Aetna Better Health®
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AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Oxaliplatin (Eloxatin)

Number: 0683

Policy

I. Aetna considers oxaliplatin injection (Eloxatin) medically necessary for the following indications:

A. Adenocarcinoma of the pancreas and ampullary and periampullary carcinomas; or
B. Advanced adenocarcinoma of the anus; or
C. Advanced appendiceal carcinoma; or
D. Advanced carcinoma of the colon or rectum, including use as adjuvant treatment in persons who have undergone complete resection of their primary tumor; or
E. Advanced epithelial ovarian carcinoma/fallopian tube carcinoma/primary peritoneal cancer; or
F. Advanced esophageal or esophagogastric junction carcinoma; or
G. Advanced gastric carcinoma; or
H. Advanced small bowel carcinoma; or
   I. Advanced testicular cancer; or
J. Cholangiocarcinoma (intrahepatic or extrahepatic); or
K. Advanced pancreatic adenocarcinoma; or
L. Carcinoma of unknown primary (occult primary); or
M. Neuroendocrine tumors
N. Relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma; or
O. Relapsed or refractory non-Hodgkin's lymphoma (adult T-cell leukemia/lymphoma, AIDS-related B-cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, gastric MALT lymphoma, nongastric MALT lymphoma, mantle cell lymphoma, mycosis fungoides/Sezary syndrome, splenic marginal zone lymphoma, peripheral T cell lymphoma (including angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, or enteropathy-associated T-cell lymphoma), primary cutaneous B-cell lymphoma, primary cutaneous anaplastic large cell lymphoma (ALCL); or
P. Unresectable or metastatic gallbladder cancer.

II. These products are NOT covered for members with the following criteria:
   • Use not approved by the FDA; AND
   • The use is unapproved and not supported by the literature or evidence as an accepted off-label use.

See also CPB 0371 - Brachytherapy, CPB 0375 - Photodynamic Therapy, CPB 0516 - Colorectal Cancer Screening, and CPB 0535 - Virtual Gastrointestinal Endoscopy.

Background

Colorectal Cancer:

Colorectal cancer is the second-leading causes of cancer death in the United States. It is the nation’s third most common cancer accounting for approximately 15% of all new cancer cases. Metastatic disease is present at diagnosis in 30% of the patients, and about 50% of early-stage patients will eventually present with metastatic disease. For many years, standard treatment of colorectal cancer was 5-fluorouracil (5-FU)-based therapy. Recent availability of newer agents, including capecitabine, irinotecan and oxaliplatin, has significantly expanded the options available for the management of patients with advanced colorectal cancer, with consequent improvements in survival. On February 12, 2004, the U.S. Food and Drug Administration (FDA) approved cetuximab (Erbitux), a monoclonal antibody, as a combination treatment with irinotecan for the treatment of patients with advanced colorectal cancer that has spread to other parts of the body; or alone if patients cannot tolerate irinotecan. Although cetuximab has been demonstrated to shrink tumors in some patients and delay tumor growth, especially when used as a combination treatment, it has not been shown to extend patients’ lives.

Oxaliplatin is a new 3rd-generation platinum analog. It is believed to work via the formation of reactive platinum complexes, which inhibit DNA synthesis by forming inter-strand and intra-strand cross-linking of DNA molecules, thus disrupting DNA replication and transcription. Oxaliplatin has been reported to exhibit cytotoxic
efficacy as well as a well-tolerated safety profile. The main side effect of oxaliplatin is a sensory neuropathy exacerbated by cold exposure. Pre-clinical studies have demonstrated that oxaliplatin is synergistic with FU and SN-38, the active metabolite of irinotecan. Furthermore, oxaliplatin has been shown to be effective when used in combination with 5-FU and leucovorin (LV) for the treatment of advanced colorectal cancer.

In January 2004, the FDA approved Eloxatin (oxaliplatin for injection) in combination with 5-FU/LV for the first-line treatment of advanced colorectal cancer. The drug was previously approved in August 2002 for second-line treatment of patients with metastatic carcinoma of the colon or rectum (patients whose disease 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). The expanded approval was based on clinical data that showed that patients with advanced colorectal cancer treated with oxaliplatin given in combination with 5-FU/LV as first-line chemotherapy had a statistically significant improvement of nearly 5 months in median survival time compared to patients treated with a standard treatment of irinotecan in combination with 5-FU/LV.

Goldberg et al (2004) suggested that oxaliplatin and 5-FU/LV should be considered standard first-line treatment for patients with advanced colorectal cancer. In this study, a total of 795 patients with metastatic colorectal cancer who had not been previously treated for advanced disease were randomized to receive (i) oxaliplatin and infused 5-FU/LV; (ii) irinotecan and bolus 5-FU/LV; or (iii) oxaliplatin and irinotecan with no 5-FU/LV. The primary end point was time to progression, with secondary end points of response rate, survival time, and toxicity. A median time to progression of 8.7 months, response rate of 45 %, and median survival time of 19.5 months were observed in the oxaliplatin/5-FU/LV group. These results were significantly superior to those observed for the irinotecan/5-FU/LV (6.9 months, 31 %, and 15.0 months) and oxaliplatin/irinotecan (6.5 months, 35 %, and 17.4 months) groups.

In addition to treatment of colorectal carcinoma, oxaliplatin has been approved by the FDA for use as adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. This approval was based on phase III clinical studies that demonstrated an improvement in disease-free survival, but no demonstrated benefit in overall survival after a median follow-up of 4 years.

The U.S. Pharmacopeial Convention has concluded that oxaliplatin is indicated for use in combination with 5-FU/LV for the treatment of advanced carcinoma of the colon or rectum. According to the USP-DI, oxaliplatin is also indicated, in combination with 5-FU/LV or capecitabine, for the first-line treatment of non-resectable, advanced, or metastatic colon or rectal carcinoma. Prior adjuvant or palliative 5-FU-based chemotherapy and radiation therapy are permitted. The U.S. Pharmacopoeia has stated that oxaliplatin is indicated for use in combination with infusional 5-FU/LV for the adjuvant treatment of stage III 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.

