National PBM Drug Monograph
Oxaliplatin (Eloxatin™)
VHA Pharmacy Benefits Management Strategic Healthcare Group
And the Medical Advisory Panel
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Introduction

Despite wide spectrums of antineoplastic activity, the current platinum based compounds (cisplatin and carboplatin) have limitations to their usefulness: first, their severe side effect profiles which includes nephrotoxicity, ototoxicity, nausea/vomiting, and peripheral neuropathies for cisplatin and hematologic toxicities with carboplatin; second they have both intrinsic resistance against common tumors like colorectal carcinomas and acquired resistance in a portion of responding tumors. These limitations have prompted the development of other platinum-based compounds with reduced limitations. Oxaliplatin is a diaminocyclohexane (DACH) carrier ligand-based platinum compound with a wide spectrum of antineoplastic activity. It lacks the nephrotoxicity and severe nausea and vomiting of cisplatin and has minimal myelosuppression when compared to carboplatin. It has shown activity in cell lines with intrinsic and acquired cisplatin resistance. It has notably shown activity in colorectal disease as a first line agent, in fluorouracil refractory patients, and has synergy with several other antineoplastic agents including fluorouracil, irinotecan, and gemcitabine. It has been approved for several years in France and fifty-nine other countries for treatment of advanced colorectal cancer as both monotherapy and in combination with fluorouracil and leucovorin. In August of 2002 the FDA approved oxaliplatin for use in combination with infusional fluorouracil and leucovorin for the treatment of patients with colorectal cancer whose disease has recurred or progressed following first-line therapy with fluorouracil and leucovorin plus irinotecan.

Pharmacology/Pharmacokinetics[1,2]

Mechanism of action: The precise mechanism of action has not been determined. The mechanism of action of platinum containing compounds is believed to be inhibition of DNA synthesis through intrastrand platinum-DNA adducts. A greater degree of inhibition of DNA synthesis has been attributed to DACH platinum adducts of oxaliplatin, probably due to the bulky DACH carrier.

	Oxaliplatin
Metabolism	Non-enzymatic biotransformation (hydrolyzed to active & inactive species)
Elimination	Primarily renal
Half-life	α = 0.2-0.46 hours β = 15-16.8 hours γ = 252-391 hours
Protein Binding	70-95%

The pharmacokinetics of oxaliplatin at 85mg/m^2 are not affected by fluorouracil nor does it affect the pharmacokinetics of fluorouracil. At 130mg/m^2, oxaliplatin may increase the plasma concentration of fluorouracil by 20%.
Pharmacokinetics in renal impairment: The AUC of platinum in patients with mild (CL_{CR} 50-80ml/min), moderate (CL_{CR} 30- <50ml/min), and severe (CL_{CR} <30ml/min) renal impairment is increased by 60,140 and 190%, respectively compared to patients with normal renal function. This analysis was performed on platinum ultrafiltrate, but the actual pharmacokinetic changes that occur biologically are unknown. Further deterioration of renal function and increased toxicity has not been observed in these patients, although there were a limited number of patients in the evaluation.

FDA Approved Indication(s) and Off-label Uses

Oxaliplatin in combination with infusional 5-fluorouracil (5-FU)/leucovorin (LV) is indicated for treatment of metastatic colorectal carcinoma that has recurred or progressed during or within 6 months of completion of first-line therapy with the combination of bolus 5-FU/LV and irinotecan. Off-label use includes combination therapy with LV and 5FU for first-line therapy of colorectal carcinomas, combination therapy for metastatic colorectal carcinoma with irinotecan, LV and 5FU, capecitabine and oxaliplatin, irinotecan and oxaliplatin, and second line therapy in advanced ovarian cancer.

Current VA National Formulary Status

Oxaliplatin is currently a non-formulary drug.

Dosage and Administration

The dosing regimen approved in refractory or relapsed colorectal cancer is based on the FOLFOX4 regimen used in the clinical trials, and was compared to 5-FU/LV alone (Arm A) and oxaliplatin alone (Arm B).

Day 1: Oxaliplatin 85mg/m^2/250-500ml D5W and leucovorin 200mg/m^2 in D5W each over 120 minutes at the same time in different bags using a Y-line, followed by 5-fluorouracil 400mg/m^2 IV bolus over 2-4 minutes, followed by 5-fluorouracil 600mg/m^2 IV infusion in 500ml D5W as a 22 hour infusion.

Day 2: Leucovorin 200mg/m^2 in D5W IV infusion over 120 minutes, followed by 5-fluorouracil 400mg/m^2 IV bolus over 2-4 minutes, followed by 5-fluorouracil 600mg/m^2 IV infusion in 500ml D5W as a 22 hour infusion.

Repeat cycle every 2 weeks.

Oxaliplatin powder for injection must NEVER BE DILUTED WITH SODIUM CHLORIDE SOLUTION OR OTHER CHLORIDE-CONTAINING SOLUTIONS. Reconstitute the lyophilized powder using 10ml (for the 50mg vial) or 20ml (for the 100mg vial) of Water for Injection or Dextrose 5% in Water.

Oxaliplatin is not compatible with alkaline solutions like 5-fluorouracil, and should not be mixed with these solutions in the same IV line. The infusion line should be flushed with Dextrose 5% in water prior to administration.

Dosage Adjustments

Table 1 Oxaliplatin Neurotoxicity Dose Adjustment Recommendations

Toxicity Grade	Duration of Toxicity		Not resolved by beginning of next cycle
	1 – 7 Days	>7 Days	
Paresthesia/dysesthesia that doesn't interfere with function	No Change	No Change	No Change
Paresthesia/dysesthesia that interferes with function but not ADLs	No Change	No Change	65mg/m^2
Paresthesia/dysesthesia with pain or functional impairment and interferes with ADLs	No Change	65mg/m^2	Stop
Paresthesia/dysesthesia that is disabling or life threatening	Stop	Stop	Stop
ACUTE: (during or after the 2-hour infusion) laryngopharyngeal dysesthesia	↑Duration of next infusion to 6 hours	↑Duration of next infusion to 6 hours	↑Duration of next infusion to 6 hours

