Freireich’s Laws in the Treatment of Sarcomas

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In his Karnofsky lecture of May 6, 1976, Dr. Emil J Freireich formalized seven of his multiple laws (1). Although this manuscript will not deal with law 7, the Regulators Creed, laws 1–6 are relevant to the treatment of sarcomas (Table 1), and I shall address several areas emphasized by Dr. Freireich in that lecture: optimism, expertise, the importance of dose, and the need for individualized therapy.

The first area is optimism. In his Karnofsky lecture, Dr. Freireich said, “If the clinical investigator is not optimistic in his choice of new treatments for his patients, who in the healthcare system will be?” (1). A recent EORTC study randomized 663 patients between Adriamycin at 75 mg/m², Adriamycin + ifosfamide at 50 mg/m² and 5 g/m², respectively, and a modified CyVADIC regimen with cyclophosphamide 500 mg/m², vincristine 1.5 mg/m², Adriamycin 50 mg/m², and DTIC 750 mg/m² given every 4 weeks (2). The response rate to the Adriamycin combination was 21%, to the ifosfamide/Adriamycin combination 25%, and to the CyVADIC regimen 27%. No significant differences were determined among the groups in response rate or survival, and the authors concluded that “single agent doxorubicin should be regarded as the standard treatment against which to test new developments for most adult patients with advanced soft-tissue sarcomas.” I have heard single-agent Adriamycin referred to by some of the authors as the “gold standard” in the management of soft-tissue sarcomas on several occasions based on this study. How can anyone refer to a drug with a 21% response rate and a median survival of 1 year as a “gold standard”? We need more positive thinking. Studies should be designed to improve our results, not to confirm their inadequacy.

Another of Freireich’s laws, number 5, also deals with optimism. Modified from the Latin translation of a statement attributed to Hippocrates, “Primum non nocere,” or “First, do no harm,” Freireich pointed out in his Karnofsky lecture, “certainly, any lay person is qualified, to ‘do no harm.’ The physician’s admonition must clearly be—do what can possibly be done and perhaps, more important, to do that which is necessary... (1). Dr. Freireich taught us to follow another of Hippocrates’ aphorisms,4 poetically rendered by Shakespeare.5 The importance of this optimistic, aggressive approach is illustrated in the following case history. A 19-year-old man with metastatic synovial sarcoma came to us with approximately two-thirds of his pulmonary parenchyma filled with massive metastases (3). He had seen several putative experts in the treatment of sarcoma at the time of initial diagnosis and was informed that synovial sarcomas rarely respond to chemotherapy. and that he was better off avoiding the toxicity associated with such treatment. Despite borderline performance status due to respiratory difficulty, we treated him with continuous infusion CyADIC chemotherapy and GM-CSF (4), and he had an extraordinary partial response; although his estimated life expectancy was, at most, 2–3 months when we first saw him, he lived for 18 months with minimal symptoms. One can only wonder whether he might have been cured had the therapy been given at an earlier stage of his disease. This case illustrates Freireich Law #9,6 “Responders always live longer than ‘non-responders’ unless they die of toxicity,” and its corollary “If not, you haven’t defined responder correctly.” Although academics may argue about the causal relationship of response and survival, they might benefit from re-reading the landmark paper published by Freireich in 1961 on the effect of chemotherapy on acute leukemia (5). In that paper, Freireich demonstrated for three subsets of patients—children with acute lymphocytic leukemia, adults with acute lymphocytic leukemia, and adults with acute myelogenous leukemia—a profound survival benefit for responding patients. Perhaps more important to understanding the causal relationship of response to survival, he demonstrated equivalent survival of all patients if the time with hematological improvement was subtracted from overall survival in responders. Thus, it was clear that the time given to a patient with improved blood counts, the direct results of a beneficial effect of chemotherapy, was the amount of time that could be expected to be added to that patient’s life. Those who have reported the effect of response on survival in patients with solid tumors have not performed this type of analysis, a possible reason for some of the controversy. I shall return to this issue in the treatment of osteosarcoma later in this manuscript.