Esophageal Cancer:
Treatments for esophageal cancer and gastroesophageal junction cancer have centered on combined-modality therapy: combinations of 5-FU, cisplatin, and radiation. More recently, oxaliplatin has been studied for the treatment of esophageal cancer. Khushalani et al (2002) examined the dosage and schedule of oxaliplatin (OXP) used in combination with protracted-infusion (PI) 5-FU and external-beam radiation therapy (XRT) for patients with primary esophageal carcinoma (EC). Eligibility included therapeutically naive EC patients with clinical disease stages II, III, or IV. Initial doses and schedules for cycle 1 consisted of OXP 85 mg/m2 on days 1, 15, and 29; PI 5-FU 180 mg/m2 for 24 hours for 35 days; and XRT 1.8 Gy in 28 fractions starting on day 8. At completion of cycle 1, eligible patients could undergo an operation or begin cycle 2 without XRT. Post-operative patients were eligible for cycle 2. Stage IV patients were allowed 3 cycles in the absence of disease progression. OXP and 5-FU increases were based on dose-limiting toxicity (DLT) encountered in cohorts of three consecutive patients. Thirty-eight eligible patients received therapy: 22 non-invasively staged as IV and 16 non-invasively staged as II and III. Thirty-six patients completed cycle 1, 29 patients started cycle 2, and 24 patients completed cycle 2. The combined-modality therapy was well-tolerated, but DLT prevented OXP and 5-FU escalation. No grade 4 hematologic toxicity was noted. Eleven grade 3 and two grade 4 clinical toxicities were noted in eight patients. After cycle 1, 29 patients (81 %) had no cancer in the esophageal mucosa. Thirteen patients underwent an operation with intent to resect the esophagus; 5 patients (38 %) exhibited pathologic complete responses. The authors concluded that OXP 85 mg/m(2) administered with PI 5-FU and XRT is safe, tolerable, and seems effective against primary EC. The role of OXP in multi-modality regimens against EC deserves further evaluation.

Oxaliplatin appears to be as effective as cisplatin for esophageal cancer, with better tolerability. Sumpter et al (2005) reported on a planned interim analysis to establish the optimal dose of capecitabine (X) to be used within a multicenter, randomized study evaluating the potential roles of oxaliplatin (O) and X in chemonaive patients with advanced esophagogastric cancer. Patients were randomized to one of four regimens: epirubicin, cisplatin, 5-fluorouracil (ECF), EOF, ECX or EOX. A total of 204 patients were randomized at the time of the protocol planned interim analysis. Combined complete and partial response rates were ECF 31% (95% confidence interval [CI]: 18.7 to 46.3), EOF 39 % (95 % CI: 25.9 to 53.1), ECX 35 % (95 % CI: 21.4 to 50.3), and EOX 48 % (95 % CI: 33.3 to 62.8). The investigators concluded that the replacement of C by O does not appear to impair efficacy.

Guidelines from the National Comprehensive Cancer Network (2006) guidelines on esophageal cancer state that an oxaliplatin-based regimen may be indicated for recurrent or metastatic disease in patients with Karnofsky performance score greater than 60 or Eastern Cooperative Oncology Group (ECOG) performance score less than or equal to 2.

Pancreatic Cancer:

Systemic chemotherapy with 5-FU-based combinations had minimal impact on natural history of pancreatic cancer. Several new agents have been identified over the past decade. Favorable adverse effect profile and tolerability are clear...
advantages of single-agent gemcitabine and enable its incorporation into combination regimens. Currently, the most widely used regimens involve combination partners such as 5-FU, cisplatin, and docetaxel. Recently, combination therapy using gemcitabine and oxaliplatin has been studied in the treatment of patients with advanced or metastatic pancreatic adenocarcinoma (ACA).

In a phase II clinical study, Alberts et al (2003) examined the effectiveness of gemcitabine and oxaliplatin in patients (n = 47) with advanced or metastatic pancreatic ACA. Oxaliplatin was given intravenously on day 1 and gemcitabine intravenously on days 1 and 8 of a 3-week cycle. The primary endpoint of the trial was 6-month survival. Secondary endpoints included response rate, overall survival, median time to progression and toxicity. Of the 46 patients assessed for the primary endpoint, 50 % lived for greater than or equal to 6 months. The median time to progression was 4.53 months. Five confirmed responses were seen with a median duration of response of 2.7 months. Overall, the treatment was well-tolerated. However, 1 patient died as a result of treatment-related hemolytic uremic syndrome. The authors concluded that gemcitabine and oxaliplatin, at doses of 1000 mg/m2 and 100 mg/m2, respectively, showed moderate activity in patients with pancreatic ACA.

In a phase II clinical study, Conroy et al (2005) examined the effectiveness of oxaliplatin with irinotecan, leukovorin and 5-fluorouracil in chemotherapy-naive patients with histologically proven pancreatic ACA. Patients were treated every 2 weeks. Forty-seven patients were entered, and 46 received treatment. Thirty-five patients (76 %) had metastatic disease. Subjects received a median of 8 cycles (range of 1 to 24 cycles). Grade 3 to 4 neutropenia occurred in 52 % of patients, including 2 patients with febrile neutropenia. Other relevant toxicities included grade 3 to 4 nausea (20 %), vomiting (17 %), and diarrhea (17 %) and grade 3 neuropathy (15 %). The confirmed response rate was 26 % (95 % CI: 13 % to 39 %), including 4 % complete responses. Median time to progression was 8.2 months (95 % CI: 5.3 to 11.6 months), and median overall survival was 10.2 months (95 % CI: 8.1 to 14.4 months). Between baseline and end of treatment, patients had improvement in all quality of life functional scales, except cognitive functioning.