Table 2 Other Dose Adjustments

Toxicity Grade	Oxaliplatin	5-Fluorouracil	Leucovorin
Grade 3/4 hematologic toxicity (neutrophils<1.5 x10^9/L or platelets <100 x10^9/L) resolved before next cycle	65mg/m^m	300mg/m^2 bolus and 500mg/m^2 infusion over 22 hours	No Change
Grade 3/4 Gastrointestinal toxicity (diarrhea, nausea, vomiting, mucositis) resolved before next cycle	65mg/m^2	300mg/m^2 and 500mg/m^2 infusion over 22 hours	No Change

Adverse Effects in the Registration Trial[3]

Adverse Event	5FU/LV (N=142)		Oxaliplatin (N=153)		Oxaliplatin + 5FU/LV (N=150)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any	98	41	100	46	99	73
Neuropathy	17	0	76	7	74	7
Acute	10	0	65	5	56	2
Persistent	9	0	43	3	48	6
Fatigue	52	6	61	9	68	7
Diarrhea	44	3	46	4	67	11
Nausea	59	4	64	4	65	11
Vomiting	27	4	37	4	40	9
Stomatitis	32	3	14	0	37	3
Abdominal pain	31	5	31	7	33	4
Fever	23	1	25	1	29	1
Anorexia	20	1	20	2	29	3
Dyspnea	11	2	13	7	20	4
Back pain	16	4	11	0	19	3
Coughing	9	0	11	0	19	1
Edema	13	1	10	1	15	1
Pain	9	3	14	3	15	2
Inj site reaction	5	1	9	0	10	3
Thromboembolism	4	2	2	1	9	8
Hypokalemia	3	1	3	2	9	4
Dehydration	6	4	5	3	8	3
Chest pain	4	1	5	1	8	1
Febrile/neutropenia	1	1	0	0	6	6
GE Reflux	3	0	1	0	5	2
Hematologic Events in >5% of patients						
Anemia	68	2	64	1	81	2
Leukopenia	34	1	13	0	76	19
Neutropenia	25	5	7	0	73	44
Thrombocytopenia	20	0	30	3	64	4
Adverse Events in ≥5% of patients but <1% Grade 3/4						
Constipation	23		31		32	
Headache	8		13		17	
Rhinitis	4		6		15	
Dyspepsia	10		7		14	
Taste perversion	1		5		13	
Dizziness	8		7		13	
Hand-foot syndrome	13		1		11	
Peripheral edema	11		5		10	
Allergic reaction	1		3		10	
Arthralgia	10		7		10	
Rash	5		5		9	
Mucositis	10		2		7	
Alopecia	3		3		7	
Abn lacrimation	6		1		7	
Rigors	6		9		7	

In clinical trials, either as a single agent or in combination with 5-fluorouracil and leucovorin, the most common adverse events have been peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea. The most common events leading to discontinuation of therapy were gastrointestinal and hematologic adverse events and neuropathies.

Neurotoxicity
Neurotoxicity was common in the registration study. In the combination arm, any type of neurotoxicity occurred in 74% of patients with acute toxicity in 67% and persistent toxicity in 40%. Previously, neurotoxicity with oxaliplatin was categorized by a combination of symptoms and duration; for example, acute toxicity consisted of cold sensitive spasms and loss of sensation. The registration study did not support this type of categorization because any symptom could occur as either an acute or persistent event. There does not seem to be a threshold of cumulative oxaliplatin dose before these events occur; higher-grade neurotoxicity can occur at any cumulative dose on any study day. In any cycle, at least 30% of patients will have a neurotoxic event; having an event does not predict subsequent neurotoxicity.

Acute Neuropathy: Acute neurotoxicity (less than 2 weeks), primarily peripheral sensory neuropathy, is common, reversible and generally not dose-limiting. It occurs within hours of treatment and may be precipitated by or exacerbated by exposure to cold temperatures. The majority last for less than 7 days and tend to recur with further dosing. Symptoms include transient paresthesia, dysesthesia, and hypoesthesia of the hands, feet, perioral area, or throat. In addition, jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and chest pressure have been observed. Ice to prevent mucositis should be avoided because it may exacerbate or precipitate acute symptoms. A sudden, self-limiting laryngopharyngeal dysesthesia, characterized by subjective sensations of dysphagia or dyspnea without laryngospasm or bronchospasm, and thought to result from decreased sensitivity of the larynx and pharynx, has been described in approximately 2%. The median duration of symptoms is 7 days, and no deaths have been associated with this acute event. Having the patient cup their hands over their mouth and nose to create a warm air environment may lessen the sensation. The sensations may last longer with successive cycles.

Persistent Neuropathy: A primarily peripheral sensory neuropathy lasting >14 days and characterized by paresthesia, dysesthesia, numbness and hypoesthesia in the extremities, legs, hip, arm, eye, jaw, throat, mouth gums, lips or tongue that may or may not be exacerbated by cold temperatures but also including deficits in proprioception that interferes with ADLs has also been associated with oxaliplatin. This form of neuropathy can occur without any prior acute neuropathy, and generally progresses with continued cycles. Symptoms may improve over time upon discontinuation of oxaliplatin. Due to the unique characteristics of the neuropathy, a neurotoxicity grading scale, distinct from the NCI-CTC was developed and used to assess neurotoxic events. The scale is as follows: 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.

Treatment or prevention of neurotoxicity using carbamazepine, alpha-lipoic acid, and glutathione has produced variable results.[4,5,6,7]

Hematologic Toxicity
The incidence of hematologic toxicities was higher in Arm C compared to Arm A and B. All hemoglobin toxicities were Grade 3 except for one Grade 4 patient in Arm B. Grade 3 neutropenia occurred in 40 patients in Arm C and Grade 4 neutropenia occurred in 26 patients. In Arm A, corresponding results were 5 patients with Grade 3 and 2 patients with Grade 4. The incidence of febrile neutropenia was 6% in Arm C and 1% in Arm A. Grade 4 thrombocytopenia occurred in one patient in Arm B; the rest were Grade 3 or less.

GI Toxicity
While oxaliplatin is associated with nausea and vomiting, it can be controlled by prophylactic use of a 5HT3 antagonist and/or dexamethasone. The combination of oxaliplatin and fluorouracil tends to enhance the incidence of fluorouracil-induced diarrhea.