The second area emphasized by Freireich was the requirement of true expertise in the management of any patient. In his

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3 The abbreviations used are: EORTC, European Organization for Research and Treatment of Cancer; DTIC, dacarbazine; GM-CSF, granulocyte-macrophage colony-stimulating factor; MAID, mesna, Adriamycin, ifosfamide, and DTIC; CyADIC, cyclophosphamide, Adriamycin, and DTIC; CyVADIC, CyADIC plus vincristine.
4 The usual translation of this aphorism is, “For extreme illnesses extreme measures are most fitting.”
5 W. Shakespeare, act IV, scene iii, line 9, from Hamlet: “Diseases desperate grown by desperate appliance are relieved, or not at all.”
6 Previously unpublished.
7 It should be noted that except in the Karnofsky Lecture, Dr. Freireich was not consistent in the numbering of his laws. Number 9 one day might turn out to be number 37 the next. The numbering of laws other than 1–7, therefore, is not precise.
Karnofsky lecture, he said, “There is frequently greater variability in results between cooperating institutions than there is between the treatments being compared. Isn’t it likely that there is ... a qualitative and quantitative difference between the excellence of care, of adherence to protocol, of knowledge and experience, between institutions, which ... are as much responsible for the differences observed as are the treatments being compared?” (1). Certainly, this statement applies to the management of sarcomas! Experts in sarcoma chemotherapy have known since the publication of Gottlieb in 1975 that patients with gastrointestinal leiomyosarcoma do not respond well to Adriamycin-based chemotherapy (6). The inclusion of a large number of patients with gastrointestinal leiomyosarcomas in cooperative group studies may account, in part, for the lower response rates seen in such studies compared with single institutions or other cooperative groups with more expertise in this regard.

Another area in which the expertise becomes critical is the assessment of response (3). Patients with sarcomas may have what appears to be a good partial response on X-ray, which turns out to be a complete response after pathological examination of the resected tumor area. More importantly, patients with no apparent response or even disease progression in the face of chemotherapy, whose tumors become necrotic, may have demonstrated a major response. Usually, such tumors decrease somewhat in size (but often not sufficiently to qualify for the traditional definition of partial response), but sometimes there may be no change or even progression! We use pathological confirmation to determine response, in analogy with the approach used in osteosarcoma (7). For example, a patient with a tumor that increased by approximately 25% but became essentially necrotic on chemotherapy was found to have less than 1% viable tumor when the tumor was resected. The patient continues alive and well, free of disease and off chemotherapy after resection and continued adjuvant chemotherapy, and should certainly be considered a responder! We have, on rare occasions, seen response without radiographic evidence of necrosis but where the resected tumor was purely a fibrous mass with no residual neoplastic cells. The take-home messages are that unless there is clear-cut progression of disease without increased necrosis, the patient may be responding, and therapy should not be stopped without pathological confirmation to the contrary! If such responding patients were treated by physicians with less expertise in the diseases being treated, they might be taken off effective therapy as “nonresponders” and allowed to progress and die.

A corollary to Freireich’s Law #2 is Freireich’s Law #17, "Don’t let toxicity interfere with success. Figure out a way to avoid it.” Viewed from this perspective, the previously quoted Hippocratic aphorism can be translated as “The worst toxicity is progressive cancer” (3). After all, most patients when asked whether they would rather die of progressive cancer or drug toxicity choose “None of the above,” but most whom I have asked will take whichever pathway has the lowest expected death rate, regardless of the cause.