Decreaux reported on the results of a randomized phase II, open-label multicenter study evaluating oxaliplatin alone, infusional 5-fluorouracil alone and an oxaliplatin/infusional 5-FU combination in untreated, advanced pancreatic carcinoma. Sixty-three patients were treated: 17 patients received oxaliplatin, 31 patients received oxaliplatin combined with 5-FU, and 15 patients received 5-FU, with a median of 3, 6 and 2 cycles per patient, respectively. All responses (3 partial responses) occurred in subjects receiving the oxaliplatin/5-FU combination therapy (10 % response rate). Five of 32 patients evaluable for clinical benefit were responders (oxaliplatin, 14%; oxaliplatin/5-FU combination, 21 %). Median time to progression and overall survival were higher in the combination arm (4.2 and 9.0 months, respectively) than either single-agent arm (oxaliplatin, 2.0 and 3.4 months; 5-FU, 1.5 and 2.4 months, respectively). The investigators concluded that, with a 10 % response rate, median overall survival of 9 months and an encouraging safety profile, the oxaliplatin/5-FU combination is effective, appears
superior to infusional 5-FU and warrants further studies in pancreatic adenocarcinoma patients.

Based upon results of a phase III clinical study comparing gemcitabine in combination with oxaliplatin (GEMOX) versus gemcitabine alone, guidelines on pancreatic cancer from the National Comprehensive Cancer Network (NCCN, 2010) indicate the use of oxaliplatin in combination with gemcitabine for patients with locally advanced or metastatic disease and good performance status. These guidelines also recommend the use of oxaliplatin as second-line therapy in combination with fluorouracil/leucovorin or capecitabine for patients with progressive disease and good performance status who have not received prior fluoropyrimidine-based chemotherapy.

Gastric Cancer:

The U.S. Pharmacopeial Convention (2004) has concluded that gastric cancer is an accepted off-label indication for oxaliplatin. Several clinical trials have demonstrated response rates in the order of 40 to 60% with combination chemotherapy regimens that incorporate oxaliplatin.

Zhang et al (2004) reported on the results of a controlled clinical trial involving 48 patients with advanced gastric cancer were divided into a group treated with an oxaliplatin-containing regimen (oxaliplatin, leucovorin, 5-fluorouracil, and etoposide (VP-16) and control group receiving a standard chemotherapy regimen containing DDP in place of oxaliplatin (DDP, leucovorin, 5-fluorouracil, and VP-16). The response rate was 64% (16/25) in the oxaliplatin-treatment group (25 cases) and 34.8% (8/23) in the control group receiving standard chemotherapy (23 cases), a difference that was statistically significant (p < 0.05). The median survival and 1-year survival rates were 11.5 months and 45.6% for the treatment group versus 10.5 months and 36.5% for the control group. There was, however, no statistical difference in 2 groups for overall survival (p > 0.05, log-rank test). The main differences in side effects were significantly more sensory neuritis in the treatment group and significantly more nausea and vomiting in the control group. The incidence of other side effects were similar between groups. The investigators concluded that the oxaliplatin-containing regimen was effective and well-tolerated for gastric carcinoma.

Yang et al (2004) reported on the results of a controlled clinical study comparing combination chemotherapy with oxaliplatin and hydroxycamptothecine with a standard chemotherapy regimen of VP-16, leucovorin calcium and 5-fluorouracil in 43 patients with advanced gastric cancer. The response rate was 58.3% (14/24) in the treatment group and 42.1% (8/19) in the control group, a difference that was statistically significant. The investigators reported that these chemotherapy regimens were well tolerated.

Ovarian Cancer:

Guidelines from NCCN (2006) state that oxaliplatin is an acceptable alternative chemotherapeutic regimen for recurrent epithelial ovarian cancer for Stage II, III, and IV patients with partial responses to their primary paclitaxel and platinum-based chemotherapeutic regimens. The guidelines note that oxaliplatin has been demonstrated to be active in recurrent epithelial ovarian cancer.
Testicular Cancer:

Testicular germ cell tumors represent the most frequent malignancy in young males aged 20 to 35 years. Despite the considerably high cure rates provided by first line chemotherapy, 20 to 30 % of cases with advanced disease do not achieve a long-term disease-free survival with first-line chemotherapy. Guidelines from the NCCN (2007) state that oxalliplatin is an acceptable alternative for palliative chemotherapy of testicular cancer when used in combination with gemcitabine after first-line salvage therapy with ifosfamide, cisplatin and vinblastine (VeIP) regimen.

The German Testicular Cancer Study Group (Kollmannsberger et al, 2004) investigated the activity of a gemcitabine plus oxaliplatin regimen in 35 patients with cisplatin-refractory germ cell cancer. Primary tumor localization was gonadal, retroperitoneal, or mediastinal in 30, 1, and 4 patients, respectively. Patients had been pretreated with a platinum regimen and 89 % of patients previously had experienced treatment failure after high-dose chemotherapy with peripheral-blood stem-cell transplantation. Sixty-three percent of patients were considered absolutely cisplatin-refractory or cisplatin-refractory. Three patients attained a complete remission, 2 patients attained a marker-negative partial remission, and 11 patients attained a marker-positive partial remission, resulting in an overall response rate of 46 % (95 % CI: 30% to 64%). All 3 patients with complete remission and 1 patient with a marker-negative partial remission remained disease free at 16+, 12+, 4+, and 2+ months of follow-up. Seven (44 %) of these 16 responses, including 1 complete remission, occurred in cisplatin-refractory patients. Toxicity consisted mainly of myelosuppression, with Common Toxicity Criteria grade 3 occurring in 54 % of patients. Only 9 % of patients developed neutropenic fever. The investigators concluded that gemcitabine plus oxaliplatin demonstrates antitumor activity with acceptable toxicity in heavily pretreated patients with relapsed or cisplatin-refractory germ cell tumors, and may offer a chance of long-term survival for selected patients.

