SCRIPTDOCTOR: MEDICINE IN THE MEDIA

Close to Home: NCI's 'Showbiz Outreach' for Community-Based Research & Treatment

By Andrew Holtz, MPH

Andrew Holtz, MPH, is a former CNN Medical Correspondent and the author of "The Medical Science of House, M.D." This column examines mass media programs, particularly entertainment TV, for insight into popular perceptions, so that rather than merely wincing at distortions or oversimplifications in the portrayals of medicine on these shows, health care professionals can learn something from media professionals about the way that medical and health topics are presented. ***Send questions to him about how the media treat medical topics or suggestions for future columns to OT@lwwny.com***

Today's topic can be looked at in at least two ways.

It involves taking steps toward fulfilling Objectives 5, 6, and 8 of the 2006 NCI Strategic Plan. It involves the story of "Uncle Joe," who has cancer, but can't afford to, and doesn't really want to, leave his hometown and family in Arkansas to travel to an NCI-designated Cancer Center for testing and treatment.

For our dear readers who haven't committed the NCI Strategic Plan to heart, the sections at hand involve:

- Moving more research into local communities, to better understand the factors that influence cancer outcomes (Strategy 5.5).
- Getting information to the public about prevention, treatment, and follow-up, to improve the quality of cancer care (Strategy 6.5)
- Partnering with the media to deliver timely and accurate health messages to underserved populations, to overcome cancer health disparities (Strategies 8.2 & 8.5).

"Showbiz outreach" has included TV storylines that encourage people to join clinical trials and that counter cancer myths that can discourage people from seeking treatment. New on the priority list are community-based research and treatment.

And what of Uncle Joe? Well, think about the typical setting of a TV show episode involving cancer: Usually it's a big city hospital or major academic medical center. After all, that's where people go for cancer care, right?

"The fact of the matter is: They don't. They can't afford to, and they don't. It's a select group of people who can do that or that happen to live in that area," NCI Director John E. Niederhuber, MD, said in an interview.

Dr. Niederhuber said that cancer research—and treatment—should move closer to where people live. And he wants people to see community-based cancer action on TV. And that's where Uncle Joe comes in.

"I think the great storyline, maybe, is how we are moving into a new era in which we can send Uncle Joe's CT scan electronically over the Internet and have it looked at in real-time at M. D. Anderson, even though this person might be in Arkansas. And then treatments are discussed and decisions made. If tissue samples are needed, they can be taken and analyzed anywhere in the world; they don't have to be analyzed in the community where the patient lives today," Dr. Niederhuber said.

"I could write a script around somebody getting care somewhere while a lot of the experts were in different places."

But will Hollywood write—and air—those stories? NCI Senior Science Writer Michael Miller is preparing to pitch some new ideas to TV writers and producers.

"So if they are going to do a story about a farmer, and his relative in a big city, and how someone is treated—rural versus urban—that certainly holds potential; and isn't something that I think you see depicted much on TV these days," he said.

Round of Visits to TV Studios

That's one early idea about how to present potential storylines involving community-based cancer research and treatment. Miller said that he and others involved with the "Hollywood, Health & Society" (HH&S) program are planning a round of visits to TV studios around the time of the American Association for Cancer Research Annual Meeting in Los Angeles next month.

The HH&S program, partially funded by the NCI and based at the USC Annenberg Norman Lear Center in Los Angeles, provides experts and other resources to TV writers telling tales of medicine and health. The participants also try to come up with ideas that could appeal to both writers and health agency leadership.

"We've chosen topics that we want to talk to writers and producers about, somewhat with an eye to whether it would make an interesting storyline, but also probably more so to 'How important is this particular topic to the institute, and do you really see it that much?'" Miller said.

NCI Director John E. Niederhuber, MD: "I could write a script around somebody getting care somewhere while a lot of the experts were in different places....Right now, the majority of patients in community settings do not have access to the very earliest of our studies, unless they can and will travel, sometimes great distances, to our major centers. In this day and age, we ought to be able to do better than that. I don't see why we can't open early-phase trials in the community setting, as well as in the major research universities. The agents that we are studying are less toxic. They are easier to manage."

