CMS-1429-FC-001

Submitter: Dr. Wei Fang
Date & Time: 11/24/2004
Organization: Saint Agnes Medical Center
Category: Physician
Issue Areas/Comments GENERAL

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year

To Whom It May Concern: One of the major advances in recent years is application of flow cytometry (FCM) in medicine. In the past ten years of medical practice, FCM has been proven to be essential in diagnosing complex medical conditions such as lymphomas and leukemias, especially acute leukemias in children. The following are my thoughts in response to the recently proposed changes of reimbursement for flow cytometry. 1. It is impractical, and often proven to be wrong to limit FCM panels for the following reasons:

a. FCM is most frequently used in phenotyping hematopoietic progenitors in the bone marrow in clinical conditions such as anemias, or cytopenias of unknown etiology. These account for at least two thirds of bone marrow biopsies in our practice. Since there are four major lineages in the marrow, anything wrong with any of the lineage may lead to the clinical conditions described above. Therefore, comprehensive phenotyping of four major lineages simultaneously is essential to figure out abnormalities in the bone marrow. My experience is that a panel composed of 31 markers or more is optimal for this purpose. This FCM configuration is currently widely used in major medical centers such as Johns Hopkins, Barnes-Jewish Hospital in St. Louis, UCLA as well as commercial labs including US Labs, Impath, etc.

b. The rest of cases where FCM is widely used are in the diagnosis of lymphoma in various tissues including lymph node, bone marrow, and other tissue sources. For adequate lymphoma work up, a panel composed of minimally 21 markers is essential.

c. Not infrequently, the specimens are limited in quantity. It is optimal to perform an adequate FCM panel in the first place since subsequent additional markers may use more tissue which is often proven to be impossible. Furthermore, additional markers are often performed the next day, tissue viability is a major issue which may hinder optimal staining and correct interpretation. d. Acute leukemias and some of lymphomas are of medical emergencies. These often need at least 24 or 31 marker panels. Inadequate panels may delay, even miss the diagnosis, therefore timely treatment. 2. The recently proposed changes in reimbursement, especially the professional component of FCM, do not justify the intellectual output. To be proficient at interpreting FCM data, one needs at least five years of general pathology training plus one more year of fellowship training in hematopathology. I have trainings in both general pathology and hematopathology. In addition, five years of Ph.D. training and one additional year of postdoctoral fellowship in immunology are extremely helpful to me in interpreting FCM data. 3. Poor reimbursement will make it difficult to invest in FCM, thus hinders further improvement of this technology. In

CMS-1429-FC-002

Submitter: Ms. Laurie Davis
Date & Time: 12/01/2004
Organization: Brain and NeuroSpine CLinic PC
Category: Physician
Issue Areas/Comments Issues HPSA Zip Code Areas

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

In the Cape Girardeau(63703) and surrounding 50-100 mile radius there are only 5 neurosurgeons providing care to and accepting new Medicare patients on a regular basis, to the best of my knowledge. Our group of three surgeons is among the 5. This area, including the surrounding counties and including southern Illinois, has a shortage of Neurosurgeons to provide service to the large number of Medicare patients. I believe an exception should be made to allow additional payment based on the shortage of service providers in this specialty. The additional allowance may influence other providers in this area to accept more Medicare recipients and possibly offload the demand of the few whom are taking new Medicare patients.

Thank you for your time.

summary, the recently proposed changes in billing for flow cytometry are short sighted, not medically.

Attathment:

To Whom It May Concern:

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3. Poor reimbursement will make it difficult to invest in FCM, thus hinders further improvement of this

technology.

In summary, the recently proposed changes in billing for flow cytometry are short sighted, not medically and scientifically justified.

Sincerely,

Wei Fang, MD, Ph.D.
Pathologist
Saint Agnes Medical Center
Fresno, CA 93720
Phone: 559-450-3130,
Fax: 559-450-2035

CMS-1429-FC-003

Submitter: Dr. Phillip Ruiz
Date & Time: 12/02/2004
Organization : University of Miami
Category : Physician
Issue Areas/Comments GENERAL/Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

Center for Medicare and Medicaid Services Dept. of Health and Human Services ATTN: CMS-1429-FC PO Box 8012 Baltimore, MD 21244-8012 I am writing this email to you to express my grave concern over the severe decrease in reimbursement for professional flow cytometry services proposed by CMS. As a immunopathologist and flow cytometrist I participate in the treatment of treating patients with malignancies, along the hematologist-oncologist. Flow cytometry is REQUIRED in order to adequately diagnose and treat these patients. Many of the major advances in the success of treating patients with leukemia and lymphoma over the last twenty years have been predicated on this diagnostic modality. If a cut in reimbursement were to result in decreased availability of flow cytometry services, our patients would be severely and adversely impacted. This should not be allowed to happen. This is a crucial diagnostic/prognostic pathology professional service.

Sincerely,
Phillip Ruiz, M.D., Ph.D.
Professor of Pathology and Surgery
Director, Immunopathology"

CMS-1429-FC-004

Submitter: Dr. William Finn
Date & Time: 12/06/2004
Organization: University of Michigan
Category : Physician
Issue Areas/Comments: GENERAL

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

I would like to voice my very strong concern over the recent changes to professional reimbursement for flow cytometry services. Since flow cytometry is not a high profile service in the eyes of the lay public, it is easy to underestimate the contribution of flow cytometry to the care of patients. However, flow cytometry has emerged as an essential technology for the diagnosis of leukemia and lymphoma, and now stands on par with more established services (such as histologic interpretation) that are much more generously reimbursed by Medicare. Indeed, current classifications of leukemia and lymphoma require flow cytometric analysis for the appropriate diagnosis and classification of certain disorders, making flow cytometry not an esoteric but a fundamental service. Furthermore, the interpretation of flow cytometric data in the diagnosis of leukemia and lymphoma is a complex medical interpretive task that can consume considerable amounts of professional time and energy. I do not think it is an exaggeration to say that the new reimbursement schedule will cause many laboratories to fail to break even when it comes to the cost of running and maintaining professional flow cytometry services. I urge you to readdress this issue, and to devise a fairer system of technical and professional reimbursement.