Pectasides et al (2004) investigated the efficacy and tolerability of the combination of oxaliplatin and irinotecan in 18 patients with relapsed or cisplatin-refractory germ cell tumors. The investigators reported that 7 patients (40 %) achieved a favorable response (4 complete and 3 partial responses). One of the complete responders relapsed after 2.5 months and despite further treatment with high dose chemotherapy, he died 2 months later. The investigators reported that the remaining 3 patients are continuously disease free for 11+, 14+ and 19+ months. The partial responders subsequently progressed and died after 2, 3 and 4.5 months, respectively. The investigators noted that none of the patients with extra-gonadal mediastinal germ cell tumors responded to oxaliplatin and irinotecan chemotherapy. The investigators reported that the combination of oxaliplatin and irinotecan was well-tolerated. Neutropenia related toxicity (grade 3/4, 17 %), neutropenic infections and sepsis were not common; the investigators posited that this was probably due to prophylactic use of hematopoietic colony stimulating factor. The investigators stated that thrombocytopenia and anemia were not a serious problem. Gastrointestinal side effects, specifically grade 3/4 diarrhea and nausea/vomiting were noted in 22 % and 28 % of patients, respectively. The investigators found that oxaliplatin-associated neurotoxicity was rather low; grade
3 peripheral sensory neuropathy was recorded in 11% of patients. The investigators concluded that the combination of oxaliplatin and irinotecan is feasible and associated with significant clinical antitumor activity, mild and manageable toxicity and easy outpatient administration in patients with relapsed or cisplatin-refractory germ cell cancer. This combination seems to offer a possibility for long-term disease-free status (17%), despite the poor prognostic features of the study patient group.

**Non-Hodgkin's Lymphoma:**

Oxaliplatin has been used alone or in combination in the treatment of patients with recurrent or refractory non-Hodgkin's lymphoma (NHL).

Addeo et al (2004) noted that high and intermediate grade NHL require treatments with aggressive chemotherapy schedules. However, low grade NHLs display a low chemo-responsiveness and patients aged greater than 65 years often do not tolerate anthracycline and corticosteroid-containing chemotherapy regimens. Therapeutic options in this subset of patients are watchful waiting, oral alkylating agents, purine nucleoside analogues, combination chemotherapy, interferon and monoclonal antibodies. The approval of rituximab, an unconjugated chimeric antibody against the CD20 antigen for the treatment of B-cell NHL marked a milestone in the development of antibody treatment. Moreover, promising results have also been found with oxaliplatin in patients with NHL and reversible, cumulative, peripheral sensory neuropathy is the principle dose-limiting factor of oxaliplatin therapy. On the basis of these considerations these researchers performed a feasibility study in NHL in patients aged over 65 years using as schedule: 130 mg/m² oxaliplatin every 21 days and 375 mg/m² rituximab weekly. A total of 8 patients were enrolled -- 2 males and 6 females (mean age of 69.2 +/- 3.1 years; median of 67 years) affected by intermediate or high grade stage III/IV NHL. Six patients have cardiac abnormalities (myocardial function between 45% and 50%) and 1 increase of transaminasemia due to active chronic hepatitis. All the patients included in the study were treated for at least 3 cycles and 31 cycles were completed. These researchers recorded grade I/II (CTC) neurotoxicity in 30%, grade I anemia in 25% and grade I neutropenia in 20% of the patients. No infusional reactions, liver or renal toxicity neither nausea and/or vomiting were recorded. One complete response (CR), 3 partial response (PR) and 3 minimal response were obtained at 11 months of median time follow-up. These results demonstrated the feasibility of this schedule, which offers a suitable alternative regimen to treat elderly patients with NHL and shows a good efficacy and an acceptable toxicity profile.

In a phase II clinical trial, Oki et al (2005) examined the activity of oxaliplatin in patients with recurrent or refractory NHL. Patients with recurrent and refractory NHL who received a maximum of 3 previous chemotherapy regimens were considered eligible if they had an ECOG performance status of 0 to 2 and adequate organ function. Oxaliplatin was administered in an outpatient setting at a dose of 130 mg/m(2) by 2-hour intravenous infusion every 21 days for less than or equal to 6 cycles in the absence of disease progression. A total of 31 patients (23 with aggressive NHL and 8 with indolent NHL) were enrolled, of whom 30 were assessable for toxicity, response, and survival. The median patient age was 62 years, and 20% of the patients previously received platinum-containing therapy.
Eighty-three percent of the patients were refractory to their last treatment regimens. Grade 3 and 4 toxic effects (according to the National Cancer Institute's Common Toxicity Criteria [version 2.0]) included sensory neuropathy (10 %), neutropenia (17 %), and thrombocytopenia (20 %). Objective responses occurred in 8 (27 %; 95 % CI: 13 to 47 %) of the patients. Responses were observed in platinum-naive patients as well as in those previously treated with platinum. The overall median failure-free survival duration was 3.0 months (range of 0.1 to 18.1 months). The authors concluded that oxaliplatin had favorable single-agent activity in previously treated patients with refractory lymphoma. The favorable safety profile and the ease of its administration in outpatient settings warrant investigating it in combination with other active drugs for the treatment of recurrent and refractory NHL.

In a phase II clinical trial, Alinari et al (2005) assessed the effectiveness and toxicity profile of oxaliplatin in a group of heavily pre-treated patients with NHL. A total of 19 pre-treated patients were enrolled. The drug was administered intravenously on day 1 of a 21-day schedule, at a dose of 130 mg/m2 for a total of 6 cycles. One (5 %) patient achieved CR and 5 patients (27 %) had PR, thus giving an overall response rate of 32 %. The patient in CR suffered from an aggressive B NHL. One of the 5 patients in PR had an aggressive B NHL, whereas the remaining 4 had an indolent B NHL. The treatment was well-tolerated with minimal hematologic and extra-hematologic toxicity. These data suggest and confirm the effectiveness and low toxicity of oxaliplatin in the treatment of patients with heavily pretreated NHL. Further trials using oxaliplatin alone or in combination with other conventional drugs are needed.