Dr. Freireich has followed his law #17 throughout his career. The use of platelet transfusions for thrombocytopenic hemorrhage, the use of empiric antibiotics for sepsis in neutropenic patients, and the development of protected environments are a few examples in the area of leukemia. For sarcomas, it was Dr. Freireich’s influence along these lines that got us to develop the continuous infusion of Adriamycin to reduce cardiac toxicity. After one of our meetings in 1978, Dr. Freireich came to me and said, “Benjamin, you’re supposed to know more about Adriamycin than anyone else. Why haven’t you eliminated cardiac toxicity?” This discussion stimulated our initial efforts into decreasing cardiac toxicity by prolonged continuous infusion of Adriamycin and the development of the continuous CyADIC regimen for sarcomas (4, 8–16). We demonstrated equivalent antitumor effects with decreased cardiac toxicity using continuous infusion, and other sarcoma programs since that time, including the popular MAID regimen, have used the continuous infusion approach (17–21). Our studies have indicated that, within the range of rapid administration to 96-h infusion, the longer the infusion, the less the cardiac toxicity (9, 11–14, 22–24). At the same time, we have demonstrated that the minimum infusion duration required for substantial cardiac protection is 48 h. With rapid-infusion Adriamycin, the incidence of heart failure exceeds 5% at doses just above 400 mg/m2 in our own studies and in several other studies. In contrast, 96-h Adriamycin infusion can be given to cumulative doses just above 800 mg/m2 with similar cardiac effects. Furthermore, the degree of cardiac damage actually appears to be less by endomyocardial biopsy when patients are treated by infusion as compared with bolus Adriamycin. Newer developments with the use of dexrazoxane in combination with rapid-infusion or bolus Adriamycin appear to give at least equivalent results to 96-h infusion Adriamycin in terms of cardiac protection (22, 24–29).

Another area emphasized by Dr. Freireich is the importance of dose in cancer treatment, and nowhere is the dose-response relationship more apparent than in the treatment of sarcomas. Freireich’s Law #12, another corollary to Freireich’s Law #2, states, “More is better.” When I first came to Dr. Freireich’s department in 1974, a frequently quoted dictum was “Double the dose and shorten the interval.” Finally, in the era of growth factors and stem cell support, 20 years later, this approach can now be realized! In 1974, the first Phase II dose-response study of a chemotherapeutic agent was published for Adriamycin by O’Bryan and colleagues for the Southwest On-
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cology Group (30). That study demonstrated that for patients with sarcomas, considered good risk, the response rate doubled from approximately 18 to 38%, when the dose of Adriamycin was increased from 45 to 75 mg/m². In a series of studies with ifosfamide, we demonstrated a doubling of response rate from 6 to 10 g/m² and almost another doubling when the dose was further increased to 14 g/m² (31). The ifosfamide doses had to be given by short infusion for this relationship to hold true. Both at the 8-g/m² level and the 14-g/m² level, response rates were substantially lower when the drug was given by continuous infusion (31-33).

The dose-response relationship led to a series of studies starting in 1987 in collaboration with Dr. Saroj Vadhan-Raj using growth factors to increase the dose intensity of chemotherapy for soft-tissue sarcomas (4, 15, 21, 34). Our initial study used GM-CSF with the continuous infusion CyADIC regimen (4). We found that the 96-h Adriamycin infusion caused a delay in growth factor administration such that complete protection from neutropenia was not possible; however, shortening the duration of infusion to 48-h with resulting earlier growth factor administration allowed us to reduce neutropenia, decrease mucositis, and allow dose intensification of the chemotherapy program. Unfortunately, when drug doses were not decreased for neutropenia, cumulative thrombocytopenia became dose-limiting toxicity. In a series of studies, we demonstrated reduction in thrombocytopenia with PIXY 321 with the CyADIC regimen (15, 21, 34). The response rate to the CyADIC chemotherapy program, 31%, however, was suboptimal (Table 2); therefore, we tried the more intensive and more active MAID regimen (21). Unfortunately, PIXY 321 was not able to negate the thrombocytopenia associated with MAID, and extramedullary toxicity manifested by severe fatigue and mucositis required us to reduce the dose of ifosfamide. Even then, the regimen was not well tolerated, and although the response rate was higher than seen with CyADIC, it was only 52% (Table 2).