CMS-1429-FC-005

Submitter: Tami Hoffman
Date & Time: 12/06/2004
Organization: Advanced Care Systems
Category: Individual
Issue Areas/Comments GENERAL

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

My comments are regarding Section 303 of the MMA Act, 1429FC also addressed the ASP pricing for Drugs funished in a providers office. One of my main concerns is that when CMS figures the ASP pricing for a multi-source drug quality of the product is not considered. There are some products on the market that quality, when given in large doses, is a major concern. An example is Immune Globulin - J1563. This product has 6 or more manufacturers. Each product has a differnt quality - As Neurologists we can not infuse a low quality product. We infuse, on average 90 grams of this product a month in a patient with CIDP. We must watch sucrose, IGa level and how the procduct is processed. Main concern is the sucrose level, if it is high we could risk renal failure in a pateint. THe estimate we have gotten from CMS is that this product will be reimbursed at $38.03 a unit - the cheapest We can get a quality product with low sucrose is $52 a unit. If we continue to treat with this product we will lose $1300 per patient per month, we can not do this. If we use a lesser quality product the patient could have renal failure. If we discontinue treatment, the patient will become bedridden/wheelchair bound and have a very poor quality of life. Since this product will so greatly effect quality of care and life value, we ask CMS to reconsider this products ASP pricing and/or create a separate code based on product and quality. If ASP is not changed on this product, the providers options will be - lose $1300 per patient per month (which financially can not be done), discontinue treatment - which will effect quality of care and quality of life, or treat with a lesser qaulity product and risk renal failure not an option. It is not the intent of CMS nor the MMA act to create this situation, so we are asking CMS to change this situation before patient care is effected.

Thank you

CMS-1429-FC-006

Submitter: Dr. Cherie Dunphy
Date & Time:12/06/2004
Organization: University of North Carolina
Category : Physician
Issue Areas/Comments GENERAL

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

December 6, 2004 Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry Re.: CMS-1429-FC Dear CMS, This message is to express my serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally hematopathologists, must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. We are aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, we are concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, we believe that the final assigned value for compensation is not reasonable. Flow cytometry has been growing at a very rapid pace and has been responsible for major advances in the diagnosis, prognosis and treatment of patients with serious and life threatening diseases, including virtually all bone marrow and lymphoid cancers. As in all other developed countries, no patient with leukemia in the US is treated and monitored without the diagnostic support provided by flow cytometry. With flow cytometry, many patients who once needed surgical procedures to excise large amounts of tissue can now have diagnoses rendered on small biopsies from non- invasive, and far less expensive procedures. The radical cuts in reimbursement for flow cytometric services will result in decreased availability of this essential diagnostic modality. Numerous academic, independent and hospital-based laboratories currently involved in diagnostic flow cytometry are considering discontinuing these activities in 2005 and those that carry on will be forced to reduce the quality of their services in ways not necessarily apparent to the oncologists who are dependent on them. I urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients. Sincerely, Cherie H. Dunphy, M.D. Associate Professor of Pathology and Laboratory Medicine

Director of Hematopathology and Hematopathology Fellowship Associate Director, Special Procedures and Flow Cytometry Laboratories Associate Director, Core Laboratory CB#7525 University of North

CMS-1429-FC-007

Submitter: Dr. leonel Edwards
Date & Time: 12/06/2004
Organization: Danbury Hospital
Category: Physician
Issue Areas/Comments GENERAL

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

November 30, 2004 Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry Re.: CMS-1429-FC Dear CMS, This message is to express my serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally pathologists or subspecialists like hematopathologists must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. We are aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, we are concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, we believe that the final assigned value for compensation is not reasonable. Flow cytometry has been growing at a very rapid pace and has been responsible for major advances in the diagnosis, prognosis and treatment of patients with serious and life threatening diseases, including virtually all bone marrow and lymphoid cancers. As in all other developed countries, no patient with leukemia in the US is treated and monitored without the diagnostic support provided by flow cytometry. With flow cytometry, many patients who once needed surgical procedures to excise large amounts of tissue can now have diagnoses rendered on small biopsies from non- invasive, and far less expensive procedures. The radical cuts in reimbursement for flow cytometric services will result in decreased availability of this essential diagnostic modality. Numerous academic, independent and hospital-based laboratories currently involved in diagnostic flow cytometry are considering discontinuing these activities in 2005 and those that carry on will be forced to reduce the quality of their services in ways not necessarily apparent to the oncologists who are dependent on them. I urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients.

Sincerely, Leonel W. Edwards, MD. Assistant Medical Director Clinical Laboratory
Department of Pathology and Laboratory Medicine
Danbury Hospital 24 hospital avenue Danbury CT 06810 2037977527

CMS-1429-FC-008

Submitter: Dr. Steven Sieber
Date & Time: 12/06/2004
Organization: Danbury Hospital
Category: Physician
Issue Areas/Comments GENERAL
Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

December 6, 2004 Center for Medicare and Medicaid Services Dept. of Health and Human Services ATTN: CMS-1429-FC PO Box 8012 Baltimore, MD 21244-8012 Re.: CMS-1429-FC Dear CMS, This message is to express my serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally pathologists or subspecialists like hematopathologists must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. We are aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, we are concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, we believe that the final assigned value for compensation is not reasonable. Flow cytometry has been growing at a very rapid pace and has been responsible for major advances in the diagnosis, prognosis and treatment of patients with serious and life threatening diseases, including virtually all bone marrow and lymphoid cancers. As in all other developed countries, no patient with leukemia in the US is treated and monitored without the diagnostic support provided by flow cytometry. With flow cytometry, many patients who once needed surgical procedures to excise large amounts of tissue can now have diagnoses rendered on small biopsies from non- invasive, and far less expensive procedures. The radical cuts in reimbursement for flow cytometric services will result in decreased availability of this essential diagnostic modality. Numerous academic, independent and hospital-based laboratories currently involved in diagnostic flow cytometry are considering discontinuing these activities in 2005 and those that carry on will be forced to reduce the quality of their services in ways not necessarily apparent to the oncologists who are dependent on them.

I urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients.

Sincerely,

Steven C. Sieber, M.D.
Attending Pathologist Department of Pathology and Laboratory Medicine

CMS-1429-FC-009
November 23, 2004

Centers for Medicare & Medicaid Services
Department of Health and Human Services
P.O. Box 8012
Baltimore, MD 21244-8012
Provisions Related to the Medicare Modernization Act of 2003; Section 303 – Payment for Outpatient Drugs and Biologicals; Drug Administration Policy and Coding Effective in 2005

Dear Madam or Sir:

Pharmion Corporation submits these comments in response to Section III.E.2 of the final rule with comment period published on November 15, 2004 regarding revisions to payment policies under the Physician Fee Schedule for 2005 (CMS-1429-FC).1 Pharmion requests that CMS include the subcutaneous administration of cytotoxic anti-neoplastic agents as part of the demonstration project for improved quality of care for cancer patients undergoing chemotherapy.

Pharmion is a global pharmaceutical company that is dedicated to the hematology and oncology communities. Pharmion currently is developing scientifically differentiated hematology and oncology products in order to expand therapeutic options and improve access to essential medicines. Pharmion distributes the drug Vidaza® (azacitidine for injectable suspension), which is the first approved effective treatment for patients with a collection of bone marrow disorders known as Myelodysplastic Syndrome (MDS).