Special populations
For the commonly occurring adverse events in Arm C, patients < 65 years old had more frequent paresthesias, nausea, vomiting, and sensory disturbances but less frequent fatigue, dehydration, and diarrhea when compared to those > 65 years old.

As stated earlier, the AUC of platinum increases as renal function declines. The number of patients with baseline renal dysfunction in the registration study was limited and no meaningful safety or efficacy guidelines could be made.

There were a limited number of patients with baseline liver dysfunction, although many had liver metastases. This did not allow for an accurate safety evaluation in this group.

Death
Within 30 days of treatment on Arm C there were 7 deaths (3 determined to be treatment related; associated with GI bleeding or dehydration), compared to 12 deaths in Arm B and 10 deaths in Arm A.

Extravasation: Although oxaliplatin has been classified as a non-vesicant, there have been reports of local tissue damage and even necrosis. One report of two extravasations on the same patient revealed localized symptoms characteristic of inflammation and tissue damage that peaked 8 days after the extravasation and resulted in underlying muscle damage and immobilization of an elbow joint. These symptoms lingered and gradually improved over a 5-8 week period. Treatment at the time of the extravasation included instillation of saline into the extravasation site, oral NSAIDs, opiates, and antibiotics.[8]

A retrospective review of 271 patients who received oxaliplatin found six occurrences of small volume extravasation from a peripheral vein without symptoms. In two patients with implantable ports, the needle became disengaged from the port and large volumes of diluted oxaliplatin infused into the surrounding tissue. No localized interventions were initiated. Both patients had signs and symptoms of tissue inflammation: visible swelling, pain at the site, redness, heat, and impairment of limb function. In patient one, pain was controlled with an oral NSAID. In patient two, local cool packs, a topical NSAID, and morphine controlled the pain, which lasted for 3 weeks. At 8 weeks, both patients had inflammation of subcutaneous fat visible on ultrasound.[9] Instillation or dilution of the drug with saline at the extravasation site is not recommended. Beyond that, there is no consistent information on treatment of extravasations with platinum based products.

Hypersensitivity reactions: There have been a small number of suspected anaphylactic reactions due to oxaliplatin that have been published. In one series of case reports, five patients experienced flushing, sweating, dizziness, shortness of breath, tachycardia, and hypotension following 5-12 cycles of oxaliplatin, fluorouracil, and leucovorin. The drug was reintroduced 2 weeks later with similar results[10] In a similar case, following the sixth cycle of oxaliplatin a patient experienced burning, pruritus, visual disturbances, facial and lingual edema, tachycardia, and sever hypotension which responded to epinephrine and IV steroids.[11] A third series investigated skin testing to oxaliplatin, carboplatin, and cisplatin following mild hypersensitivity reactions to oxaliplatin (rash, chills, fever, vomiting, flushing, pruritus, weakness, burning sensation, dizziness, facial edema). Cross reactivity was found in 6/8 patients with oxaliplatin and carboplatin but not cisplatin. Two patients had no skin reactions. A desensitization protocol, based on a carboplatin schedule, was initiated in one patient without incidence.[12] In 235 consecutive patients receiving oxaliplatin alone or in combination with fluorouracil and leucovorin, 8% experienced hypersensitivity reactions after a median of 6 cycles. Pre-treatment with a H1 and H2 blocker, steroids, APAP, a 5HT3 antagonist and prolongation of the oxaliplatin infusion prevented subsequent reactions in 10 patients.[13]

Pulmonary Toxicity: Dyspnea and cough were reported more often in the oxaliplatin combination arm than in the other two arms of the registration trial. Pulmonary fibrosis, which may be fatal, has been reported in 0.7% of study patients.

Postmarketing Experience: There has been extensive use of oxaliplatin outside of the United States for several years. Safety reports have been similar to those in the registration trial. Several safety issues, which did not show up in the registration trial, include reports of hemolytic uremic syndrome, pancreatitis, interstitial pneumonitis, cranial nerve palsies and fasciculations.

Precautions/Contraindications

Anaphylactic-like reactions have been reported to occur within minutes of starting the infusion. Treatment with epinephrine, corticosteroids, and antihistamines can alleviate symptoms.

Contraindications: known allergies to oxaliplatin or other platinum compounds; pregnancy category D

Precautions: Two types of neuropathy have been reported and graded using study-specific neurotoxicity different from the National Cancer Institute CTC.
Pulmonary fibrosis, which is sometimes fatal, has been associated with oxaliplatin in a small number of study patients.

Drug Interactions

In vitro displacement of platinum from plasma proteins did not occur with the following drugs: erythromycin, salicylates, sodium valproate, granisetron, or paclitaxel. Oxaliplatin is not metabolized by nor does it inhibit cytochrome P450 isoenzymes.

Efficacy Measures

In the registration trial, the primary objective was the overall survival of patients with metastatic colorectal cancer that recurred following first-line therapy with weekly irinotecan/fluorouracil/leucovorin who were then randomized to receive fluorouracil/leucovorin, oxaliplatin, or fluorouracil/leucovorin + oxaliplatin. At the time of the interim analysis, the survival data was not mature, and approval was granted based on the probable clinical benefit of 2 secondary endpoints: Response Rate (RR) and Time to Progression (TTP).

Clinical Trials

Efficacy of oxaliplatin (OXA) as second-line therapy in metastatic colorectal cancer (See Appendix)