Our first study with GM-CSF plus CyADIC could not be evaluated for response because the criteria for entry on that study required evidence of response to CyADIC (or use as adjuvant chemotherapy) plus documented prior neutropenia <500/μl. Further evidence for a dose-response curve for the MAID regimen is provided in Table 3, which compares a number of variations of the MAID regimen in different publications. Our data (21) are similar to the Cancer and Leukemia Group B data published by Elias et al. (19) and the original pilot data from Elias and Antman (18). All of the above regimens used doses of 6-7.5 gm/m² of ifosfamide and 60 mg/m² of Adriamycin. In contrast, the study of Bramwell et al. (35) using 50 mg/m² of Adriamycin and 5 gm/m² of ifosfamide had only about one-half the response rate. The outlying study is the intergroup study chaired by Antman et al. (17) where, despite similar doses to those used in the initial studies, the overall response rate was only 32%.

Table 2 shows the response rate to two-drug Adriamycin/ifosfamide combinations in a series of studies. The initial EORTC study using 5 g/m² of ifosfamide and 50 mg/m² of Adriamycin showed only a 25% response rate (2). The intensified study from the EORTC increased Adriamycin dose to 75 mg/m² and the response rate to 45% (36). The Eastern Cooperative Oncology Group study using 7.5 g/m² of ifosfamide and 60 mg/m² of Adriamycin had a 34% response rate (37). Based on these data, we initiated two pilot studies of patients treated with 10 g/m² of ifosfamide and Adriamycin at 75-90 mg/m². Thus far, we have treated 49 patients with a response rate of 67% (38). Although there is clearly substantial room for improvement, these are our best results to date. Furthermore, subjective tolerance of the intensive Adriamycin-ifosfamide regimen is superior to that which we saw with MAID chemotherapy. Dose-limiting toxicity, however, remains cumulative thrombocytopenia, and we have presently initiated a study using thrombopoietin to ameliorate this toxicity.

Freireich’s Law #4, the statistician’s creed, indicates that the best therapeutic research gives the best results. In his Karnofsky lecture, he pointed out the “good is bad, bad is good” principle (1). An illustration of this principle is shown in Fig. 1; a study of 37 patients with osteosarcoma with a 56% 5-year continuous disease-free survival might be criticized as bad science because it used a historical control (39, 40). If 37 patients had been randomized to receive chemotherapy and 31 had been randomized not to receive chemotherapy, then those randomized to receive chemotherapy would have the 56% 5-year continuous disease-free survival and the others a 10% 5-year continuous disease-free survival; this might be called by some good science.

### Table 2: PIXY 321 + CyADIC/MAID in sarcoma

<table>
<thead>
<tr>
<th></th>
<th>CyADIC</th>
<th>MAID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (%)</td>
<td>No. of patients (%)</td>
</tr>
<tr>
<td>Evaluable patients</td>
<td>62</td>
<td>31</td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Partial response</td>
<td>19 (31)</td>
<td>15 (48)</td>
</tr>
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</table>

