

WELLCOVORIN® TABLETS (leucovorin calcium)

Leucovorin in convenient
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 $5 \times 10^{-8}M$.^{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}

1. Bleyer WA: The Clinical Pharmacology of Methotrexate. *Cancer*, 41(1):36-51, 1978.
2. Frei E, Blum RH, Pitman SW, et al: High Dose Methotrexate with Leucovorin Rescue: Rational and Spectrum of Antitumor Activity. *Am J Med*, 68:370-376, 1980.
3. Golde DW, Bersch N, Quan SG: Trimethoprim and Sulpha-methoxazole Inhibition of Haematopoesis in Vitro. *Br J Haematol*, 40(3): 363-367, 1978.
4. Steinberg SE, Campbell CL, Rabinovitch PS, et al: The Effect of Trimethoprim/Sulfamethoxazole on Friend Erythroleukemia Cells. *Blood*, 55(3): 501-504, 1980.
5. Mahmoud AAF and Warren KS: Algorithms in the Diagnosis and Management of Exotic Disease. XX Toxoplasmosis. *J Infect Dis*. 135(3): 493-496, 1977.

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ONCOLOGY DRG RESEARCH PRODUCES KEY FINDINGS FOR CANCER PROGRAM MANAGERS AND POLICY MAKERS

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The broad scale DRG research studies undertaken by ACCC over the past two and a half years have produced important findings that should continue to impact reimbursement policies and the decisions of cancer program managers. Several of the studies reported in this issue of *The Journal of Cancer Program Management* provide us with new data about the potential negative effects of prospective payment and capitated payment on cancer programs.

"...capitation without severity adjustment could significantly impact the ability of sophisticated cancer programs to deliver quality care."

In their analysis of cancer patient severity of illness in hospitals with and without cancer programs, Drs. Susan Horn and Phoebe Sharkey of the Johns Hopkins Center for Hospital Finance and Management, report several major findings that may impact on the ability of cancer programs to deliver high quality care. Horn's most central finding is that university and community hospitals see patients that are more severely ill, and, as she concludes:

"...prospective payment based on fixed DRG payments could be very inequitable to these and other institutions that attract the more severely ill patients. Prospective payment programs should identify costs directly attributed to patients' severity of illness, the long term consequences of not doing so could include closure of specialty treatment centers, refusal to admit certain patients, or reduction in quality of care."

These problems have already been demonstrated with the leukemia DRGs.

Hospitals did refuse to treat leukemia patients, or suggested that these patients be referred to other facilities, given the significant losses generated. While ACCC research data has had a significant impact on the leukemia DRGs, problems still exist with chemotherapy reimbursement, and others will continue to emerge. Indeed, Horn's study suggests that capitated oncology will do major damage to programs that attempt to regularly manage patients with advanced disease and difficult management problems. Essentially, capitation without severity adjustment could significantly impact the ability of sophisticated cancer programs to deliver quality care.

Perhaps the other major finding is the disparity between the current DRGs and severity-adjusted DRGs in explaining resource utilization for cancer patients. Horn's data note that DRGs alone account for only 15.2% of the variation in cost per case, while DRGs that have

been adjusted by severity of illness and procedure-adjusted explain 58.4% of the cost per case variation. Clearly, sophisticated cancer programs are already paying a penalty for advanced cancer patient management.

ACCC DRG Research: Winners and Losers

Over the past two and a half years, ACCC member institutions have provided funding and data on oncology DRGs. These investments have had substantial returns for sponsors and oncology programs in general. Specifically, DRG research sponsors have been able to obtain detailed information on cancer DRGs through two monographs (the second is to be released this month). These monographs contain excellent data on discharges, charges, reimbursement, costs (when available), and charges to reimbursement, and costs to reimbursement ratios. The best performances of contributing institutions have been analyzed, allowing sponsors to compare their data to other similar institutions. These investments have also allowed us to sponsor other research efforts, such as the data described in this issue.

Data from all of the studies was vital in putting forth hard evidence of the major deficits experienced by cancer programs as they tried to manage leukemia patients under the DRG system. Our evidence, provided to ProPAC and other government agencies, led to the recent DHHS decision to recalibrate leukemia reimbursements.

Defining the Oncology Product Line

All three of the articles in this issue of *The Journal of Cancer Program Management* describe the oncology DRGs and, as you read them, you will recognize differences in definitions from previous publications, and also some disparities that require further research. In our original ACCC research projects, we defined 70 DRGs by reviewing each DRG for ICD-9-CM codes that indicated malignancy or procedures that could be considered part of the cancer program product line.

To assure that there was no

confusion in Horn's analysis, we agreed with Horn's suggestion that her analysis be based on only those 40 "pure" cancer DRGs that are indisputably the core of cancer program activities. Data by Mortenson and Baum indicate that these 40 DRGs account for 80% of all primary cancer DRG discharges.

The proper definition of the oncology program product line is larger than either of these groupings, however, since cancer patients are admitted under a wide variety of diagnoses throughout the course of their treatment. Research by Lion and Malbon and by Mortenson and Baum begins to define this broader set of DRGs. Data from the Massachusetts Rate Setting Commission and the CHOP-DS system both indicate a far wider range of DRGs (over 200) under which cancer patients are discharged. These include diagnoses, like pneumonia, which may or may not have cancer listed as a secondary diagnosis. While some only rarely occur, the total composite picture of oncology program resource utilization and income cannot be understood if these DRGs are not included in the analysis.

As cancer program administrators begin to fine tune their program management activities, it is clear that data gathering will need to be done by tracing the cancer patient through multiple DRGs, rather than by just specifying 40 or 70 key DRGs. For example, as a hospital attempts to determine the impact of lung cancer patients on its bottom line, it will need to include information on DRGs 82 and 410 (lung cancer and chemotherapy) and also a proportion of its DRG 89 discharges (pneumonia with complications) and several other related DRGs.

Our initial findings in site-specific DRG research are reported in detail in the second ACCC DRG monograph.

The Implications of ACCC DRG Research Activities

Given that there are different approaches to studying cancer DRGs represented by these three papers, what is important and what are the major caveats we must consider?

Of these three articles, Horn's is the most provocative, and it has the most significant long term implications for cancer programs. Her strong case for severity-

adjusted DRGs points out that sophisticated cancer programs are using more resources because they see sicker patients and, thus, are experiencing smaller margins or larger losses. Under the capitated system proposed by some Administration officials, there would be no severity-adjustment. This could easily result in significant incentives to dump programs and program components, and to discourage certain kinds of patients and care delivery in facilities.

The Massachusetts data utilized in the Lion and Malbon article is from 1983, and, thus demonstrates a situation prior to the implementation of DRGs as a reimbursement mechanism in the State (Massachusetts was a waived State until recently). Obviously, it cannot reflect the anomalies now being created by PRO standards, which are keeping people out of hospitals and pushing more discharges into lower weighted DRGs (such as 410). Nonetheless, it gives us a good picture of the potential disparities in types of cancer patients seen at various kinds of institutions and of the range of cancer DRGs within the cancer program product line.

Finally, the Mortenson and Baum article gives us more validating information on winners, losers, and the growing problem with chemotherapy reimbursement.

All of these studies expand our understanding of cancer program management. The research also makes us acutely aware of the major changes that reimbursement will continue to make on how we can deliver care. ■