"So if it's something that every show has been doing ad nauseum, then the odds of them wanting to do it again aren't as likely; but if we have something that has not been done that much, particularly in an entertainment-based show, and it is a priority to us, then we think it might be something they'd be interested in."

Miller and cancer experts he's recruited have suggested storylines intended to encourage people to join clinical trials, to counter cancer myths that can discourage people from seeking treatment, and other topics. Some of these suggestions have germinated into major and minor plotlines on *ER*, *Grey's Anatomy*, *As the World Turns*, and other popular shows. Now community-based research and treatment have joined the priority list for showbiz outreach.

Miller recognizes that the top medical series are set in or near big cities or major academic centers—*Grey's Anatomy* is set in Seattle; *ER*, in Chicago; and *House*, near Princeton, NJ—so it may take some creative storytelling to move the focus out to the smaller communities where most people live.

"If they do storylines that aren't in large urban settings, or they have to deal with people who are not right there to receive the care they administer, how do they deal with getting the care to them? Is it telemedicine? Strengthening of community cancer centers?"

Or perhaps they might reach out to shows set in smaller towns, and suggest a cancer story that could fit the show's formula.

Growing Numbers of Older Americans

Dr. Niederhuber said he has no doubt the stories are there, with so many families facing tension between home and treatment, especially the growing numbers of older Americans entering the years of highest cancer risk.

"The older population tends to be less mobile, and certainly much more dependent on family and friends for help getting them to their care," he points out.

In January, the NCI

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ELOXATIN®
(oxaliplatin injection)

WARNING
ELOXATIN (oxaliplatin injection) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylactic-like reactions to ELOXATIN have been reported, and may occur within minutes of ELOXATIN administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms (see WARNINGS and ADVERSE REACTIONS).

INDICATIONS AND USAGE
ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. The indication is based on an improvement in disease-free survival, with no demonstrated benefit in overall survival after a median follow up of 4 years.

ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for the treatment of advanced carcinoma of the colon or rectum.

CONTRAINDICATIONS
ELOXATIN should not be administered to patients with a history of known allergy to ELOXATIN or other platinum compounds.

WARNINGS
As in the case for other platinum compounds, hypersensitivity and anaphylactic/anaphylactoid reactions to ELOXATIN have been reported (see ADVERSE REACTIONS). These allergic reactions were similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. These reactions occur within minutes of administration and should be managed with appropriate supportive therapy. Drug-related deaths associated with platinum compounds from this reaction have been reported.

Pregnancy Category D
ELOXATIN may cause fetal harm when administered to a pregnant woman. Pregnant rats were administered 1 mg/kg/day oxaliplatin (less than one-tenth the recommended human dose based on body surface area) during gestation days 1-5 (pre-implantation), 6-10, or 11-16 (during organogenesis). Oxaliplatin caused developmental mortality (increased early resorptions) when administered on days 6-10 and 11-16 and adversely affected fetal growth (decreased fetal weight, delayed ossification) when administered on days 6-10. 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 ELOXATIN.

PRECAUTIONS
General
ELOXATIN should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Neuropathy
Patients with Stage II or III Colon Cancer
Neuropathy was graded using a prelisted module derived from the Neuro-Sensory section of the NCI CTC scale version 1, as follows:

Table 12 -NCI CTC Grading for Neuropathy in Adjuvant Patients

NCI Grade	Definition
Grade 0	No change or none
Grade 1	Mild paresthesias, loss of deep tendon reflexes
Grade 2	Mild or moderate objective sensory loss, moderate paresthesias
Grade 3	Severe objective sensory loss or paresthesias that interfere with function
Grade 4	Not applicable

Peripheral sensory neuropathy was reported in adjuvant patients treated with the ELOXATIN combination with a frequency of 92% (all grades) and 13% (grade 3). At the 28-day follow-up after the last treatment cycle, 60% of all patients had any grade (Grade 1=39.6%, Grade 2=15.7%, Grade 3=5.0%) peripheral sensory neuropathy decreasing to 39% at 6 months follow-up (Grade 1=30.5%, Grade 2=7.4%, Grade 3=1.3%) and 21% at 18 months of follow-up (Grade 1=17.2%, Grade 2=3.0%, Grade 3=0.5%).

Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer
Neuropathy was graded using a study-specific neurotoxicity scale, which was different than the National Cancer Institute Common Toxicity Criteria, Version 2.0 (NCI CTC) (see below).

In the previously treated study, neuropathy information was collected to establish that ELOXATIN is associated with two types of neuropathy:

- **An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing.** The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received ELOXATIN with 5-FU/LV. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. Ice (mucositis prophylaxis) should be avoided during the infusion of ELOXATIN because cold temperature can exacerbate acute neurological symptoms (see DOSAGE AND ADMINISTRATION: Dose Modifications).

  An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing).
- **A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception).** These forms of neuropathy occurred in 48% of the study patients receiving ELOXATIN with 5-FU/LV. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of ELOXATIN.

Overall, neuropathy was reported in patients previously untreated for advanced colorectal cancer in 82% (all grades) and 19% (grade 3/4), and in the previously treated patients in 74% (all grades) and 7% (grade 3/4) events. Information regarding reversibility of neuropathy was not available from the trial for patients who had not been previously treated for colorectal cancer.

Neurotoxicity scale:
The grading scale for paresthesias/dysesthesias was: Grade 1, resolved and did not interfere with functioning; Grade 2, interfered with function but not daily activities; Grade 3, pain or functional impairment that interfered with daily activities; Grade 4, persistent impairment that is disabling or life-threatening.

Pulmonary Toxicity
ELOXATIN has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade 3) with no grade 4 events in the ELOXATIN plus infusional 5-FU/LV arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5-FU/LV alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the ELOXATIN combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the ELOXATIN plus 5-FU/LV arm compared to 32% (any grade) and 5% (grade 3 and 4) in the irinotecan plus 5-FU/LV arm of unknown duration for patients with previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, ELOXATIN should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Hepatotoxicity
Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57% vs. 34%) and alkaline phosphatase (42% vs. 20%) was observed more commonly in the ELOXATIN combination arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases.

Information for Patients
Patients and patients' caregivers should be informed of the expected side effects of ELOXATIN, particularly its neurologic effects, both the acute, reversible effects and the persistent neurosensory toxicity. Patients should be informed that the acute neurosensory toxicity may be precipitated or exacerbated by exposure to cold or cold objects. Patients should be instructed to avoid cold drinks, use of ice, and should cover exposed skin prior to exposure to cold temperature or cold objects.

Patients must be adequately informed of the risk of low blood cell counts and instructed to contact their physician immediately should fever, particularly if associated with persistent diarrhea, or evidence of infection develop.

Patients should be instructed to contact their physician if persistent vomiting, diarrhea, signs of dehydration, cough or breathing difficulties occur, or signs of allergic reaction appear.

Laboratory Tests
Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistries (including ALT, AST, bilirubin and creatinine) is recommended before each ELOXATIN cycle (see DOSAGE AND ADMINISTRATION).

Laboratory Test Interactions
None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of oxaliplatin. Oxaliplatin was not mutagenic to bacteria (Ames test) but was mutagenic to mammalian cells *in vitro* (L5178Y mouse lymphoma assay). Oxaliplatin was clastogenic both *in vitro* (chromosome aberration in human lymphocytes) and *in vivo* (mouse bone marrow micronucleus assay).