Reference	No. of patients	Treatment (mg/m^2/day) [Frequency]	Response Rate (% patients) [CR + PR]	Median TTP	Median Duration of survival
Registration Trial Sanofi-Synthelabo	Arm A: 151 Arm B: 156 Arm C: 152	A: LV 200 2h inf /5FU 400 B + 600 22h inf d1-2 [q2wk] B: OXA 85 2h inf [q2wk] C: OXA 85 2h inf d-1 + LV 200 2h inf d1-2 5FU 400 B + 600 22h inf d1-2 [q2wk]	A: 0 [0 + 0] B: 1 [0 + 1] C: 9 [0 + 9]	A: 2.7 mo (CI: 1.8-3.0) B: 1.6 mo (CI: 1.4-2.7) C: 4.6 mo (CI: 4.2-6.1)	NA
Q 2 Week Studies De Gramont 1997 Debiopharm	46	FOLFOX 2 OXA 100 2h inf d-1 LV 500 2h inf d1-2 5FU 1500-2000 24 inf d1-2 [q2wk]	45.6 [2 + 43.5]	7 mo	17 mo
Andre 1998 Debiopharm and Sanofi	30	FOLFOX 3 OXA 85 2h inf d-1 LV 500 2h inf d1-2 5FU 1500-2000 22h inf d1-2 [q2wk]	20 [NA]	26 wks	57 wks
Andre 1999 Sanofi	FOLFOX 3: 38 FOLFOX 4: 51	FOLFOX 3 OXA 85 2h inf d1 LV 500 2h inf d1-2 5FU 1500 22h inf d1-2 [q2wk] FOLFOX 4 OXA 85 2h inf d1 LV 200 2h inf d1-2 5FU 400 B + 600 22h inf d1-2 [q2wk]	FOLFOX 3: 18.4 [0 + 18.4] FOLFOX 4: 23.5 [0 + 23.5]	FOLFOX 3: 4.6 mo FOLFOX 4: 5.1 mo	FOLFOX 3: 10.6 mo FOLFOX 4: 11.1 mo
Maindrault-Goebel 1999 Sanofi	60	FOLFOX 6 OXA 100 2h inf d1 LV 400 2h inf d1 5FU 400 B + 5FU 2400-3000 46h inf d 1 [q2wk]	27 [3 + 23]	5.3 mo	10.8 mo
Lee 2001	39	OXA 85 2h inf d1 LV 20mg B d1-2 5FU 1200 6h inf d 1-2 [q2wk]	42 [9.7 + 32.3]	18.8 weeks	Not yet reached
Maindrault-Goebel 2001 Sanofi-Synthelabo	48	FOLFOX 7 OXA 130 2h inf d1 x8 cycles LV 400 2h inf d1 5FU 400 B + 2400 46h inf d1 [q2wk]	42 [0 + 42]	6 mo	16.1 mo
Other regimens as 2nd line therapy Bertheault-Cvitkovic 1996[14] Brienza 1999[15] Gerard 1998[16] Janinas 2000[17] Levi 1992[18]	 50 206 36 32 46	 OXA/LV/5FU CM OXA q2-3wks, var. LV/5FU OXA q2wk, LV/5FU qwk OXA/LV/5FU qwk OXA/LV/5FU CM	 48 25.5 28 13 57	 9.3 mo 4.1 mo NA 3 mo 10 mo	 16.9 mo 9.6 mo 10 mo 9 mo 13 mo

LV=leucovorin, OXA= oxaliplatin, 5FU=fluorouracil, TTP= Time to progression, B= bolus, inf=infusion, CM= chronomodulated

Single agent oxaliplatin produces responses in chemotherapy naïve metastatic colorectal carcinoma patients that are similar to other active single agents for this indication (e.g. fluorouracil, irinotecan, raltitrexed) with response rates of 18-20%. In addition, oxaliplatin monotherapy has some activity in patients previously treated with and refractory to fluorouracil.[19] Monotherapy will not be considered at this time due to the additive and synergistic activity observed in combination with fluorouracil.

De Gramont, et al, have systematically studied the combination of a short infusion of oxaliplatin with fluorouracil and leucovorin in a 48-hour infusion/bolus regimen in patients with metastatic colorectal carcinoma previously treated with fluorouracil. The combination is known as the FOLFOX regimen (FOLinic acid, Fluorouracil, OXaliplatin). The FOLFOX regimen has been modified several times in an attempt to simplify the fluorouracil administration, reduce the leucovorin dose, augment the oxaliplatin dose and dose intensity, and minimize toxicity producing seven FOLFOX regimens. All of the FOLFOX regimens have shown similar toxicities, primarily neutropenia and sensory neuropathies without the toxicities normally attributed to other platinum-based compounds: renal toxicity, ototoxicity, thrombocytopenia, grade 4 nausea and vomiting. The FOLFOX 4 regimen was chosen for the US registration trial. The combination of bolus and infusional fluorouracil is a standard in Europe, while bolus leucovorin and fluorouracil has been the standard in the United States. The registration trial examined the second line use of oxaliplatin in combination with leucovorin and fluorouracil for patients who had recurred or progressed during or within 6 months of completion of first-line therapy with irinotecan, fluorouracil, and leucovorin. If patients fail this first-line therapy, there is no standard second line therapy that produces consistent objective responses. For comparison, in the European FOLFOX trials patients were eligible if they had progressive disease on therapy (all studies), or recurred within 6 months of adjuvant therapy (some trials) with leucovorin and fluorouracil given as a long infusion.

The US registration trial interim analysis revealed a Response Rate in 9% on the combination arm (C) versus 0% on leucovorin + fluorouracil (A) and 1% on oxaliplatin alone (B) [p=0.0002 for A versus C]. Assessment of response was based on radiographic measurements and was reviewed by an independent consulting group blinded to treatment and investigator's assessment of response. Time to progression (TTP) analysis occurred when approximately 50% of events were recorded and yielded a 2 month advantage for the combination therapy (C) versus standard leucovorin + fluorouracil (A) [P< 0.0001]. About 18% (82) of patients were excluded from this analysis due lack of follow-up radiographs or lack of submission of follow-up radiographs. The overall survival rate, the primary outcome, has not been evaluated as that data is still being collected. Another secondary endpoint, time to symptomatic worsening (TTSW) was not evaluated as <50% of the events had occurred at the time of the interim analysis.

Early studies with this combination in Europe utilized chronomodulated drug delivery to minimize toxicity of fluorouracil and maximize efficacy. While chronomodulated delivery has produced increased response rates and longer Time to Progression, it has not consistently translated into better overall survival. Similarly, giving larger doses of oxaliplatin every 3 weeks has not produced response rates, time to progression, and overall survival advantages over administration every 2 weeks at the same dose intensity.