A. CMS Demonstration Project for Improved Quality of Care for Cancer Patients Undergoing Chemotherapy

In the final rule with comment period regarding the 2005 Physician Fee Schedule, CMS announced that it would be initiating an important one-year demonstration project to improve the quality of care for cancer patients undergoing chemotherapy.2 We agree with CMS that this demonstration project will provide incentives for economy, while maintaining or improving quality in the provision of health services. Pharmion shares CMS's goal of improving patient outcomes by developing objective data on managing pain, minimizing nausea and vomiting, and limiting fatigue.

According to the Physician Fee Schedule final rule, participating practitioners will report data to Medicare on three factors associated with the administration of chemotherapy in the office setting: nausea and/or vomiting; pain; and lack of energy.3 To receive the additional payment for reporting this data, practitioners will enter three new G-codes in conjunction with each chemotherapy encounter. CMS has established a total of 12 new G-codes to describe patient status after each encounter.4

For purposes of the demonstration project, CMS has defined each patient encounter as a day when chemotherapy is administered through intravenous infusion or push.5 For the reasons discussed below,

Pharmion requests that CMS include in this definition non-hormonal chemotherapy injections, in order to assure that data relating to the care of MDS patients treated with Vidaza® is collected under the demonstration.

B. Administration of Vidaza®

Vidaza® has been approved by FDA for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.6 MDS is a collection of disorders in which the bone marrow does not function normally and not enough normal blood cells are made. It is estimated that 15,000 to 20,000 new cases of MDS are diagnosed each year in the United States. Although MDS can occur in all age groups, the highest prevalence is in people over 60 years of age. Typical symptoms include weakness, fatigue, infections, easy bruising, pallor, bleeding, and fever.

Vidaza® was approved by FDA as an orphan drug, and after review of information submitted by Pharmion, CMS recently added Vidaza® (HCPCS code C9218) to its list of single indication orphan drugs eligible for separate payment under the Hospital Outpatient Prospective Payment System (OPPS).7 The FDA-approved labeling for Vidaza® states that it is a cytotoxic anti-neoplastic agent that is administered subcutaneously.8 Thus, under the 2005 Physician Fee Schedule final rule, the drug administration code for Vidaza® would be G0355 for chemotherapy administration, subcutaneous or intramuscular, non-hormonal anti-neoplastic.9

C. Subcutaneous Administration of Non-hormonal Anti-neoplastic Agents Such as Vidaza® Should be Reported as a Patient Encounter Under the Medicare Demonstration Project for Improved Quality of Care for Cancer Patients Undergoing Chemotherapy

Reporting subcutaneous injection as a patient encounter would be entirely consistent with the stated goal of the demonstration project. The purpose of the project is to improve patient care by assessing the levels of pain, nausea and/or vomiting, and fatigue experienced by chemotherapy patients. Patients who receive Vidaza® through a chemotherapy injection will experience precisely the events that the demonstration project seeks to assess. The most commonly occurring adverse reactions to subcutaneous administration of Vidaza® are: nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, fatigue, injection site erythema, constipation, neutropenia, and ecchymosis.10 To improve patient care most effectively, CMS needs comprehensive assessments of patients experiencing these reactions.

Accordingly, Pharmion respectfully requests that administration code G0355 for chemotherapy administration, subcutaneous or intramuscular, non-hormonal anti-neoplastic, be added to the physician reporting codes for the demonstration project for improved care for patients undergoing chemotherapy. Should you have any questions about Vidaza® or this request, please contact Linnea Tanner, Director of Regulatory Affairs, by telephone at 720.564.9106, by fax at 720.564.9191, or by e-mail at

ltanner@pharmion.com.

Sincerely,
/s/
John A. Walker
Director, National Accounts

Attachment

Version: 08-31-04

Vidaza™
(azacitidine for injectable suspension) Rx only

For subcutaneous use only

DESCRIPTION
Vidaza™ (azacitidine for injectable suspension) contains azacitidine, which is a pyrimidine nucleoside analog of cytidine. Azacitidine is 4-amino-1-?-D-ribofuranosyl-s-triazin-2(1H)-one. The structural formula is as follows:

The empirical formula is C8H12N4O5. The molecular weight is 244. Azacitidine is a white to off-white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

The finished product is supplied in a sterile form for reconstitution and subcutaneous injection only. Vials of Vidaza contain 100 mg of azacitidine and 100 mg mannitol as a sterile lyophilized powder.

CLINICAL PHARMACOLOGY
Mechanism of Action

Vidaza is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Non proliferating cells are relatively insensitive to Vidaza.

Pharmacokinetics

The pharmacokinetics of azacitidine were studied in six MDS patients following a single 75 mg/m2 subcutaneous (SC) dose and a single 75 mg/m2 intravenous (IV) dose. Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over three days. Mean excretion of radioactivity in urine following SC administration of 14C-azacitidine was 50%. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after IV and SC administrations, about 4 hours.

Special Populations

The effects of renal or hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied (see CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

Drug interaction studies with azacitidine have not been conducted.

An in vitro study of azacitidine incubation in human liver fractions indicated that azacitidine may be metabolized by the liver. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied.

The potential of azacitidine to inhibit cytochrome P450 (CYP) enzymes is not known.

In vitro studies with human cultured hepatocytes indicate that azacitidine at concentrations of 1.0 µM to 100 µM does not induce CYP 1A2, 2C19, or 3A4/5.

II.

CLINICAL STUDIES

A randomized, open-label, controlled trial carried out in 53 U.S. sites compared the safety and efficacy of subcutaneous Vidaza plus supportive care with supportive care alone (“observation”) in patients with any of the five FAB subtypes of myelodysplastic syndromes (MDS): refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL). RA and RARS patients were included if they met one or more of the following criteria: required packed RBC transfusions; had platelet counts ? 50.0 x 109/L; required platelet transfusions; or were neutropenic (ANC < 1.0 x 109/L) with infections requiring treatment with antibiotics. Patients with acute myelogenous leukemia (AML) were not intended to be

included. Baseline patient and disease characteristics are summarized in Table 1; the 2 groups were similar.

Vidaza was administered at a subcutaneous dose of 75 mg/m2 daily for seven days every four weeks. The dose was increased to 100 mg/m2 if no beneficial effect was seen after two treatment cycles. The dose was decreased and/or delayed based on hematologic response or evidence of renal toxicity. Patients in the observation arm were allowed by protocol to cross over to Vidaza if they had increases in bone marrow blasts, decreases in hemoglobin, increases in red cell transfusion requirements, or decreases in platelets, or if they required a platelet transfusion or developed a clinical infection requiring treatment with antibiotics. For purposes of assessing efficacy, the primary endpoint was response rate (as defined in Table 2).