In a fertility study, male rats were given oxaliplatin at 0, 0.5, 1, or 2 mg/kg/day for five days every 21 days for a total of three cycles prior to mating with females that received two cycles of oxaliplatin on the same schedule. A dose of 2 mg/kg/day (less than one-seventh the recommended human dose on a body surface area basis) did not affect pregnancy rate, but caused developmental mortality (increased early resorptions, decreased live fetuses, decreased live births) and delayed growth (decreased fetal weight).

Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs administered oxaliplatin at 0.75 mg/kg/day x 5 days every 28 days for three cycles. A no effect level was not identified. This daily dose is approximately one-sixth of the recommended human dose on a body surface area basis.

Pregnancy Category D - See WARNINGS

Nursing Mothers - It is not known whether ELOXATIN or its derivatives are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ELOXATIN, a decision should be made whether to discontinue nursing or delay the use of the drug, taking into account the importance of the drug to the mother.

Pediatric Use - The safety and effectiveness of ELOXATIN in pediatric patients have not been established.

Patients with Renal Impairment - The safety and effectiveness of the combination of ELOXATIN and 5-FU/LV in patients with renal impairment have not been evaluated. The combination of ELOXATIN and 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate, and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

Geriatric Use - No significant effect of age on the clearance of ultrafilterable platinum has been observed. In the adjuvant therapy colon cancer randomized clinical trial, (see CLINICAL STUDIES) 723 patients treated with ELOXATIN and infusional 5-FU/LV were < 65 years and 400 patients were ≥ 65 years. In the previously untreated for advanced colorectal cancer randomized clinical trial (see CLINICAL STUDIES) of ELOXATIN, 160 patients treated with ELOXATIN and 5-FU/LV were < 65 years and 99 patients were ≥65 years. The same efficacy improvements in response rate, time to tumor progression, and overall survival were observed in the ≥65 year old patients as in the overall study population. In the previously treated randomized clinical trial (see CLINICAL STUDIES) of ELOXATIN, 95 patients treated with ELOXATIN and 5-FU/LV were < 65 years and 55 patients were ≥65 years. The rates of overall adverse events, including grade 3 and 4 events, were similar across and within arms in the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope were higher in patients ≥65 years old. No adjustment to starting dose was required in patients ≥65 years old.

Drug Interactions - No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m² ELOXATIN and 5-FU/LV has been observed in patients treated every 2 weeks. Increases of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/m² ELOXATIN dosed every 3 weeks. Since platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS
More than 1100 patients with stage II or III colon cancer and more than 4,000 patients with advanced colorectal cancer have been treated in clinical studies with ELOXATIN either as a single agent or in combination with other medications. The most common adverse reactions in patients with stage II or III colon cancer receiving adjuvant therapy, were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. The most common adverse reactions in previously untreated and treated patients were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea (see PRECAUTIONS).

Combination Adjuvant Therapy with ELOXATIN and infusional 5-FU/LV in Patients with Stage II or III Colon Cancer.

One thousand one hundred and eight patients with stage II or III colon cancer, who had undergone complete resection of the primary tumor, have been treated in a clinical study with ELOXATIN in combination with infusional 5-FU/LV (See CLINICAL STUDIES). The incidence of grade 3 or 4 adverse events was 70% on the ELOXATIN combination arm, and 31% on the infusional 5-FU/LV arm. The adverse reactions in this trial are shown in the tables below. Discontinuation of treatment due to adverse events occurred in 15% of the patients receiving ELOXATIN and infusional 5-FU/LV. Both 5-FU/LV and ELOXATIN are associated with gastrointestinal or hematologic adverse events. When ELOXATIN is administered in combination with infusional 5-FU/LV, the incidence of these events is increased.

The incidence of death within 28 days of last treatment, regardless of causality, was 0.5% (n=6) in both the ELOXATIN combination and infusional 5-FU/LV arms, respectively. Deaths within 60 days from initiation of therapy were 0.3% (n=3) in both the ELOXATIN combination and infusional 5-FU/LV arms, respectively. On the ELOXATIN combination arm, 3 deaths were due to sepsis/neutropenic sepsis, 2 from intracerebral bleeding and one from eosinophilic pneumonia. On the 5-FU/LV arm, one death was due to suicide, 2 from Steven-Johnson Syndrome (1 patient also had sepsis), 1 unknown cause, 1 anoxic cerebral infarction and 1 probable abdominal aorta rupture.