Supporting Data: Efficacy of oxaliplatin as 1st line therapy in metastatic colorectal cancer

Reference	No. of patients	Treatment (mg/m^2/day) [frequency]	Response Rate (% of patients) [CR + PR]	Median TTP	Median Duration of survival
Comparative De Gramont 2000[20]	A: n=210 B: n=210	Group A: LV 200 2h inf d 1-2 5FU 400 B + 600 22h inf d1-2 (q2wk) Group B: (FOLFOX 4) OXA 85 2h inf d 1 LV 200 2h inf d 1-2 5FU 400 B + 600 22h inf d1-2 [q2wk]	ITT A: 21.9 (CI 17.9-25.9) B: 50.0 (CI 46.1-54.9)	A: 6.2 mo B: 9 mo	A: 14.7 mo B: 16.2 mo
Giacchetti 2000[21]	200	Arm 1: LV 300 CM d 1-5 5FU 700 CM d 1-5 Arm 2: OXA 125 CM d 1 LV 300 CM d 1-5 5FU 700 CM d 1-5 [q 3wk]	Arm 1: 16 [0 + 16] Arm 2: 53 [3 + 50]	Arm 1: 6.1 mo Arm 2: 8.7 mo	Arm 1: 19.9 mo Arm 2: 19.4 mo
Levi 1994[22]	92	Constant: OXA 20 d 1-5 LV 300 d 1-5	Constant: 32 [4 + 28]	Constant: 8 mo CM: 11 mo	Constant: 14.9 mo

		5FU 300 d 1-5 CM: OXA 20 CM d 1-5 LV 300 CM d 1-5 5FU 300 CM d 1-5 [q 21 days]	CM: 53 [7 + 46]		CM: 19 mo
Levi 1997[23]	186	Constant: OXA 20 d 1-5 LV 300 d 1-5 5FU 300 d 1-5 CM: OXA 20 CM d 1-5 LV 300 CM d 1-5 5FU 300 CM d 1-5 [q 21 days]	Constant: 29 [3 + 26] CM: 51 [5 + 45]	Constant: 7.9 mo CM: 9.8 mo	Constant: 16.9 mo CM: 15.9 mo

Oxaliplatin is approved for first-line use in many European countries. When compared to leucovorin + fluorouracil, the oxaliplatin containing regimens produced higher response rates, but only modest or no change in TTP and overall survival. The original application in the United States for first-line therapy in 2000 was denied because of similar results.

Acquisition Costs

Drug	FSS Price
Oxaliplatin 50mg injection	$577.52
Oxaliplatin 100mg injection	$1155.04

Dose	Cost per cycle	Cost per month
85 mg/m^2 X 2m^2 = 170mg	$2310.08	$4620.16
85 mg/m^2 X 1.73m^2 = 147mg	$1732.56	$3465.12

Utilization (August 2002 – November 2002)

VISN	Oxaliplatin 50mg	Oxaliplatin 100mg	Total $
1	3	16	19,748.24
2	3	8	11,572.00
3	5	18	23,985.18
4	1	17	19,748.23
5	2	4	7,771.16
6	11	15	23,133.69
7	14	36	51,105.10
8	20	65	87,189.91
9	10	30	41,628.20
11	8	4	9,027.80
12	12	28	39,432.44
13	2	4	5,642.36
14	12	16	26,827.08
15	33	44	72,268.57
16	12	37	53,428.73
17	1	15	17,491.29
18	2	2	3,385.42
19	10	26	36,685.66
20	8	14	21,164.02
21	3	15	18,619.77
22	18	32	48,396.16
Total			638,251.01

Conclusions

Clinical efficacy:

- In the US registration trial in patients with progression or early recurrence after treatment with irinotecan, leucovorin, and fluorouracil, the combination of oxaliplatin, leucovorin, and fluorouracil produced response rates and time to progression that were statistically significantly greater than similar patients receiving leucovorin and fluorouracil. Although the more important endpoint of survival advantage has not been measured yet, there is a high likelihood of clinical benefit based on this interim data. There is no standard second line therapy to compare to in this population.

- The combination of oxaliplatin, leucovorin, and fluorouracil has been studied systematically in Europe for second line treatment of colorectal carcinomas. European data supports the second-line response rates and time to progression reported in the US studies but there are no comparative studies, and the patients in Europe failed on leucovorin and fluorouracil combination therapy without irinotecan. Whether this population is similar to the US registration trial population who failed irinotecan, leucovorin, and fluorouracil is unknown.

- First line therapy with oxaliplatin, leucovorin, and fluorouracil supports the evidence for activity of this combination in colorectal carcinomas.

Safety:

- The most common toxicities reported in the medical literature and in the US registration trial were peripheral sensory neuropathies, neutropenia, nausea, emesis, diarrhea, and fatigue all of which were manageable in most patients.

- The incidence of febrile neutropenia was low in the combination arm. There was no grade IV thrombocytopenia in the oxaliplatin combination arm.

- Nausea and emesis was primarily grades I and II and was controlled with typical $5HT_3$ antagonist therapy.

- Peripheral sensory neuropathies are unique to oxaliplatin and include neuropathies exacerbated or precipitated by exposure to cold. The most disconcerting neuropathy is the sudden, but self-limiting laryngopharyngeal dysesthesia characterized by the sensation of dyspnea. While these are not typical of other platinum based compounds, they can be effectively managed with patient education.

- There were a limited number of patients with decreased renal function in clinical trials. The AUC of platinum was increased in those patients, but the significance is unknown. There were also a limited number of patients with liver dysfunction on which to evaluate dosing in that population, although many patients had liver metastases.

Recommendation

There is no survival data or symptom improvement data at this time. Publication of the complete registration trial is not available. We recommend that costs per clinical outcome and quality of life be assessed before approval for addition to the national formulary. Oxaliplatin will not be added to the national formulary or to VISN formularies at this time.

Appendix

Clinical Trials- Second line therapy 2-weekly treatment

<table>
<tr><th>Trial</th><th>Treatment/Dose (mg/m^2)</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>DeGramont 1997[24]
N=46
FOLFOX 2

Debiopharm</td>
<td>OXA 100 over 2 hours d 1
LV: 500 over 2 hours d 1-2
5FU 1500-2000 over 24 hrs d 1-2</td>
<td>
<table>
<tr><td>Age</td><td>59.4 years</td></tr>
<tr><td>Male
Female</td><td>29
17</td></tr>
<tr><td># involved sites
1
2
>2</td><td>
31
9
6</td></tr>
<tr><td>WHO
0
1
2</td><td>
22
14
5</td></tr>
<tr><td>Previous Chemotherapy
LV/5FU B + CI
LV/5FU B
LV/5FU High dose
CI ±IFN
LV/5FU other</td><td>
18
5