Woehrer et al (2005) stated that patients with relapsed diffuse large B-cell lymphoma (DLBCL) who are either not suitable for stem cell transplantation or suffer from relapsed disease after standard 2nd-line chemotherapy face a dismal prognosis. Most of them have a reduced performance status and do not tolerate intensive chemotherapy. These researchers reported their findings on 20 patients with relapsed DLBCL who were given rituximab 375 mg/m(2) intravenously on day 1, Ara-C 2 x 1,000 mg intravenously on day 2, dexamethasone 40 mg intravenously on days 1-4, and oxaliplatin 130 mg/m(2) intravenously over 2 hours on day 3 (R-ADOx). Five patients (25 %) achieved CR, 9 (45 %) had a PR, 2 (10 %) had stable disease with improvement in performance status, while 4 patients (20 %) progressed. The median survival was 11 months (range of 1 to 13). Despite extensive pre-treatment, side effects were relatively mild and consisted of thrombocytopenia WHO grade III in 9 (45 %) and grade IV in 2 (11 %) patients, leukocytopenia WHO grade III in 10 (50 %) cases (with infectious episodes in 2 patients), and transient peripheral neuropathy in 9 (45 %) patients. The authors concluded that R-ADOx is well-tolerated in heavily pretreated patients with an impaired performance status. In addition, it displays impressive therapeutic activity given the highly unfavorable patient characteristics and should be further investigated for treatment of DLBCL.

In a pilot study, Corazzelli and colleagues (2006) evaluated the clinical activity, toxicity and mobilizing capacity of a new salvage regimen, which combines gemcitabine and oxaliplatin with ifosfamide and rituximab (R-GIFOX) in patients with relapsed and refractory CD20(+) NHL. Patients were scheduled to receive 3 courses of therapy followed by mobilization and autologous stem cell
transplantation (ASCT) or 3 more courses if ineligible for ASCT. R-GIFOX consisted of rituximab (375 mg/m(2) on day 1, gemcitabine (1000 mg/m(2) on day 2, oxaliplatin (130 mg/m(2)) on day 3 and ifosfamide (5 g/m(2)) on day 3 as a 24-hour single infusion in patients aged less than or equal to 65 years, or fractionated over 3 days (days 3 to 5) in patients aged over 65 years. Treatment was given every 2 weeks with G-CSF support (5 microg/kg/day or 10 microg/kg/day at the end of the third course for stem cell mobilization). Responses were evaluated by the integrated FDG-PET/IWC criteria after the 3rd course and at the end of the entire program. A total of 14 patients (median age of 63 years, range of 37 to 78 years) with relapsed (n = 9) or primary progressive (n = 5) aggressive (diffuse large cell, mantle cell, follicular G3), advanced (stage IV 71 %), poor risk (IPI 3 to 5, 50 %) NHL were accrued in this study. Patients had received a median of 2 previous treatment lines (range of 1 to 4). The median number of R-GIFOX courses delivered was 4 (range of 1 to 6). Thirteen patients completed at least 3 courses of therapy and were evaluable for response. The overall response rate assessed after 3 courses of R-GIFOX was 77 %, with 7 CR and 3 PR. Effective CD34(+) cell mobilization was obtained in 4 of 6 eligible patients and 2 had ASCT. Hematologic and extra-hematologic toxicity was tolerable. Failure-free survival was 79.6 % at median follow-up of 6 months (range of 2 to 12). Molecular remissions were documented in 2 patients with mantle cell NHL. The authors concluded that the R-GIFOX regimen is feasible, tolerable, effective and able to mobilize peripheral stem cells in patients with relapsed and refractory aggressive NHL.

In a phase II clinical trial, El Gnaoui et al (2007) assessed the effectiveness and toxicity of rituximab, gemcitabine and oxaliplatin (R-GemOx) for patients with relapsed or refractory B-cell lymphoma who are not candidates for high-dose therapy. Rituximab, gemcitabine and oxaliplatin are active as single agents in relapsed or refractory lymphoma, and have demonstrated synergistic effects in vitro and in vivo. Forty-six patients with relapsed or refractory B-cell lymphoma received up to 8 cycles of R-GemOx (rituximab 375 mg/m2 on day 1, gemcitabine 1000 mg/m2 and oxaliplatin 100 mg/m2 on day 2). The majority (72 %) had diffuse large B-cell lymphoma. After 4 cycles of R-GemOx, the overall response rate was 83 % [50 % complete response (CR)/unconfirmed CR (CRu)]. High CR/CRu rates were observed in all histological subtypes. In patients who had previously received rituximab, the CR/CRu rate after eight cycles was 65 %. The 2-year event-free and overall survival rates (median follow-up of 28 months) were 43 % and 66 %, respectively. Among responders, the probability of being disease free for 2 years was 62 %. Treatment was generally well-tolerated. The investigators reported that R-GemOx shows promising activity with acceptable toxicity in patients with relapsed/refractory B-cell lymphoma who are not eligible for HDT.

Rodríguez, et al. (2007) reported the results of R-GemOx, in 14 patients with relapsing (n = 9) or refractory (n = 5) mantle cell lymphoma. The median number of cycles was 5.5 for a total of 72 cycles. The median age was 69.5 years with high-risk features. Patients received a mean number of prior treatment lines of 1.79. Sixty-four percent achieved a total response rate of 85%. With a median follow-up of 11 months, overall survival and progression-free survival were 58% and 45% at 12 months. The major toxicity was thrombopenia grade III-IV (35%). Factors related with overall survival were ECOG performance status and adjusted
International Prognostic Index (a-IPI) at GEMOX-R. The authors concluded that R-GemOx displays an outstanding efficacy with an excellent toxicity profile in a pretreated elderly population.