The following table provides adverse events reported in the adjuvant therapy colon cancer clinical trial (see CLINICAL STUDIES) by body system and decreasing order of frequency in the ELOXATIN and infusional 5-FU/LV arm for events with overall incidences ≥ 5% and for NCI grade 3/4 events with incidences ≥ 1%. This table does not include hematologic and blood chemistry abnormalities; these are shown separately below.

Table 13 - Adverse Experiences Reported in Patients with Stage II or III Colon Cancer receiving Adjuvant Treatment (≥5% of all patients and with ≥1% NCI Grade 3/4 events)

	ELOXATIN + 5-FU/LV N=1108		5-FU/LV N=1111	
Adverse Event (WHO/Pref)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Event	100	70	99	31
Allergy/Immunology				
Allergic Reaction	10	3	2	<1
Constitutional Symptoms/Pain				
Fatigue	44	4	38	1
Abdominal Pain	18	1	17	2
Dermatology/Skin				
Skin Disorder	32	2	36	2
Injection Site Reaction[1]	11	3	10	3
Gastrointestinal				
Nausea	74	5	61	2
Diarrhea	56	11	48	7
Vomiting	47	6	24	1
Stomatitis	42	3	40	2
Anorexia	13	1	8	<1
Fever/Infection				
Fever	27	1	12	1
Infection	25	4	25	3
Neurology				
Overall Peripheral Sensory Neuropathy	92	12	16	<1

[1] Includes thrombosis related to the catheter

The following table provides adverse events reported in the adjuvant therapy colon cancer clinical trial (see CLINICAL STUDIES) by body system and decreasing order of frequency in the ELOXATIN and infusional 5-FU/LV arm for events with overall incidences ≥ 5% but with incidences <1% NCI grade 3/4 events.

Table 14 - Adverse Experiences Reported in Patients with Stage II or III Colon Cancer receiving Adjuvant Treatment (≥ 5% of all patients, but with <1% NCI Grade 3/4 events)

	eloxatin + 5-FU/LV N=1108	5-FU/LV N=1111
Adverse Event (WHO/Pref)	All Grades (%)	All Grades (%)
Allergy/Immunology		
Rhinitis	6	8
Constitutional Symptoms/Pain/Ocular/Visual		
Epistaxis	16	12
Weight Increase	10	10
Conjunctivitis	9	15
Headache	7	5
Dyspnea	5	3
Pain	5	5
Lacrimation Abnormal	4	12
Dermatology/Skin		
Alopecia	30	28

ScriptDoctor
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received more than 40 applications for grants to support community-based cancer research, generally in conjunction with established big-city NCI-designated cancer centers. Dr. Niederhuber said he expects a handful of three-year pilot projects to win approval.

"It's a very exciting time, but I think we are going to have a great deal of difficulty getting our best science, our best new knowledge, to people in the communities where they live," he said.

The community-based research projects are intended to address that need.

"The goal is to see if we can study how best to bring our state-of-the-art science to patients in these community settings—that is, through early-phase clinical trials," Dr. Niederhuber said. "Right now, the majority of patients in community settings do not have access to the very earliest of our studies, unless they can and will travel, sometimes great distances, to our major centers.

"I think in this day and age, with UPS and FedEx and satellite communications, we ought to be able to do better than that. I don't see why we can't open early-phase trials in the community setting, as well as in the major research universities. The agents that we are studying are less toxic. They are easier to manage."

And even as cancer researchers are grappling with the challenges of moving research and treatment closer to patients' homes, the media outreach program is trying to bring the public along, by pitching a new kind of TV story about cancer.