### Table 3: MAID regimens

<table>
<thead>
<tr>
<th>Dose/Schedule</th>
<th>Ref.</th>
<th>No. of patients</th>
<th>CR%</th>
<th>PR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifex,* 7.5 g/m² bolus over 5 days</td>
<td>(18)</td>
<td>20</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Adria, 60-75 mg/m² CI over 5 days</td>
<td>DTIC, 900 mg/m² CI over 5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifex, 7.5 g/m² CI 72 h</td>
<td>(19)</td>
<td>105</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Adria, 60 mg/m² CI 72 h</td>
<td>DTIC, 900 mg/m² CI 72 h (marked toxicity requiring dose reduction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifex, 6-7.5 g/m² bolus over 3 days</td>
<td>(21)</td>
<td>31</td>
<td>3</td>
<td>48</td>
</tr>
<tr>
<td>Adria, 60 mg/m² CI over 2 days</td>
<td>DTIC, 900 mg/m² CI over 2 days (marked toxicity requiring dose reduction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifex, 6-7.5 g/m² bolus over 3 days</td>
<td>(45)</td>
<td>170</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>Adria, 60 mg/m² CI over 3 days</td>
<td>DTIC, 1000 mg/m² CI over 3 days (marked toxicity requiring dose reduction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifex, 5 g/m² CI 24 h</td>
<td>(35)</td>
<td>40</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Adria, 50 mg/m² bolus</td>
<td>DTIC, 850 mg/m² bolus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ifex, ifosphamide; Adria, Adriamycin; CI, continuous infusion.
The overall 5-year continuous disease-free survival of the patients on that study, however, would be about 35%; clearly a bad result compared with the 56% 5-year continuous disease-free survival rate if the study were performed using a historical control; thus, according to Freireich's Law #4, it would have been bad science.

Because of the controversy surrounding the varied results with initial adjuvant chemotherapy programs for osteosarcoma and the retrospective analysis from the Mayo Clinic suggesting that the natural history of the disease had improved during the 1970s unrelated to the use of chemotherapy, many investigators felt compelled to demonstrate whether chemotherapy was helpful in the management of patients with osteosarcoma, and a multi-institutional randomized trial was performed. That study, published in the New England Journal of Medicine, thus presumably good science, indicated that patients randomized not to receive adjuvant chemotherapy for osteosarcoma had a 17% 2-year disease-free survival compared with 66% for patients treated with chemotherapy (41). The differences were statistically significant, and the study was of tremendous importance because it definitively laid to rest questions in the academic oncological community regarding the use of adjuvant chemotherapy for osteosarcoma; however, it is an example of the "good is bad, bad is good" phenomenon, and it would not have passed muster according to Freireich's Law #4. The authors concluded that the "beneficial effects on relapse-free survival attributed to adjuvant chemotherapy in previous uncontrolled trials are likely to be real" (41). Some of Dr. Freireich's comments from his 1976 Karnofsky lecture are again relevant. "Some have confined the term 'controlled' to studies which have the characteristics of prospective, randomized, and concurrent studies and frequently refer to other types of investigations as 'uncontrolled.'" One might reasonably conclude from the multi-institutional osteosarcoma study that historical controls in osteosarcoma are, indeed, valid, and that the "uncontrolled" studies referred to were actually well controlled, albeit without concurrent, randomized controls.

The controversies that surrounded the treatment of osteosarcoma in the 1980s led a large number of physicians to omit the use of chemotherapy in the treatment of primary osteosarcoma because they were not convinced of its benefit. The most notable example was the highly publicized Canadian patient, Terry Fox. He undertook a journey walking across Canada on his crutches to raise money for research because he had been
told by his physicians that it was not clear that chemotherapy was of any benefit while it was certainly associated with terrible toxic side effects. What was the major cause of death for patients with osteosarcoma in the 1980s? Misguided physicians. The medical profession must, in my opinion, accept responsibility for the fact that our failure to use logic in developing better treatment strategies for these patients resulted in a number of unnecessary deaths. I am not referring to the few patients randomized not to receive chemotherapy but rather to those who were not offered chemotherapy or to those like Terry Fox, where it was offered without recommendation or enthusiasm because we, the medical profession, required the results of a randomized trial before we would believe them. After all, given that osteosarcoma is likely to be a systemic disease in at least 50% of patients (based on the Mayo Clinic data; Ref. 42) and as many as 80–90% of patients (based on other institutions’ data; Ref. 43), how can one hope to improve the cure rate by withholding systemic chemotherapy? Granted, the results of treatment were inadequate, and not all investigators have been able to obtain 70–90% cure rates in these patients, but the road to improvement must be through finding better chemotherapy, not by withholding it.