In a phase II trial, López, et al. (2008) assessed the results of a R-GemOx regimen in patients with refractory or relapsing diffuse large-cell lymphoma (DLCL). A total of 32 patients received R-GemOx regimen in 2-week intervals if feasible or every 3 weeks for a planned six to eight courses. The median age of the population was 69 years. Forty-one percent of the patients were primary refractory and 59% after relapsing. At R-GemOx, 75% of patients had a stage III-IV and an a-IPI greater than 1 was observed in 69%. The response rate was 43% with 34% complete response. Neutropenia and thrombopenia grade III-IV were observed in 43% of the patients and neurotoxicity grade III-IV in 7% of cases. Median follow-up for alive patients was 13 months and the median survival was 9.1 months. At 12 months, the overall survival and progression-free survival were 41% and 29%, respectively. The investigators concluded that R-GemOx is a new salvage regimen for DLCL with high activity and relatively safe toxicity profile, which can be offered to elderly patients not candidates of ASCT consolidation. The high efficacy of the regimen in this unfavorable population and also in immunocompromised situations warrant further investigation of this regimen in all salvage situations of this type of lymphomas.

Guidelines from NCCN (2012) state that oxaliplatin with gemcitabine (GemOx) is an acceptable alternative chemotherapeutic regimen for relapsed or refractory non-Hodgkin's lymphoma (diffuse large B-cell lymphoma, follicular lymphoma, nodal marginal zone lymphoma, MALT lymphoma, mantle cell lymphoma, splenic marginal zone lymphoma, peripheral T cell lymphoma, mycosis fungoides/Sezary syndrome, primary cutaneous B cell lymphoma, AIDS-related B-cell lymphoma) as a second-line agent.

NCCN guidelines (2010) also indicate oxaliplatin for relapsed or refractory small lymphocytic lymphoma/chronic lymphocytic leukemia, as a component of OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab) regimen: 1) in patients less than 70 years of age or older patients without significant comorbidities with CLL without del (17p) with a short response (less than 2 years) to first-line therapy; and 2) in patients with CLL with del (17p).

**Small Bowel Cancers and Other Indications:**

Locher, et al. (2005) evaluated the effectiveness of 5-FU and either platinum compounds or irinotecan in patients with advanced small bowel adenocarcinoma (SBA), for whom data on the effectiveness of chemotherapy are scarce. These researchers reviewed data on all patients with advanced SBA who received chemotherapy over a 9-year period at their institution. A total of 20 patients with advanced SBA received a median of 6 cycles (range of 2-15) of chemotherapy with 5-FU and either cisplatin (n = 15), carboplatin (n = 2), or oxaliplatin (n = 3). The overall response rate was 21%, and median progression-free and overall survival 8 and 14 months, respectively. Toxicity was moderate. Second-line chemotherapy with 5-FU and irinotecan resulted in disease stabilization in 4 (50%) of 8 patients (median progression-free survival of 5 months), and in a biological CR in another patient with non-measurable peritoneal carcinomatosis, allowing surgical cytoreduction surgery and hyperthermic intra-peritoneal chemotherapy.
No tumor response or disease stabilization was seen among the patients who received protracted venous infusion of 5-FU (n = 4) or infusional 5-FU and cisplatin (n = 1) as second-line chemotherapy. The authors concluded that chemotherapy with 5-FU and platinum compounds seems effective and well-tolerated in patients with advanced SBA; and 5-FU-irinotecan combination chemotherapy deserves further investigation in the first-line setting.

Oh et al (2007) stated that docetaxel chemotherapy is the current standard of care for metastatic hormone-refractory prostate cancer (HRPC). Platinum chemotherapy drugs (e.g., cisplatin and carboplatin) have moderate single-agent activity in HRPC. Next-generation platinum drugs (e.g., satraplatin and oxaliplatin) may have additional activity in the management of HRPC. Furthermore, neuroendocrine differentiation may play a role in disease progression, providing a rationale for platinum-based chemotherapy in the management of HRPC. These investigators reviewed the Medline database for reports related to platinum-based chemotherapy in patients with advanced prostate cancer and evaluated studies that reviewed the role of neuroendocrine differentiation in the progression of HRPC. Older studies from the 1970s and 1980s suggested a lack of activity of cisplatin and carboplatin; however, those studies were flawed at least in part by their methods of response assessment. More recent phase II clinical trials of carboplatin suggested a moderate level of clinical and palliative activity when it was used as a single agent. However, when carboplatin was combined with a taxane and estramustine, high response rates were observed in several recent studies. In addition, a randomized trial suggested that satraplatin plus prednisone improved progression-free survival compared with prednisone alone. For patients who progressed after docetaxel, no standard options existed in the literature that was reviewed. Several preliminary reports suggested that carboplatin and oxaliplatin may have activity as second-line chemotherapy. Platinum chemotherapeutic drugs historically have been considered inactive in HRPC, although a review of the data suggested otherwise. In particular, carboplatin induced very high response rates when it was combined with estramustine and a taxane, but it also appeared to have activity in patients who progressed after docetaxel. Satraplatin plus prednisone is being investigated in a large phase III trial as second-line chemotherapy for HRPC.