Of the 191 patients included in the study, independent review (adjudicated diagnosis) found that 19 had the diagnosis of AML at baseline. These patients were excluded from the primary analysis of response rate, although they were included in an intent-to-treat (ITT) analysis of all patients randomized. Approximately 55% of the patients randomized to observation crossed over to receive Vidaza treatment.

Table 1. Baseline Demographics and Disease Characteristics

	Vidaza (N=99)	Observation (N=92)
Gender (n%)		
Male	72 (72.7)	60 (65.2)
Female	27 (27.3)	32 (34.8)
Race (n%)		
White	93 (93.9)	85 (92.4)
Black	1 (1.0)	1 (1.1)
Hispanic	3 (3.0)	5 (5.4)
Asian/Oriental	2 (2.0)	1 (1.1)
Age (years)		

N
99
91
Mean ± SD
67.3 ± 10.39
68.0 ± 10.23
Range
31 - 92
35 - 88
Adjudicated MDS diagnosis at study entry (n%)
RA
21 (21.2)
18 (19.6)
RARS
6 (6.1)
5 (5.4)
RAEB
38 (38.4)
39 (42.4)
RAEB-T
16 (16.2)
14 (15.2)
CMMoL
8 (8.1)
7 (7.6)
AML
10 (10.1)
9 (9.8)
Transfusion product used in 3 months before study entry (n%)
Any transfusion product
70 (70.7)
59 (64.1)
Blood cells, packed human
66 (66.7)
55 (59.8)
Platelets, human blood
15 (15.2)
12 (13.0)
Hetastarch
0(0.0)
1(1.1)
Plasma protein fraction
1(1.0)

0(0.0)
Other
2(2.0)
2(2.2)
Table 2. Response Criteria
RA
RARS
RAEB
RAEB-T
CMMoL
Complete
Response
(CR), duration ? 4 weeks
Marrow
< 5% blasts
Peripheral
Blood
Normal CBC if abnormal at baseline
Absence of blasts in the peripheral circulation
Partial
Response
(PR), duration ? 4 weeks
Marrow
No marrow requirements
? 50% decrease in blasts
Improvement of marrow dyspoiesis
Peripheral
Blood
? 50% restoration in the deficit from normal levels of baseline white cells, hemoglobin and platelets if abnormal at baseline
No blasts in the peripheral circulation
For CMMoL, if WBC is elevated at baseline, a ? 75% reduction in the excess count over the upper limit of normal

The overall response rate (CR +PR) of 15.7% in Vidaza-treated patients without AML (16.2% for all Vidaza randomized patients including AML) was statistically significantly higher than the response rate of 0% in the observation group ($p<0.0001$) (Table 3). The majority of patients who achieved either CR or PR had either 2 or 3 cell line abnormalities at baseline (79%; 11/14) and had elevated bone marrow blasts or were transfusion dependent at baseline. Patients responding to Vidaza had a decrease in bone marrow blasts percentage, or an increase in platelets, hemoglobin or WBC. Greater than 90% of the responders initially demonstrated these changes by the 5th treatment cycle. All patients who had been transfusion dependent became transfusion independent during PR or CR. The mean and median duration of clinical response of PR or better was estimated as 512 and 330 days, respectively; 75% of the

responding patients were still in PR or better at completion of treatment. Response occurred in all MDS subtypes as well as in patients with adjudicated baseline diagnosis of AML.

Table 3. Response Rates
Vidaza
(N=89)
Observation Before Crossover
(N=83)
Response
n (%)
N (%)
P value
Overall (CR+PR)
14 (15.7)
0 (0.0)
(<0.0001)
Complete (CR)
5 (5.6)
0 (0.0)
(0.06)
Partial (PR)
9 (10.1)
0 (0.0)
--

Patients in the observation group who crossed over to receive Vidaza treatment (47 patients) had a response rate of 12.8%.

A multi-center, open-label, single-arm study of 72 patients with RAEB, RAEB-T, CMMoL, or AML was also carried out. Treatment with subcutaneous Vidaza resulted in a response rate (CR + PR) of 13.9%, using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 810 and 430 days, respectively; 80% of the responding patients were still in PR or better at the time of completion of study involvement. In another open-label, single-arm study of 48 patients with RAEB, RAEB-T, or AML, treatment with intravenous Vidaza resulted in a response rate of 18.8%, again using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 389 and 281 days, respectively; 67% of the responding patients were still in PR or better at the time of completion of treatment. Response occurred in all MDS subtypes as well as in patients with adjudicated baseline diagnosis of AML in both of these studies. Vidaza dosage regimens in these 2 studies were similar to the regimen used in the controlled study.

Benefit was seen in patients who did not meet the criteria for PR or better, but were considered “improved.” About 24% of Vidaza-treated patients were considered improved, and about 2/3 of those

lost transfusion dependence. In the observation group, only 5/83 patients met criteria for improvement; none lost transfusion dependence. In all three studies, about 19% of patients met criteria for improvement with a median duration of 195 days.

Response rate estimates were similar regardless of age or gender.

INDICATIONS AND USAGE

Vidaza is indicated for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.

CONTRAINDICATIONS

Vidaza is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol. Vidaza is also contraindicated in patients with advanced malignant hepatic tumors. (See PRECAUTIONS).

WARNINGS

Pregnancy - Teratogenic Effects: Pregnancy Category D

Vidaza may cause fetal harm when administered to a pregnant woman. Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single IP (intraperitoneal) injection of 6 mg/m2 (approximately 8% of the recommended human daily dose on a mg/m2 basis) azacitidine on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15 at doses of ~3-12 mg/m2 (approximately 4%-16% the recommended human daily dose on a mg/m2 basis).

In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4-8 (postimplantation) at a dose of 6 mg/m2 (approximately 8% of the recommended human daily dose on a mg/m2 basis), although treatment in the preimplantation period (on gestation days 1-3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single IP dose of 3 to 12 mg/m2 (approximately 8% the recommended human daily dose on a mg/m2 basis) given on gestation day 9, 10, 11 or 12. In this study azacitidine caused fetal death when administered at 3-12 mg/m2 on gestation days 9 and 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

There are no adequate and well-controlled studies in pregnant women using Vidaza. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be

apprised of the potential hazard to the fetus.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Vidaza.

Use in Males

Men should be advised to not father a child while receiving treatment with Vidaza. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility for discussion of pre-mating effects of azacitidine exposure on male fertility and embryonic viability.)

PRECAUTIONS

General

Treatment with Vidaza is associated with neutropenia and thrombocytopenia. Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be reduced or delayed based on nadir counts and hematologic response as described in DOSAGE AND ADMINISTRATION.

Safety and effectiveness of Vidaza in patients with MDS and hepatic or renal impairment have not been studied as these patients were excluded from the clinical trials.

Because azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors (See CONTRAINDICATIONS).

Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported rarely in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for non-MDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, the dosage should be reduced or held as described in DOSAGE AND ADMINISTRATION.

Patients with renal impairment should be closely monitored for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys (see DOSAGE AND ADMINISTRATION section).

Information for Patients

Patients should inform their physician about any underlying liver or renal disease.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Vidaza.

Men should be advised to not father a child while receiving treatment with Vidaza.

Laboratory Tests

Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each cycle. Liver chemistries and serum creatinine should be obtained prior to initiation of therapy.

Drug Interactions

No formal assessments of drug-drug interactions between Vidaza and other agents have been conducted. (See CLINICAL PHARMACOLOGY.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg (6.6 mg/m2, approximately 8% the recommended human daily dose on a mg/m2 basis) administered IP three times per week for 52 weeks. An increased incidence of tumors in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine IP at 2.0 mg/kg (6.0 mg/m2, approximately 8% the recommended human daily dose on a mg/m2 basis) once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 15 or 60 mg/m2 (approximately 20-80% the recommended human daily dose on a mg/m2 basis) revealed an increased incidence of testicular tumors compared with controls.

The mutagenic and clastogenic potential of azacitidine was tested in in vitro bacterial systems Salmonella typhimurium strains TA100 and several strains of trpE8, Escherichia coli strains WP14 Pro, WP3103P, WP3104P, and CC103; in in vitro forward gene mutation assay in mouse lymphoma cells and human lymphoblast cells; and in an in vitro micronucleus assay in mouse L5178Y lymphoma cells and Syrian hamster embryo cells. Azacitidine was mutagenic in bacterial and mammalian cell systems. The clastogenic effect of azacitidine was shown by the induction of micronuclei in L5178Y mouse cells and Syrian hamster embryo cells.

Administration of azacitidine to male mice at 9.9 mg/m2 (approximately 9% the recommended human daily dose on a mg/m2 basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats three times per week for 11 or 16 weeks at doses of 15 to 30 mg/m2 (approximately 20-40%, the recommended human daily dose on a mg/m2 basis) resulted in decreased

weight of the testes and epididymides, and decreased sperm counts accompanied by decreased pregnancy rates and increased loss of embryos in mated females. In a related study, male rats treated for 16 weeks at 24 mg/m2 resulted in an increase in abnormal embryos in mated females when examined on day 2 of gestation. See WARNINGS.

Pregnancy

Teratogenic Effects: Pregnancy Category D. See WARNINGS section.

Nursing Mothers

It is not known whether azacitidine or its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for azacitidine in animal studies and the potential for serious adverse reactions, women treated with azacitidine should not nurse.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients in the three clinical studies described in CLINICAL STUDIES, above, 62 percent were 65 years and older and 21 percent were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In addition there were no relevant differences in the frequency of adverse events observed in patients 65 years and older compared to younger patients.

Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION section).

ADVERSE REACTIONS

Overview

Adverse Reactions Described in Other Labeling Sections: neutropenia, thrombocytopenia, elevated serum creatinine, renal failure, renal tubular acidosis, hypokalemia, hepatic coma.

Most Commonly Occurring Adverse Reactions (SC Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, fatigue, injection site erythema, constipation, neutropenia, ecchymosis.

Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (SC Route):
Discontinuation: leukopenia (5.0%), thrombocytopenia (3.6%), neutropenia (2.7%).
Dose Held: leukopenia (4.5%), neutropenia (4.5%), febrile neutropenia (2.7%).
Dose Reduced: leukopenia (4.5%), neutropenia (4.1%), thrombocytopenia (3.2%).

Discussion of Adverse Reactions Information

The data described below reflect exposure to Vidaza in 268 patients, including 116 exposed for 6 cycles (approximately 6 months) or more and 60 exposed for greater than 12 cycles (approximately one year). Vidaza was studied primarily in supportive care-controlled and uncontrolled trials (n= 150 and n=118, respectively). The population in the subcutaneous studies (n = 220) was 23 to 92 years old (mean 66.4 years), 68% male, and 94% white, and had MDS or AML. The population in the IV study (n = 48) was 35 to 81 years old (mean 63.1 years), 65% male, and 100% white. Most patients received average daily doses between 50 and 100 mg/m2.

The following table presents the most common adverse events, whether or not considered drug related by investigators, occurring in at least 5% of patients treated with Vidaza in the supportive care-controlled trial and the uncontrolled subcutaneous trial combined. It is important to note that duration of exposure was longer for the Vidaza-treated group than for the observation group: patients received Vidaza for a mean of 11.4 months while mean time in the observation arm was 6.1 months.

Table 4: Most Frequently Observed Adverse Events (? 5% in All Vidaza)*

Preferred Term**	All Vidaza‡ (N=220)	Observation† (N=92)
At least 1 TEAE	219 (99.5)	89 (96.7)
Nausea	155 (70.5)	16 (17.4)
Anemia	153 (69.5)	59 (64.1)
Thrombocytopenia	144 (65.5)	42 (45.7)
Vomiting	119 (54.1)	5 (5.4)

Pyrexia
114 (51.8)
28 (30.4)
Leukopenia
106 (48.2)
27 (29.3)
Diarrhea
80 (36.4)
13 (14.1)
Fatigue
79 (35.9)
23 (25.0)
Injection site erythema
77 (35.0)
0
Constipation
74 (33.6)
6 (6.5)
Neutropenia
71 (32.3)
10 (10.9)
Ecchymosis
67 (30.5)
14 (15.2)
Cough
65 (29.5)
14 (15.2)
Dyspnea
64 (29.1)
11 (12.0)
Weakness
64 (29.1)
19 (20.7)
Rigors
56 (25.5)
10 (10.9)
Petechiae
52 (23.6)
8 (8.7)
Injection site pain
50 (22.7)
0
Arthralgia

49 (22.3)
3 (3.3)
Headache
48 (21.8)
10 (10.9)
Anorexia
45 (20.5)
6 (6.5)
Pain in limb
44 (20.0)
5 (5.4)
Pharyngitis
44 (20.0)
7 (7.6)
Back pain
41 (18.6)
7 (7.6)
Contusion
41 (18.6)
9 (9.8)
Dizziness
41 (18.6)
5 (5.4)
Edema peripheral
41 (18.6)
10 (10.9)
Erythema
37 (16.8)
4 (4.3)
Chest pain
36 (16.4)
5 (5.4)
Epistaxis
36 (16.4)
9 (9.8)
Febrile neutropenia
36 (16.4)
4 (4.3)
Myalgia
35 (15.9)
2 (2.2)
Weight decreased
35 (15.9)