22
1</td></tr>
</table>
</td>
<td>
<table>
<tr><td></td><td colspan="2">All (n=46)</td><td colspan="2">Previous resistance to same LV/5FU regimen (n=22)</td></tr>
<tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td></tr>
<tr><td>CR</td><td>1</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>PR</td><td>20</td><td>43</td><td>10</td><td>45</td></tr>
<tr><td>SD</td><td>21</td><td>46</td><td>10</td><td>45</td></tr>
<tr><td>PD</td><td>3</td><td>7</td><td>2</td><td>9</td></tr>
<tr><td>ORR</td><td></td><td>46</td><td></td><td>45</td></tr>
</table>
AE:
<table>
<tr><td>Neutropenia Gr III/IV</td><td>39%</td></tr>
<tr><td>Febrile neutropenia</td><td>9</td></tr>
<tr><td>Peripheral neuropathy Gr II/III</td><td>33</td></tr>
<tr><td>Thrombocytopenia Gr III</td><td>11</td></tr>
<tr><td>Diarrhea Gr III</td><td>9</td></tr>
<tr><td>Diarrhea Gr I/II</td><td>52</td></tr>
<tr><td>Mucositis Gr III</td><td>13</td></tr>
<tr><td>Nausea Gr I/II</td><td>69</td></tr>
<tr><td></td><td></td></tr>
</table>
</td>
</tr>
<tr>
<td>Andre 1998[25]
N=30
FOLFOX 3

Debiopharm & Sanofi</td>
<td>LV: 500 over 2 hrs d 1-2
5FU 1500 over 22 hours d 1-2
OXA 85 over 2 hours d 1

Repeat q2 weeks
(for 3rd and subsequent cycles, 5FU 2000 over 22hrs if max toxicity is < grade 2)</td>
<td>
<table>
<tr><td>Age</td><td>57.9</td></tr>
<tr><td>Male
Female</td><td>14
16</td></tr>
<tr><td># Involved sites
1
2
>2</td><td>
20
7
3</td></tr>
<tr><td>Type of previous chemotherapy
LV-5FU 2X/month
LV-FU ± IFN</td><td>
25
5</td></tr>
</table>
</td>
<td>
<table>
<tr><td>ORR</td><td>20% (95% CI 8-39)</td></tr>
<tr><td>SD</td><td>50</td></tr>
<tr><td>PD</td><td>30</td></tr>
<tr><td>Overall Survival</td><td>57 weeks</td></tr>
<tr><td>Duration of Response</td><td>37 weeks</td></tr>
</table>
Median number of cycles: 9.5

AE:
<table>
<tr><td></td><td>≥Grade 3 (%)</td></tr>
<tr><td>Neutropenia</td><td>20</td></tr>
<tr><td>Thrombocytopenia</td><td>13</td></tr>
<tr><td>Alopecia</td><td>10</td></tr>
<tr><td>Acute laryngospasm (without recurrence when OXA administered over 6 hrs)</td><td>7</td></tr>
<tr><td>Sensory neuropathy Grade 2</td><td>13</td></tr>
<tr><td>Peripheral neuropathy gr 1-2</td><td>90</td></tr>
</table>
Stopped Treatment: 5 patients
4 with sensory neuropathy
1 with anaphylaxis after OXA that fully regressed
</td>
</tr>
<tr>
<td>Andre 1999[26]
N=38
FOLFOX 3
(2 additional patients were excluded from analysis)
N=51
FOLFOX 4
(6 additional patients were excluded from analysis)</td>
<td>FOLFOX 3:
OXA 85 over 2 hours d 1
LV 500 over 2 hours d 1-2
5FU 1500 over 22 hours d 1-2
repeat q2 weeks

FOLFOX 4:
OXA 85 over 2 hours d 1
LV 200 over 2 hours d 1-2
5FU 400 B + 600 over</td>
<td>
<table>
<tr><td></td><td>FOLFOX 3</td><td>FOLFOX 4</td></tr>
<tr><td>Age</td><td>60.2</td><td>64.3</td></tr>
<tr><td>Male
Female</td><td>26
14</td><td>37
20</td></tr>
<tr><td># involved sites
1
2
3
>3</td><td>
16
13
8
3</td><td>
26
16
4
11</td></tr>
<tr><td>Prior adjuvant tx</td><td>14</td><td>18</td></tr>
<tr><td>Prior metastatic</td><td></td><td></td></tr>
</table>
</td>
<td>
Median of 10 cycles given
<table>
<tr><td></td><td>FOLFOX 3</td><td>FOLFOX 4</td></tr>
<tr><td>PR</td><td>18.4%</td><td>23.5%</td></tr>
<tr><td>SD</td><td>29</td><td>31.4</td></tr>
<tr><td>PD</td><td>42.1</td><td>39.2</td></tr>
<tr><td>PFS</td><td>4.6 mos</td><td>5.1 mos</td></tr>
<tr><td>OS</td><td>10.6 mos</td><td>11.1 mos</td></tr>
</table>
AE
<table>
<tr><td>(Grades III/IV)</td><td>FOLFOX 3</td><td>FOLFOX 4</td></tr>
<tr><td>Neutropenia</td><td>15%</td><td>36.9% (p=0.02)</td></tr>
<tr><td>Thrombocytopenia</td><td>2.5</td><td>7 (NSS)</td></tr>
</table>
</td>
</tr>
</table>

Sanofi	22 hours d 1-2 repeat q2 weeks	metastatic tx LV5FU FOLFUHD	28 12	48 8

Nausea/vomiting	5	7
Diarrhea	5	5.2
Stomatitis	17.5	5.3 (p= 0.08)
Sensory neuropathy	27.5	15.8
Hand-foot syndrome	3 cases	7 cases

1 Grade IV febrile neutropenia →died
Discontinued therapy: 20.6%
(1 death, 19 sensory neuropathy)

Maindrault-Goebel 1999[27]
N=60
FOLFOX 6

Sanofi

OXA 100 over 2 hours d 1
LV 400 over 2 hours d 1
5FU 2400 over 46 hours
repeat q 2 weeks
(if toxicities are < grade 2 after 2 cycles, increase 5FU to 3000 over 46 hours)

Group A: refractory to bimonthly simplified LV and 5FU regimen, < 75 yo, alk phos <3X ULN