In a phase II clinical trial, Bidoli and colleagues (2007) evaluated the response rate safety of new platinum analog regimens, randomizing 147 patients with non-operable IIIB/IV non-small-cell lung cancer (NSCLC) to (i) carboplatin (area under the curve = 5 mg min/ml) on day 1 plus gemcitabine (GEM) (1000 mg/m(2)) on days 1 and 8 for 6 cycles; (ii) same regimen for 3 cycles followed by docetaxel (Taxotere) (40 mg/m(2)) on days 1 and 8 plus GEM (1250 mg/m(2)) on days 1 and 8 for 3 cycles; (iii) oxaliplatin (130 mg/m(2)) on day 1 plus GEM (1250 mg/m(2)) on days 1 and 8 for 6 cycles. Intention-to-treat objective response rates were 25 %, 25 % and 30.6 % in arms A, B and C, respectively. Median survival was 11.9, 9.2 and 11.3 months in arms A, B and C, respectively. Grade 3/4 neutropenia/anemia occurred in 29 %/12.5 %, 10 %/16.5 % and 8 %/6 % of arms A, B and C, respectively; grade 3/4 thrombocytopenia in 20.5 %, 16.5 % and 6 %; grade 1/2 neurological toxicity in 43 % of arm C. The authors concluded that oxaliplatin/GEM (arm C) had similar activity to carboplatin/GEM (arm A), but milder hematological toxicity and may be worth testing in a phase III study against
carboplatin/GEM in patients not suitable for cisplatin. The sequential regimen gave no additional benefit.

Raez et al (2010) reviewed the available clinical data from studies investigating the third-generation platinum analog oxaliplatin in patients with advanced NSCLC. Information was obtained from the PubMed database and from recent presentations at national and international meetings. Oxaliplatin has been studied as monotherapy and in combination with a wide range of other chemotherapies (alkaloids, gemcitabine, pemetrexed, taxanes, and vinca), mainly in phase II trials. Preliminary results from studies in which oxaliplatin-based doublets have been combined with targeted agents (e.g., bevacizumab) are now available. In general, the clinical activity observed with oxaliplatin-based therapy is similar to that seen with other currently used platinum regimens, although outcomes varied between individual trials (response rates, 23% to 48%; median progression-free survival, 2.7 to 7.3 months; median overall survival, 7.3 to 13.7 months). The toxicity profile of oxaliplatin, particularly when compared with cisplatin, makes it an alternative treatment, especially in patients unable to tolerate cisplatin. However, the authors noted that well-conducted randomized phase III trials are needed to clarify which particular groups of patients with NSCLC may benefit from oxaliplatin-based therapy.

In a phase II clinical trial, Hainsworth and associates (2010) examined the combination of oxaliplatin and capecitabine in patients with recurrent and refractory carcinoma of unknown primary site (CUP). Patients with CUP who had received at least 1 previous chemotherapy regimen were treated with oxaliplatin (130 mg/m(2) intravenously on day 1) and capecitabine (1000 mg/m(2) orally twice-daily on days 1 to 14). Treatment cycles were repeated every 21 days. Patients with objective response or stable disease after 2 cycles continued treatment for 6 cycles or until disease progression. Nine of 48 patients (19%) had objective responses to treatment; an additional 22 patients had stable disease at the time of first re-evaluation. After a median follow-up of 17 months, the median progression-free and overall survivals were 3.7 months and 9.7 months, respectively. This regimen was reasonably well-tolerated by most patients. The authors concluded that the combination of oxaliplatin and capecitabine was found to have activity as a salvage treatment for patients with CUP. This regimen should be considered in patients with clinical and pathological features suggesting a primary site in the gastrointestinal tract. They stated that further development of the regimen as a first-line therapy, or with bevacizumab added, is indicated.

Moller et al (2010) reported the results obtained with oxaliplatin and capecitabine as second-line therapy in 25 recurrent/refractory CUP patients following first-line treatment with paclitaxel, cisplatin and gemcitabine. Patients received capecitabine orally (1000 mg/m(2)) twice-daily, days 1 to 14, and oxaliplatin (130 mg/m(2)) intravenously on day 1 in a 3-week schedule. A total of 25 CUP patients received a median of 3 cycles of capecitabine and oxaliplatin as second-line treatment. Histopathological assessments suggested the primary site to be of gastro-intestinal tract origin in the majority of the patients (76%). These investigators found an objective response rate of 13%, a median progression-free survival and overall survival rate of 2.3 and 3.9 months, respectively, and 32% of patients alive at 1 year after initiation of second-line therapy. The regimen was well-tolerated by most patients. The authors concluded that these
findings showed that there is still a significant need for improved second-line therapy in CUP patients.

Rabinowits et al (2010) examined the effects of fixed-dose every-other-week capecitabine and oxaliplatin for refractory squamous cell carcinoma of the head and neck (SCCHN). Patients received fixed-dose capecitabine (1500 mg orally twice-daily) on days 1 to 7 and oxaliplatin (85 mg/m) days 1 and 14. A total of 15 patients with refractory SCCHN were enrolled. All patients had relapsed after surgery and had failed radiation therapy. Overall, 13 patients (87 %) had progressed after chemotherapy. The most common toxicities were grades 1 or 2 fatigue and anemia. There was a 13 % partial response rate and 33 % stable disease rate for a clinical benefit of 46 % by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The authors concluded that fixed-dose capecitabine and oxaliplatin combination on an every-other-week schedule showed activity in refractory SCCHN. The simplicity and toxicity profile of this regimen compares favorably with other commonly used chemotherapies and should be tested in larger studies.

In a phase II study, Locke and colleagues (2010) examined the effects of oxaliplatin, docetaxel, and GM-CSF in patients with previously treated advanced melanoma. Eligibility included adequate organ function, performance status less than or equal to 2, at most one prior chemotherapy and one prior immunotherapy, no prior treatment with oxaliplatin or taxanes and no chremophor allergy. After pre-medication, docetaxel was administered day 1 at 75 mg/m2, then oxaliplatin on day 2 at 85 mg/m2. GM-CSF (250 mcg/m2) was administered subcutaneously days 3 to 12. Cycles were 21 days in length, and disease re-evaluation was performed every 2 cycles by RECIST criteria. A total of 19 patients received at least 1 cycle, 8 with one prior systemic therapy, 5 with 2 prior systemic therapies. Five patients did not complete 2 cycles and were not formally evaluable for response. Five patients had stable disease, including 1 who failed 2 prior therapies and went on to receive 10 cycles. The remaining 9 patients displayed progressive disease after 2 cycles. Notable toxicities included 7 cases (37 %) of grade III/IV neutropenia and 2 (11 %) hyper-sensitivity reactions. The authors concluded that this combination of oxaliplatin, docetaxel, and GM-CSF has limited clinical activity in previously treated patients with advanced melanoma. Exploration in treatment-naïve patients may still be warranted.