10 (10.9)
Abdominal pain
34 (15.5)
12 (13.0)
Pallor
34 (15.5)
7 (7.6)
Nasopharyngitis
32 (14.5)
3 (3.3)
Pitting edema
32 (14.5)
9 (9.8)
Skin lesion
32 (14.5)
8 (8.7)
Dyspnea exertional
31 (14.1)
15 (16.3)
Injection site bruising
31 (14.1)
0
Rash
31 (14.1)
9 (9.8)
Injection site reaction
30 (13.6)
0
Anxiety
29 (13.2)
3 (3.3)
Appetite decreased
28 (12.7)
8 (8.7)
Fatigue aggravated
28 (12.7)
4 (4.3)
Hypokalemia
28 (12.7)
12 (13.0)
Upper respiratory tract infection
28 (12.7)
4 (4.3)

Pruritus
27 (12.3)
11 (12.0)
Abdominal tenderness
26 (11.8)
1 (1.1)
Depression
26 (11.8)
7 (7.6)
Productive cough
25 (11.4)
4 (4.3)
Insomnia
24 (10.9)
4 (4.3)
Malaise
24 (10.9)
1 (1.1)
Pain
24 (10.9)
3 (3.3)
Pneumonia
24 (10.9)
5 (5.4)
Abdominal pain upper
23 (10.5)
3 (3.3)
Crackles lung
23 (10.5)
8 (8.7)
Sweating increased
23 (10.5)
2 (2.2)
Cardiac murmur
22 (10.0)
8 (8.7)
Rhinorrhea
22 (10.0)
2 (2.2)
Gingival bleeding
21 (9.5)
4 (4.3)
Lymphadenopathy

21 (9.5)
3 (3.3)
Herpes simplex
20 (9.1)
5 (5.4)
Hematoma
19 (8.6)
0
Night sweats
19 (8.6)
3 (3.3)
Rales
19 (8.6)
8 (8.7)
Tachycardia
19 (8.6)
6 (6.5)
Wheezing
19 (8.6)
2 (2.2)
Cellulitis
18 (8.2)
4 (4.3)
Dysuria
18 (8.2)
2 (2.2)
Breath sounds decreased
17 (7.7)
1 (1.1)
Lethargy
17 (7.7)
2 (2.2)
Oral mucosal petechiae
17 (7.7)
3 (3.3)
Stomatitis
17 (7.7)
0
Urinary tract infection
17 (7.7)
5 (5.4)
Peripheral swelling
16 (7.3)

5 (5.4)
Dyspepsia
15 (6.8)
4 (4.3)
Hemorrhoids
15 (6.8)
1 (1.1)
Hypotension
15 (6.8)
2 (2.2)
Injection site pruritus
15 (6.8)
0
Transfusion reaction
15 (6.8)
0
Pleural effusion
14 (6.4)
6 (6.5)
Abdominal distension
13 (5.9)
4 (4.3)
Muscle cramps
13 (5.9)
3 (3.3)
Post procedural hemorrhage
13 (5.9)
1 (1.1)
Postnasal drip
13 (5.9)
3 (3.3)
Rhonchi
13 (5.9)
2 (2.2)
Syncope
13 (5.9)
5 (5.4)
Urticaria
13 (5.9)
1 (1.1)
Anemia aggravated
12 (5.5)
5 (5.4)

Loose stools
12 (5.5)
0
Nasal congestion
12 (5.5)
1 (1.1)
Atelectasis
11 (5.0)
2 (2.2)
Chest wall pain
11 (5.0)
0
Dry skin
11 (5.0)
1 (1.1)
Dysphagia
11 (5.0)
2 (2.2)
Dyspnea exacerbated
11 (5.0)
3 (3.3)
Hypoesthesia
11 (5.0)
1 (1.1)
Injection site granuloma
11 (5.0)
0
Injection site pigmentation changes
11 (5.0)
0
Injection site swelling
11 (5.0)
0
Mouth hemorrhage
11 (5.0)
1 (1.1)
Post procedural pain
11 (5.0)
2 (2.2)
Sinusitis
11 (5.0)
3 (3.3)
Skin nodule

11 (5.0)
1 (1.1)
Tongue ulceration
11 (5.0)
2 (2.2)
* Mean Vidaza exposure = 11.4 months. Mean time in observation arm = 6.1 months.
** Multiple reports of the same preferred terms for a patient are only counted once within each treatment group.
† Includes events from observation period only; excludes any events after crossover to Vidaza.
‡ Includes events from all patients exposed to Vidaza, including patients after crossing over from observation.

Nausea, vomiting, diarrhea, and constipation all tended to increase in incidence with increasing doses of Vidaza. Nausea, vomiting, injection site erythema, constipation, rigors, petechiae, injection site pain, dizziness, injection site bruising, anxiety, hypokalemia, insomnia, epistaxis, and rales tended to be more pronounced during the first 1 2 cycles of SC Vidaza treatment compared with later cycles of treatment. There did not appear to be any adverse events that increased in frequency over the course of treatment. There did not appear to be any relevant differences in adverse events by gender.

In clinical studies of either SC or IV Vidaza, the following serious treatment-related adverse events occurring at a rate of <5% (not described in Table 4) were reported:
Blood and lymphatic system disorders: agranulocytosis, bone marrow depression, splenomegaly.
Cardiac disorders: atrial fibrillation, cardiac failure, cardiac failure congestive, cardio-respiratory arrest, congestive cardiomyopathy.
Gastrointestinal disorders: diverticulitis, gastrointestinal hemorrhage, melena, perirectal abscess.
General disorders and administration site conditions: catheter site hemorrhage, general physical health deterioration, systemic inflammatory response syndrome.
Hepatobiliary disorders: cholecystitis.
Immune system disorders: anaphylactic shock, hypersensitivity.
Infections and infestations: abscess limb, bacterial infection, blastomycosis, injection site infection, Klebsiella sepsis, pharyngitis streptococcal, pneumonia Klebsiella, sepsis, Staphylococcal bacteremia, Staphylococcal infection, toxoplasmosis.
Metabolism and nutrition disorders: dehydration.
Musculoskeletal and connective tissue disorders: bone pain aggravated, muscle weakness, neck pain.
Neoplasms benign, malignant and unspecified: leukemia cutis.
Nervous system disorders: convulsions, intracranial hemorrhage.
Psychiatric disorders: confusion.
Renal and urinary disorders: hematuria, loin pain, renal failure.
Respiratory, thoracic and mediastinal disorders: hemoptysis, lung infiltration, pneumonitis, respiratory distress.
Skin and subcutaneous tissue disorders: pyoderma gangrenosum, rash pruritic, skin induration.
SurgiCal and medical procedures: cholecystectomy.
Vascular disorders: orthostatic hypotension.

OVERDOSAGE

One case of overdose with Vidaza was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single IV dose of approximately 290 mg/m2, almost 4 times the recommended starting dose. The events resolved without sequelae, and the correct dose was resumed the following day. In the event of overdosage, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for Vidaza overdosage.