Group B: at least one of the following: Refractory to LV and 5FU regiment other than the simplified regimen
Age >75
Non-measurable lesion

	A (n=39)	B (n=21)
Age	62.3	61.2
>75 years old	0	6
# involved sites 1 2 >2	 27 9 3	 14 7 0
Simplified LV 5FU Other LV5FU	39 0	9 12

Median 6.7 cycles given

	A	B	ALL
CR	5%	0%	3
PR	26	19	23
SD	54	29	45
PD	133	48	25
ORR	31	19	27
Duration of response			8.1 mos
PFS	6.2 mos	4.4 mos	5.5 mos
OS	14.3 mos	8.8 mos	10.8 mos

AE

Grade III/IV	%
Neutropenia	24 (non were d/c'd because of neutropenia)
Sensory neuropathy Gr III	16 (10 pts stopped therapy)
Thrombocytopenia Gr III	2
Nausea Gr III	7
Diarrhea Gr III	7
Mucositis Gr III	5
Severe anaphylaxis	2 patients→d/c OXA

Lee 2001[28]
N=39

OXA 85 over 2 hours d 1
LV 20 B d 1-2
5FU 1200 over 6 hours d 1-2

Age	57
Male Female	59% 41
# involved sites 1 2 ≥3	 10% 36 54

Median 6 cycles administered

OR (n=31) [CR + PR]	42% [9.7 + 32.3]
SD	22.5
PD	35.5
Duration of response	91 days
PFS	132 days
OS	Median not yet reached (median follow-up 177 days)

AE

Nausea/vomiting ≤gr 2	70%
Peripheral neuropathy ≤gr II	61
Neutropenia gr II/IV	12
Stomatitis gr 3	1 patient
No treatment related deaths	

Maindrault-Goebel 2001[29]
N=48

FOLFOX7

Sanofi-Synthelabo

OXA 130 over 2 hours d 1 X8 cycles only
LV 400 over 2 hours d 1
5FU 400 B + 2400 over 46 hours

repeat q 2weeks

Group A: progressive disease while on simplified LV5FU

Group B: progressive disease while on other bimonthly LV5FU regimens

	A	B
Age	67	63
Male	61%	67%

	A	B	All
ORR	44%	33%	42%
Duration of response			6.9 mos
SD	36	50	40
PD	19	17	19
PFS			6 mos
OS			16.1mos

Female	39	33
# involved sites		
1	61%	75%
≥2	39	25

Withdrawal due to toxicity 8%

AE

Neutropenia gr III	9%
Sensory neuropathy gr III	15%
Nausea/vomiting gr III/IV	17
Mucositis gr I/II	42
Laryngospasm	11 (did not recur when OXA infusion given over 6 hours)

Prepared by: Mark C. Geraci, Pharm.D.
Date: December 2002

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National PBM Drug Monograph
Oxaliplatin (Eloxatin™)
Addendum May 2004
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

See the original oxaliplatin drug monograph at: http://www.vapbm.org/monograph/Oxaliplatin2.pdf

Introduction

Oxaliplatin was originally approved by the FDA in August 2002 for second-line therapy in combination with infusional leucovorin and 5-fluourouracil (FOLFOX4) for metastatic colorectal carcinoma that has recurred or progressed within 6 months of completion of first-line therapy with leucovorin, 5-fluourouracil, and irinotecan. At that time, there were two, small randomized trials in Europe showing good results when used as first-line combination therapy compared to 5-fluourouracil and leucovorin alone.

In January 2004, the FDA approved a new indication for FOLFOX4 as first-line therapy in patients with metastatic colorectal carcinoma. The results of this new trial information and a supporting trial will be reviewed.

Efficacy

Additional Data on First-line Therapy in Metastatic Colorectal Carcinoma

<table>
<tr><th>Study</th><th>Number of patients</th><th>Treatment Arms</th><th>Outcomes</th></tr>
<tr><td>Goldberg, et al.[1] Submitted to FDA</td><td>795</td><td>Arm 1: IFL (Control)
Irinotecan 125mg/m^2
5FU bolus 500mg/m^2
Leucovorin 20mg/^{2}
Weekly X4 every 6 weeks

Arm 2: FOLFOX4
Oxaliplatin 85mg/m^2 day 1
Leucovorin 200mg/m^2 day 1 & 2
5FU 400mg/m^2 bolus followed by
5FU 600mg/m^2 over 22 hours d 1&2
Every 2 weeks

Arm 3: IROX
Irinotecan 200mg/m^2
Oxaliplatin 85mg/m^2
Every 3 weeks</td><td>
<table>
<tr><th>Outcome</th><th>IFL (n=264)</th><th>FOLFOX (n=267)</th><th>IROX (n=264)</th></tr>
<tr><td>TTP (months)</td><td>6.9</td><td>8.7 (p=0.0014)</td><td>6.5* (p>0.5)</td></tr>
<tr><td>OS (months)</td><td>15</td><td>19.5 (p=0.001)</td><td>17.4** (p=0.04)</td></tr>
<tr><td>RR (%)</td><td>31</td><td>45 (p=0.002)</td><td>35* (p=0.34)</td></tr>
</table>
*No difference between IROX and IFL
** No difference between FOLFOX and IROX

Median follow-up of 24 months
</td></tr>
<tr><td>Tournigand, et al.[2]</td><td>226</td><td>Arm A: FOLFIRI
Leucovorin 200mg/m^2 day 1
5FU 400mg/m^2 bolus followed by
5FU 2400-3000mg/m^2/46 hours D 1
Irinotecan 180mg/m^2 day 1
Every 2 weeks

Arm B: FOLFOX6
Leucovorin 200mg/m^2 day 1
5FU 400mg/m^2 bolus followed by
5FU 2400-3000mg/m^2/46 hours D 1
Oxaliplatin 100mg/m^2 day 1
Every 2 weeks

Give A or B until progression or toxicity, then give opposite therapy until progression or death</td><td>
<table>
<tr><th>Outcome</th><th>FOLFIRI (n=109)</th><th>FOLFOX6 (n=111)</th></tr>
<tr><td>Second PFS (months)</td><td>14.2</td><td>10.9 (p=0.64)</td></tr>
<tr><td>OS (months)</td><td>21.5</td><td>20.6 (p=0.99)</td></tr>
<tr><td>RR (%)
First-line
Second-line</td><td>
56
4</td><td>
54
15 (p=0.05)</td></tr>
<tr><td>Median # cycles
First-line
Second-line</td><td>
13
6</td><td>
12
8</td></tr>
</table>
</td></tr>
</table>

