients. It seems, therefore, that the cardiotoxic effect may be principally due to peripheral vascular effects of interferon which reflexly stress the heart. A different mechanism has to be considered to explain the revers-
Cardiotoxicity of Interferon (Sonnenblick, Roesin)

Cardiotoxicity

Advisable feron by whether rate cause of adenosine decrease fibrosis, myofibrillar immune deficiency the ible rat recent a direct or the decrease in myocardial function. mechanism cardiac or the decrease shown in interferon-induced effect for non-small cell carcinoma of the lung: a phase II trial. J Biol Response Mod 1983; 2:343-47


Different in vitro studies have been carried out to investigate the effect of interferon on cardiac cells. Lampidis and Brouty-Boyé studied steadily pulsating rat cardiac cells in culture that were continuously exposed to rat interferon for 24 h and showed a decrease in the beating rate. Although in that study the mechanism for the action of interferon on cardiac cell function was not investigated, it was thought that adenosine triphosphate (ATP) levels are significantly altered in interferon-treated cells. Another possibility suggested is the interchange shown between the action of interferon and noradrenaline in cultured cells.

The long-standing stimulation of noradrenaline may cause some eventual impairment of myocyte contractile function. However, another in vitro study investigating the effect of interferon on neonatal rat heart myocytes failed to show any adverse effect on beating rate or any reduction in the ATP/protein ratio. It is therefore not clear from the different in vitro studies whether interferon-induced myocardial depression is by a direct effect or is indirectly mediated by changes in functional cellular elements in response to interferon administration.

Since interferon has been introduced principally as antineoplastic therapy and has been administered to patients in a debilitated state, it is possible that some of the cardiovascular sequelae of interferon have been overlooked. From the cases of cardiotoxicity reviewed, one can point to several possible predisposing conditions. Patients with documented or symptomatic heart disease may show aggravation of ischemic symptoms. Therefore, interferon should not be given in the presence of unstable angina. Patients with effort angina or previous ischemic events should be under careful cardiac observation following the first dose of interferon until the cessation of the flulike reaction. It is advisable to commence treatment with small doses and increase them gradually. Arrhythmias, should they occur, must be treated symptomatically, the interferon treatment may be continued, usually without risk. Awareness of the possibility of cardiomyopathy, even in patients without previous cardiac disease, should focus attention on the cardiovascular tolerance of a patient receiving prolonged interferon treatment. If symptoms develop, tests of myocardial function and ejection fraction should be carried out. In older subjects, a routine electrocardiogram should be done before commencing treatment. The present review emphasizes the importance of recognizing the different adverse cardiotoxic consequences of interferon, especially in view of reported evidence of the potential reversibility following the discontinuation of the drug therapy.

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