DOSAGE AND ADMINISTRATION

First Treatment Cycle

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m2 subcutaneously, daily for seven days. Patients should be premedicated for nausea and vomiting.

Subsequent Treatment Cycles

Cycles should be repeated every four weeks. The dose may be increased to 100 mg/m2 if no beneficial effect is seen after two treatment cycles and if no toxicity other than nausea and vomiting has occurred. It is recommended that patients be treated for a minimum of 4 cycles. However, complete or partial response may require more than 4 treatment cycles. Treatment may be continued as long as the patient continues to benefit.

Patients should be monitored for hematologic response and renal toxicities (see PRECAUTIONS), and dosage delay or reduction as described below may be necessary.

Dosage Adjustment Based on Hematology Laboratory Values:

* For patients with baseline (start of treatment) WBC ?3.0 x109/L, ANC ?1.5 x109/L, and platelets ? 75.0 x109/L, adjust the dose as follows, based on nadir counts for any given cycle:

Nadir Counts	% Dose in the Next Course
ANC (x109/L)	
<0.5	50%
0.5 –1.5	67%
>1.5	100%
Platelets (x109/L)	
<25.0	50%
25.0-50.0	67%
>50.0	100%

* For patients whose baseline counts are WBC <3.0 x109/L, ANC<1.5 x109/L, or platelets <75.0 x109/L, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in

which case the dose of the current treatment should be continued.

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)	Dose in the Next Course
30-60	15-30	100
15-30	<15	50
<15	50 - 75	33
50 - 75	> 75	75
> 75		50
		33

If a nadir as defined in the table above has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are >25% above the nadir and rising. If a >25% increase above the nadir is not seen by day 28, counts should be reassessed every 7 days. If a 25% increase is not seen by day 42, then the patient should be treated with 50% of the scheduled dose.

Dosage Adjustment Based on Renal Function and Serum Electrolytes: If unexplained reductions in serum bicarbonate levels to less than 20 mEq/L occur, the dosage should be reduced by 50% on the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment course (see PRECAUTIONS section).

Use in Geriatric Patients: Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS section).

Preparation of Vidaza

Vidaza is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Vidaza suspensions. Please refer to Handling and Disposal section.

If reconstituted Vidaza comes into contact with the skin, immediately and thoroughly wash with soap

and water. If it comes into contact with mucous membranes, flush thoroughly with water.

Vidaza should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. The vial should be inverted 2-3 times and gently rotated until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/mL.

Preparation for Immediate Administration: Doses greater than 4 mL should be divided equally into two syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for Delayed Administration: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into two syringes. The product must be refrigerated immediately, and may be held under refrigerated conditions (2ºC - 8ºC, 36ºF- 46ºF) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Administration

To provide a homogeneous suspension, the contents of the syringe must be re-suspended by inverting the syringe 2-3 times and gently rolling the syringe between the palms for 30 seconds immediately prior to administration.

Vidaza is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

Stability

Reconstituted Vidaza may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2 and 8°C (36 and 46°F). The Vidaza vial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded properly. See Handling and Disposal. Do not save any unused portions for later administration.

HOW SUPPLIED

Vidaza (azacitidine for injectable suspension) is supplied as a lyophilized powder in 100 mg single-use vials packaged in cartons of 1 vial (NDC 67211-102-01).

Storage

Store unreconstituted vials at 25º C (77º F); excursions permitted to 15º-30º C (59º-86º F) (See USP

Controlled Room Temperature).

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be applied. Several guidelines on this subject have been published1-8. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

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1 69 Fed. Reg. 66235, 66303 (Nov. 15, 2004).
2 Id. at 66308.
3 Id.
4 Id.
5 Id.

6 FDA-Approved Prescribing Information for Vidaza®, at 3 available at http://www.vidaza.com/corporateweb/vidazaus/home.nsf/AttachmentsByTitle/FullPrescribingInformationforVidaza.pdf/$FILE/FullPrescribingInformationforVidaza.pdf (Aug. 31, 2004) (attached).
7 69 Fed. Reg. 65681, 65808 (Nov. 15, 2004).
8 FDA-Approved Prescribing Information for Vidaza®, at 1.
9 In the final rule, CMS stated that the codes for chemotherapy administration are to be used for reporting the administration of anti-neoplastic agents provided for treatment of noncancer diagnoses. 69 Fed. Reg. 66235, 66303-66308.
10 FDA-Approved Prescribing Information for Vidaza®, at 10.

CMS-1429-FC-010

November 30, 2004
Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry

Dear CMS,

This message is to express my serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally hematopathologists, must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. We are aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, we are concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, we believe that the final assigned value for compensation is not reasonable.

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I urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients.

Sincerely,

Kevin W. Radford
Brown Cancer Center
529 S. Jackson St.
Louisville, KY 40202
(502)852-5464

CMS-1429-FC-011
December 6, 2004

Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry

Dear CMS,

This message is to express my serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally hematopathologists, must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. We are aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, we are concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, we believe that the final assigned value for compensation is not reasonable.

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Sincerely,

Lou Ann Eskildsen
Manager, Flow Cytometry Lab
Brown Cancer Center
529 South Jackson Street, Room 4B
Louisville, Kentucky 40202

CMS-1429-FC-012

December 6, 2004
Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry

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Sincerely,
Irina Grigorieva, PhD
Director, Flow Cytometry Laboratory,
Northside Hospital
1000 Johnson Ferry Rd., Atlanta GA 30342
Voice: (404)-851-6541, Fax: (404)-845-5353
E-mail: irina.grigorieva@northside.com

CMS-1429-FC-013

December 6, 2004
Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry

Dear CMS,

On behalf of the Immunology Laboratory at Children's National Medical Center, I'd like express our serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally hematopathologists, must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. We are aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, we are concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, we believe that the final assigned value for compensation is not reasonable.

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I urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients.

Sincerely,

David Leitenberg, M.D., Ph.D.
Assistant Professor
Departments of Immunology, Pediatrics and Pathology
George Washington University and
Director of Immunology

CMS-1429-FC-014

December 6, 2004

Re.: Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry

Dear CMS,

This message is to express my serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally hematopathologists, must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. I am aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, I am concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, I believe that the final assigned value for compensation is not reasonable.

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I urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients.

Sincerely,

Anand Shreeram Lagoo, MD, PhD
Director, Clinical Flow Cytometry Laboratory

CMS-1429-FC-015

Submitter: Dr. sophie song
Date & Time: 12/06/2004
Organization: UCLA Medical Center
Category: Physician
Issue Areas/Comments GENERAL GENERAL

See Attachment CMS-1429-FC-15-Attach-1.DOC

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

Department of Health and Human Services
Centers for Medicare and Medicaid (CMS)
7500 Security Blvd
Baltimore, Maryland 21244

Below you will find a brief explanation why an attachment can not be provided at this time on a particular document at this time, which was as indicated by the commenter. If you wish to view those attachments that have not been posted, please call CMS at 410-786-9994 or 410-786-7195 Monday through Friday to schedule an appointment.

