

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-fluorouracil (FOLFOX4) for metastatic colorectal carcinoma that has recurred or progressed within 6 months of completion of first-line therapy with leucovorin, 5-fluorouracil, 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-fluorouracil 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

Study	Number of patients	Treatment Arms	Outcomes			
			Outcome	IFL (n=264)	FOLFOX (n=267)	IROX (n=264)
Goldberg, et al. ¹ Submitted to FDA	795	Arm 1: IFL (Control) Irinotecan 125mg/m ² 5FU bolus 500mg/m ² Leucovorin 20mg/m 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	TTP (months)	6.9	8.7 (p=0.0014)	6.5* (p>0.5)
			OS (months)	15	19.5 (p=0.001)	17.4** (p=0.04)
			RR (%)	31	45 (p=0.002)	35* (p=0.34)
			*No difference between IROX and IFL ** No difference between FOLFOX and IROX Median follow-up of 24 months			
Tournigand, et al. ²	226	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	Second PFS (months)	14.2	10.9 (p=0.64)	
			OS (months)	21.5	20.6 (p=0.99)	
			RR (%) First-line Second-line	56 4	54 15 (p=0.05)	
			Median # cycles First-line Second-line	13 6	12 8	

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

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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 Thrombosis Hypotension	6 5	5 3
Constitutional Fatigue Abdominal pain Myalgia Pain	70 29 14 7	7 8 2 1
Dermatology Skin reaction- hand/foot Injection site reaction	7 6	1 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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References:

¹ Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Onc* 2004;22:23-30.

² Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Onc* 2004;22:229-237.