The Multi-Institutional Osteosarcoma Study (41) did demonstrate, conclusively, that chemotherapy had a role in the treatment of primary osteosarcoma, and thus, saved the lives of many patients from whom chemotherapy would previously have been withheld. It changed the practice of medicine, while sacrificing the lives of only a few patients on the study. One can only hope that we will be able to devise study designs that are equally convincing without sacrificing a single patient. One potential approach is the individualization of therapy as illustrated below.

Dr. Freireich frequently pointed out the need to separate observations in single patients from those in groups of patients. In his Karnofsky lecture, he stated, “Differences between average patients are often minor, while significant improvement is observed in a smaller fraction of patients... We always need to be alert to identify the characteristics of those patients that do respond favorably” (1). Implied in these remarks is a call for individualization of therapy: identify the subset of patients who will respond favorably to a given treatment, and give them that treatment. This approach is best exemplified by the strategy of neoadjuvant chemotherapy. In the early 1980s, we treated a group of patients with osteosarcoma of the extremities with preoperative administration of 90 mg/m² Adriamycin as a 96-h i.v. infusion followed by 120 mg/m² cisplatin as a 2-h intraarterial infusion (8, 39, 40, 44). Postoperatively, patients continued the same therapy until neurotoxicity required discontinuation of cisplatin, at which time we substituted DTIC. We examined a number of pretreatment prognostic factors; however, the single most important factor, at least three logs more powerful than all pretreatment prognostic factors combined, was the response to chemotherapy in terms of the extent of tumor necrosis noted at the time of surgery (8, 39). Patients with <90% tumor necrosis had 10-year survival of 80%, whereas those with <90% necrosis had only 20% 10-year survival. The comparison was performed using landmark analysis, measuring survival from the time of surgery, to eliminate any inherent bias in comparing responding and nonresponding patients (Fig. 2). Furthermore, to determine that we had not merely selected patients with intrinsically good prognosis as responders and those with intrinsically poor prognosis as poor responders, we compared relapse-free survival of patients with <90% tumor necrosis to a historical control series of patients treated with surgery only (Fig. 3). The survival curves of the later two groups were superimposable, showing that only patients whose primary tumors were almost totally destroyed by preoperative chemotherapy had a survival benefit with that particular chemotherapy regimen. This approach is completely analogous to the one used by Dr. Freireich in 1961, noted earlier in this report (5). Clearly, if a substantial subset of the patients treated (approximately 50%) benefit from Adriamycin/cisplatin chemotherapy but a substantial proportion do not benefit, different chemotherapy is required for those who do not respond adequately. This approach, to me, is the essence of the neoadjuvant strategy: changing postoperative adjuvant chemotherapy in patients judged to have an inadequate response to preoperative chemotherapy. For osteosarcoma, we have demonstrated that patients with <90% tumor necrosis following initial Adriamycin/cisplatin chemotherapy benefit from the addition of high-dose methotrexate and ifosfamide in postoperative therapy and that individualizing chemotherapy based on the response to preoperative therapy can
improve the prognosis of poor responders from that of untreated controls to that of patients with good response to induction chemotherapy (44).

This report is an attempt to demonstrate how Dr. Freireich's teachings of 20 years ago have influenced our work in the treatment of sarcomas. Many of his teachings are more relevant today than they were 20 years ago because of advances in supportive care. The availability of potent broad spectrum antibiotics, hemopoietic growth factors, and stem cell support allow us to take advantage of the steep dose-response curve of sarcomas to chemotherapy. Unfortunately, the limited number of active chemotherapeutic agents severely restricts the successful application of current chemotherapy in the treatment of sarcomas. We must only hope that further understanding of these diseases on a molecular level will provide new insight as to appropriate targets for chemotherapy or alternative strategies in the management of these tumors in the years to come.

References


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