In the Goldberg trial patients had good performance status (0-2) and measurable or assessable disease. The primary objective was Time To Progression and IFL served as the control regimen. More patients in the control arm (67% vs. 42% in FOLFOX arm and 55% in IROX arm) discontinued therapy because of

progression. More patients in the experimental arms discontinued therapy due to adverse events; it is likely that patients stopping without progression will have a better outcome. This is supported by the fact that the time to treatment discontinuation was similar in all three arms but survival was different. Second-line therapy was allowed and reported but not specified in the protocol. In the FOLFOX arm, 60% received second-line therapy with irinotecan. Only 24% of patients in the IFL arm were treated with oxaliplatin-based therapy due to its limited availability during the trial. The availability of second-line therapy probably contributed to overall survival, but does not explain the increased time to progression and response rate seen in the FOLFOX arm. Patients receiving IFL had higher rates of nausea, diarrhea, vomiting, dehydration and febrile neutropenia while FOLFOX patients had higher rates of paresthesias, and neutropenia that was seldom associated with clinical infection. The rate of grade 3 toxicity in the IROX arm was similar to IFL.

The Tournigand study utilized a simplified leucovorin and infusional 5-fluorouracil regimen in combination with either irinotecan or oxaliplatin to determine the best sequence when treating metastatic colorectal carcinomas. Patients were randomly assigned to receive either the irinotecan-based regimen or oxaliplatin-based regimen until progressive disease, and then switch to the opposite regimen. The primary objective was second Progression Free Survival (time from entry into the study to progression after the second-line treatment). Second-progression free survival, first progression free survival, overall survival, and first-line response rates did not differ between the two arms. There was an imbalance in the number of patients who received second-line therapy- 74% of FOLFIRI patients received FOLFOX6 second-line, and 62% of FOLFOX6 patients received FOLFIRI second-line. Improvement in performance status was similar between first and second-line therapies. During first-line therapy, grade 3/4 febrile neutropenia, nausea, vomiting, mucositis, and fatigue were more frequent in the FOLFIRI arm, while grade 3 sensory neurotoxicity, grade 3/4 neutropenia, and thrombocytopenia were more common in the FOLFOX6 arm. During second-line therapy, toxicity differences were minor. Elderly patients did not experience more toxicity than younger patients. The results of the FOLFIRI first-line therapy compares favorably to the traditional IFL given by the Saltz regimen. FOLFOX 6 in first-line and second-line therapy produced results similar to FOLFOX4 despite an increased dose of oxaliplatin. The study failed to demonstrate an advantage for one sequence over another; however, there were factors that could not be accounted for, such as secondary surgeries for metastases, therapeutic breaks, and delays in starting second-line therapies as well as the imbalance in patients receiving second-line therapy.

Safety

Adverse events with oxaliplatin and 5-fluorouracil/leucovorin used in previously untreated patients with metastatic colorectal carcinomas were similar to those seen when used for previously treated patients. Gastrointestinal, hematologic, and neurologic adverse events occurred more frequently in the oxaliplatin group when used as first-line therapy.

Selective Adverse Events of Oxaliplatin used in Previously Untreated Patients (≥5% of patients and with ≥1% Grade 3/4 events)

Adverse Event	All Grades (%)	Grade 3/4 (%)
Allergy/Immunology		
Hypersensitivity	12	2
Cardiovascular		
Thrombosus	6	5
Hypotension	5	3
Constitutional		
Fatigue	70	7
Abdominal pain	29	8
Myalgia	14	2
Pain	7	1
Dermatology		
Skin reaction- hand/foot	7	1
Injection site reaction	6	0
Gastrointestinal		
Nausea	71	6

Diarrhea	56	12
Vomiting	41	4
Stomatitis	38	0
Anorexia	35	2
Constipation	32	4
Hematology		
Infection no ANC	10	4
Infection – ANC	8	8
Lymphopenia	6	2
Febrile neutropenia	4	4
Hepatic/Metabolic/Renal		
Hyperglycemia	14	2
Hypokalemia	11	3
Dehydration	9	5
Hypoalbuminemia	8	0
Hyponatremia	8	2
Neurology		
Paresthesias	77	18
Pharyngo-laryngeal dysesthesias	38	2
Neurosensory	12	1
Pulmonary		
Cough	35	1
Dyspnea	18	7

Recommendation:

The Goldberg trial found that FOLFOX4 was more active (increased response rate, time to progression, and overall survival) and better tolerated than full dose IFL when used as first-line therapy in colorectal cancers. Because of increased toxicity with IFL in several clinical trials, the doses of irinotecan and 5-fluorouracil were later reduced, but those patients are not reported here. Reduced doses of IFL decrease toxicity, but it is uncertain how it will affect response and survival. In the Tournigand study, the two sequences of FOLFIRI and FOLFOX6 were found to be equivalent in terms of survival. The difference is in the adverse events: more neuropathy with FOLFOX6 and more diarrhea and asthenia with FOLFIRI.

It appears that the doublets (FOLFOX and FOLFIRI) are the most efficacious combinations available. They are more toxic than infusional 5-fluorouracil alone. 5-fluorouracil remains the basis of both regimens, however toxicity is reduced when giving it as an infusion versus giving it as bolus. While infusional 5-fluorouracil is common in Europe, it is less common in the United States and will need to be utilized in order to achieve similar results. Bevacizumab plus FOLFOX4 also achieves high survival rates although with increased toxicity. The lack of head-to-head trials makes it difficult to compare regimens.

Oxaliplatin was originally reviewed for formulary status in March of 2003 for second-line therapy after relapse or progression on an irinotecan-containing therapy. It was voted on to remain as nonformulary at that time. New data shows oxaliplatin in a combination regimen has more activity and less toxicity than IFL. There is also data to support no difference in survival and no best sequencing of administration in first and second-line therapy when comparing FOLFOX and FOLFIRI. Oxaliplatin should be available as one choice for first-line therapy of metastatic colorectal carcinomas for those patients who can tolerate an intensive therapy.

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