

CCOP Report Card

Dr. Enck's report card for CCOP in the Fall 1987 issue of the Journal of Cancer Program Management, was an interesting collection of subjective impressions, many of which were quite perceptive. Unfortunately, he did not have the advantage of the elaborate CCOP evaluation undertaken by the Statistical Analysis and Quality Control Center, Fred Hutchinson Cancer Center, through a National Cancer Institute (NCI)-funded contract. The results have not yet been published, although many of the findings have been discussed in multiple settings. From my perspective, I would like to add a few subjective bottom-line impressions as a supplement to Dr. Enck's report card.

Overall, the CCOP has been a successful program as measured by accrual of patients to NCI National Cancer Research Clinical Trials. In addition, it may claim some credit, especially through its widely criticized "log," for pointing out some deficiencies in the clinical trials program, including (1) the relative dearth of patients over the age of 65 (14 percent) when at least half of cancer patients are in that age bracket; (2) the number of patients with common diseases for whom there are no studies; and (3) the number of clinically eligible patients who do not go on study (about 70 percent).

While the log indicates that about half of clinically eligible patients do not go on protocol as a result of physician decision-making, the causes are not detailed and require further evaluation, especially if NCI hopes to attract a large number of new community physicians to participate in high-priority protocols.

In addition to NCI's current recognition of the need for faster answers to major clinical questions through the accrual of more patients to priority studies, CCOP physicians who work with more than one research base have been asking for standardized toxicity and response definitions, as well as simplified requirements and forms. Many community physicians have pushed for the use of personal computers to reduce data burdens and to enhance data quality. These areas are now receiving attention. CCOPs have taken the lead in showing that it is possible to relate year two and year three budgets to accrual. This experience helps to justify the NCI's hope of attracting physicians who are not now in the system by offering to underwrite extra data costs for each patient entered in a high-priority protocol.

As Dr. Enck suggested, the lack of influence of CCOP physicians on other physi-

cians in community hospitals is unfortunate. All too often, numerical accrual successes are the result of a few dedicated physicians and their nurse data managers, while support from many non-CCOP community oncologists is often absent.

More work is needed to make clinical research part of community practice. Some CCOP physicians have shown that this is possible. The results of such research also need to be translated into state-of-the-art care. It is important to understand the factors that foster diffusion and to develop interventions to capitalize on that information. We need better ways to measure quality as well as quantity, especially in matters of diffusion, if we are to improve the transfer and application of basic research knowledge to community cancer practice.

The addition of cancer control research should be welcomed by the community for several reasons. First, it concerns items of specific interest to community physicians, including research in supportive care, which is the major activity of most medical oncologists. Second, by adding prevention and early detection, CCOP oncologists are encouraged to communicate with primary care physicians and to involve community resources in the effort to make cancer control a community project. CCOP II has become a stimulant to the entire NCI clinical trials program by including cancer control in its program. Well-established NCI clinical resources have become involved in research in prevention, screening, supportive care, and rehabilitation, as well as treatment studies. The alternative would be to invite less clinically-oriented investigators to lead the effort to reduce cancer mortality by 50 percent (the goal for the year 2000), because it has been predicted that most of that reduction will come from prevention and early detection.

In criticizing NCI leadership, community physicians should remember that they too live in glass houses. Dr. Moertel, in the same issue of JCPM, pointed out the difficulties Dr. DeVita had to overcome to get the program started. In addition, without the leadership of Dr. Jerry Yates and the support of Dr. Peter Greenwald, it would have been difficult for CCOP I to succeed.

Few community oncologists have been willing to accept the overhead costs of data management as part of their practice. However, many are finding ways to continue to be active in NCI clinical trials without funding. We need to understand what motivates those community oncologists to persist and persevere in clinical research

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5 mg and 25 mg tablets

Before prescribing WELLCOVORIN® Tablets, please consult complete prescribing information. The following is a brief summary.

INDICATIONS AND USAGE: Wellcovorin (leucovorin calcium) is indicated for the prophylaxis and treatment of undesired hematopoietic effects of folic acid antagonists (see WARNINGS).

CONTRAINDICATIONS: Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B₁₂. A hematologic remission may occur while neurologic manifestations remain progressive.

WARNINGS: In the treatment of accidental overdosage of folic acid antagonists, leucovorin should be administered as promptly as possible. As the time interval between antifolate administration (e.g. methotrexate) and leucovorin rescue increases, leucovorin's effectiveness in counteracting hematologic toxicity diminishes.