1. The commenter failed to complete all steps required in order to process their comments. All required fields must be completed in order to attach an attachment.

2. The commenter was referring to another comment received, but did not attach the information they were referring to.

3. The commenter intended to attach more then on attachment. But for some reason, CMS only received one or neither of their attachment.

4. The commenter provided sensitive information, that CMS felt was inappropriate to be posted on the web site.

CMS-1429-FC-016

Submitter: Mrs. Eti Rosenthal
Date & Time: 12/07/2004
Organization: Sheba Medical Center, Israel
Category : Health Care Professional or Association
Issue Areas/Comments GENERAL

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005

See Attachment CMS-1429-FC-16-Attach-1.DOC

CMS-1429-FC-016 Attach

December 7, 2004
Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry

Dear CMS,

This message is to express my (our) serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally hematopathologists, must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. We are aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, we are concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, we believe that the final assigned value for compensation is not reasonable.

Flow cytometry has been growing at a very rapid pace and has been responsible for major advances in the diagnosis, prognosis and treatment of patients with serious and life threatening diseases, including virtually all bone marrow and lymphoid cancers. As in all other developed countries, no patient with leukemia in the US is treated and monitored without the diagnostic support provided by flow cytometry. With flow cytometry, many patients who once needed surgical procedures to excise large amounts of tissue can now have diagnoses rendered on small biopsies from non-invasive, and far less expensive procedures. The radical cuts in reimbursement for flow cytometric services will result in decreased availability of this essential diagnostic modality. Numerous academic, independent and hospital-based laboratories currently involved in diagnostic flow cytometry are considering discontinuing these activities in 2005 and those that carry on will be forced to reduce the quality of their services in ways not necessarily apparent to the oncologists who are dependent on them.

I (we) urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients.

Although I'm from Israel, and not depended on US rules, I think the change will influence the rules in many organizations around the world, as we also work according the same CPT numbers, and similar fees.
Sincerely,

Eti Rosenthal, Hematology, Sheba Medical Center, Tel Hashomer, Israel
Mail : reti@inter.net.il

CMS-1429-FC-017

Submitter: No Name
Date & Time: 12/08/2004
Organization: N/A
Category: Hospice
Issue Areas/Comments GENERAL

Regarding the Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005prehospice eval, would the medical director keep the record of the visit/service and not the hospice? would this mean that the medical director would have to either give a report via telephone to the attending physician or would he/she have to physically go the the attending's office or fax a report to the attending?

CMS-1429-FC-018

Submitter: Mr. Eric Ho
Date & Time: 12/09/2004
Organization: Columbia University Medical Center
Category: Other Practitioner
Issue Areas/Comments GENERAL

Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005
November 30, 2004 Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow
cytometry Re.: CMS-1429-FC

Dear CMS,

This message is to express my serious concern regarding the drastic decrease in reimbursement for professionalflow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally hematopathologists, must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations;and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. We are aware of the process used to establish the new compensation proposedfor this complicated activity under the 2005 CMS rules. However, we are concerned that the process wasflawed because we were forced to compare to inappropriate reference codes. As a result, we believe that the final assigned value for compensation is not reasonable. Flow cytometry has been growing at a very rapid pace and has been responsible for major advances in the diagnos0is, prognosis and treatment of patients with serious and life threatening diseases, including virtually all bone marrow and lymphoid cancers. As in all other developed countries, no patient with leukemia in the US is treated and monitored without the diagnostic support provided by flow cytometry. With flow cytometry, many patients who once needed surgical procedures to excise large amounts of tissue can now have diagnoses rendered on small biopsies from non- invasive, and far less expensive procedures. The radical cuts in reimbursement for flow cytometric services will result in decreased availability of this essential diagnostic modality. 0Numerous academic, independent and hospital-based laboratories currently involved in diagnostic flow cytometry are considering discontinuing these activities in 2005 and those that carry on will be forced to reduce the quality of their services in ways not necessarily apparent to the oncologists who are dependent on them. I urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients.

Sincerely,

CMS-1429-FC-019

November 30, 2004
Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry

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I (we) urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients.

Sincerely,

Stephen Golding BSMT (ASCP).

Community Blood Centers of South Florida,
Lauderhill, FL 33313.
954-777-2674. stevengolding@cbcsf.org

CMS-1429-FC-020

Submitter: Dr. Thomas Brien
Date & Time: 12/14/2004
Organization: Memorial Hospital
Category: Physician
Issue Areas/Comments GENERAL

December 14, 2004
Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005; Response to CMS November 2004 ruling regarding changes to CPT code 88180 for flow cytometry Re.: CMS-1429-FC Dear CMS, This message is to express my serious concern regarding the drastic decrease in reimbursement for professional flow cytometry services proposed by CMS for 2005. The flow cytometric analysis of hematologic malignancies is a laborious procedure that combines sophisticated laboratory analysis with a significant component of physician work. Physicians, generally hematopathologists, must spend considerable time to make decisions on sample handling and selection of reagents appropriate to a clinical context; examine complex graphical data; correlate results with microscopic observations; and generate meaningful interpretations that are often discussed, and always transmitted in writing to treating physicians. I am aware of the process used to establish the new compensation proposed for this complicated activity under the 2005 CMS rules. However, I am concerned that the process was flawed because we were forced to compare to inappropriate reference codes. As a result, I believe that the final assigned value for compensation is not reasonable. Flow cytometry has been growing at a very rapid pace and has been responsible for major advances in the diagnosis, prognosis and treatment of patients with serious and life threatening diseases, including virtually all bone marrow and lymphoid cancers. As in all other developed countries, no patient with leukemia in the US is treated and monitored without the diagnostic support provided by flow cytometry. With flow cytometry, many patients who once needed surgical procedures to excise large amounts of tissue can now have diagnoses rendered on small biopsies from non- invasive, and far less expensive procedures. The radical cuts in reimbursement for flow cytometric services will result in decreased availability of this essential diagnostic modality. Numerous academic, independent and hospital-based laboratories currently involved in diagnostic flow cytometry are considering discontinuing these activities in 2005 and those that carry on will be forced to reduce the quality of their services in ways not necessarily apparent to the oncologists who are dependent on them. I urge the CMS to begin a dialogue with those affected by the reimbursement cuts to reevaluate the proposed fee schedules and prevent an adverse impact on patients. Sincerely, Thomas Brien MD Department of Pathology

Memorial Hospital 2525 deSales Ave Chattanooga, TN 37404 phone: (423) 495-8703 e-mail: tom_brien@memorial.org