PRECAUTIONS:

General: Following chemotherapy with folic acid antagonists, parenteral administration of leucovorin is preferable to oral dosing if there is a possibility that the patient may vomit and not absorb the leucovorin. In the presence of pernicious anemia a hematologic remission may occur while neurologic manifestations remain progressive. Leucovorin has no effect on other toxicities of methotrexate, such as the nephrotoxicity resulting from drug precipitation in the kidney.

Drug Interactions: Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Wellcovorin. It is also not known whether Wellcovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Wellcovorin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Wellcovorin is administered to a nursing mother.

Pediatric Use: See "Drug Interactions."

ADVERSE REACTIONS: Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

OVERDOSAGE: Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.

DOSAGE AND ADMINISTRATION: Leucovorin is a specific antidote for the hematopoietic toxicity of methotrexate and other strong inhibitors of the enzyme dihydrofolate reductase. Leucovorin rescue must begin within 24 hours of antifolate administration. A conventional leucovorin rescue dosage schedule is 10 mg/m² orally or parenterally followed by 10 mg/m² orally every six hours for seventy-two hours. If, however, at 24 hours following methotrexate administration the serum creatinine is 50% or greater than the pre-methotrexate serum creatinine, the leucovorin dose should be immediately increased to 100 mg/m² every three hours until the serum methotrexate level is below 5 x 10⁻⁶M.^{1,2}

The recommended dose of leucovorin to counteract hematologic toxicity from folic acid antagonists with less affinity for mammalian dihydrofolate reductase than methotrexate (i.e. trimethoprim, pyrimethamine) is substantially less and 5 to 15 mg of leucovorin per day has been recommended by some investigators.^{3,4,5}

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the interpretation of the data," Kennedy says, because it is not "standard practice" to treat those patients with chemotherapy. Nevertheless, Kennedy estimates that the "GAO data probably comprises 50 percent of stage I patients." There is "no rational conclusion but that the GAO looked at the data [under this category] improperly," he says.

GAO on small-cell lung cancer: Twenty-five percent of small-cell lung cancer patients were not receiving treatment in 1985.

Kennedy: Because of the higher age group of small-cell lung cancer patients and other medical conditions, such as cardiovascular disease, which enter into treatment decisions, "75 percent of patients receiving adjuvant therapy is a good percentage," Kennedy says.

GAO on non-Hodkins lymphoma: The number of eligible, untreated non-Hodgkin's lymphoma patients declined 10 percent from 1979 to 1985, but one-

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studies. Are they the ones who recognize the value of such involvement as a means of providing quality care? Are those who prefer to develop their own studies, or insist that only they know the right answers for their patients, providing state-of-the-art care? How many understand that 408 patients with small-cell carcinoma of the lung who are studied on a single protocol are more likely to provide helpful answers than the same number of patients managed on 16 different routines? (See Dr. Rodger Winn's article in the same issue.)

When the reasons for success and failure are more fully understood, both graduate and post graduate medical education will be impacted, as well as clinical trials and, indirectly, cancer care. Only then will the legacy of the CCOPs be appreciated and a more complete report card be possible.—*R. W. Frelick, M.D., Wilmington, DE.* ■

fifth of eligible patients remained untreated.

Kennedy: If 80 percent of patients with diffuse, intermediate or high-grade lymphomas are receiving therapy, "in other words, 4 out of 5 patients," that's a good result, Kennedy contends. Moreover, these types of lymphomas "can be managed on an outpatient basis, and you find that more and more of the patients who are being hospitalized are only those who are very ill, which again raises other treatment factors, such as overall health, age, and the patient's treatment wishes."

GAO on Hodgkin's disease: At least 18 percent of eligible patients with advanced Hodgkin's disease did not receive chemotherapy in any year following 1977.

Kennedy: Once again, Kennedy says, the GAO study doesn't mention "age, noncompliance, and other medical conditions." Nevertheless, he points out that if 80 percent of patients were being given chemotherapy by 1985, "we are doing well. Even if medical care was absolutely free, 100 percent of the population would not take advantage of it." Another disadvantage of the GAO report, according to Kennedy, is that "it does not include conclusions of the most recent reports."

Perhaps the most important caveat raised with regard to the GAO study is the historical under-reporting of chemotherapy treatment (as high as 25 percent of all patients) in hospital



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tumor registry data, because of limited follow-up of the therapy patients receive as outpatients or in physicians' offices. This is a data collection problem that NCI itself is investigating and which has prompted it to examine such options as pursuing active follow-up on every patient or even ceasing to collect any SEER data on chemotherapy treatment. And, it is a problem that is expected to grow worse as the number of alternate delivery systems, such as ambulatory surgery clinics, which do not have the same reporting requirements as hospitals, increase in number. In short, Kennedy says, "if we are to have adequate data on neoplasms, we need a better system than one that depends only on hospital records." ■