Cassier et al (2009) evaluated the effectiveness of gemcitabine-oxaliplatin combination (GEMOX) in the treatment of patients with metastatic neuroendocrine tumors. A total of 20 consecutive patients with progressive disease were treated with GEMOX, in most cases after failure of other chemotherapy regimens (median = 2). Patients were followed for evidence of toxicity, response, and survival. Two patients were chemotherapy-naive at treatment initiation and were excluded from the efficacy analysis. Toxicity was manageable overall; however, 6 (30 %) patients had to discontinue treatment because of oxaliplatin-induced neurotoxicity (grade 2). Three (17 %) of 18 patients had a partial response, median progression-free survival was 7.0 months, and median overall survival was 23.4 months. The authors concluded that gemcitabine-oxaliplatin combination shows interesting activity and is well-tolerated in pretreated patients with neuroendocrine tumors. These findings need to be validated by well-designed studies.
UpToDate reviews on “Treatment of non-muscle-invasive bladder cancer” (O'Donnell, 2013), “Neoadjuvant treatment of muscle-invasive urothelial (transitional cell) bladder cancer” (Raghavan, 2013), and “Overview of the management of urothelial (transitional cell) bladder cancer” (Lerner and Raghavan, 2013) do not mention the use of oxaliplatin as a therapeutic option.

An UpToDate review on “Treatment of metastatic urothelial cancer of the bladder and urinary tract” (MacVicar et al, 2013) states that “Although a significant number of patients have an objective response to first-line therapy, most eventually progress and may be candidates for second-line chemotherapy. A number of contemporary chemotherapy agents have clinical activity after patients have progressed despite MVAC or GC. However, none of these agents have been approved for use in patients with metastatic urothelial carcinoma nor have their activity been validated in phase III clinical trials. These agents include pemetrexed, vinflunine (not approved in the USA), paclitaxel, docetaxel, gemcitabine, ifosfamide, and oxaliplatin. Reported response rates with single agents in the larger series have generally been 20 percent or less. Although these drugs have also been combined with either each other or with other agents, no one regimen is considered to be the standard second-line therapy”. Also the 2013 NCCN’s Drugs and Biologics Compendium does not list bladder cancer as an indication of oxaliplatin.

Kuo et al (2010) examined the effectiveness and toxicity of paclitaxel and oxaliplatin in patients with recurrent or metastatic cervical cancer. Patients with histologic confirmation of primary metastatic or recurrent cervical cancer not amenable to surgical management were eligible. Treatment consisted of paclitaxel 175 mg/m² IV and oxaliplatin 130 mg/m² IV every 21 days. The primary endpoints were toxicity, recorded every cycle, and response, determined by RECIST criteria and were assessed every 9 weeks, with subsequent confirmation as required. Sample size determinations were made using a Simon's 2-stage design with a projected overall response proportion of 13 % with cisplatin alone. Survival rates were calculated with Kaplan-Meier methods. Of the 35 patients enrolled, 32 were evaluable. The median age was 56 (27 to 78); 30 had had prior radiation (23 concomitant with cisplatin). Patients completed a mean of 4.2 cycles (1 to 11). There were 2 complete and 5 partial responses for a total response rate of 7/32 (22 %; 95 % CI: 9.3 % to 40.0 %). Eight patients had stable disease for an overall clinical benefit rate of 15/32 (47 %; 95 % CI: 29.1 % to 65.3 %). The mean time to best response was 13.5 weeks (95 % CI: 10.6 to 16.4). The mean progression-free survival was 21 weeks (95 % CI: 14.7 to 27.2) and mean overall survival was 52 weeks (95 % CI: 39.4 to 64.8). A total of 135 cycles were administered. There were 28 (20.1 %) grade 3/4 hematologic toxicities and 46 (34.1 %) grade 3/4 non-hematologic toxicities, which were predominantly sensory neuropathy. There were 13 treatment delays, 4 dose reductions, and no treatment-related deaths. The authors concluded that the combination of paclitaxel and oxaliplatin is an effective regimen in patients with recurrent or persistent cervical cancer including a majority previously exposed to cisplatin. Moreover, they stated that further study and comparison with other platinum-based regimens is warranted. This was a small study and its findings were confounded by the combinational use of paclitaxel and oxaliplatin.
UpToDate reviews on “Management of locally advanced cervical cancer” (De Los Santos and Straughn, 2013a), “Management of early stage cervical cancer” (De Los Santos and Straughn, 2013b), and “Management of recurrent or metastatic cervical cancer” (Wright, 2013) do not mention the use of oxaliplatin as a therapeutic option. Also, the 2013 NCCN’s Drugs and Biologics Compendium does not list cervical cancer as a recommended indication of oxaliplatin.

An UpToDate review on “Overview of the treatment of classical Hodgkin lymphoma in adults” (Mauch and Canellos, 2013) does not mention the use of oxaliplatin. Also, the 2012 NCCN’s Drugs and Biologics Compendium does not list Hodgkin’s lymphoma as an indication of oxaliplatin.

The NCCN guidelines for anal carcinoma (Version 2.2013) state that “Other types of cancers occurring in the anal regions, such as adenocarcinomas or melanoma, are addressed in other NCCN guidelines; anal adenocarcinoma and anal melanoma are managed according to the NCCN guidelines for rectal cancer and the NCCN guideline for melanoma, respectively”.

Abdel-Rahman (2014) noted that hepato-cellular carcinoma (HCC) is a global health problem, as it is the 6th most common cancer in the world and the 3rd leading cause of cancer-related death. Many patients with HCC present with disease that is not suitable for any potentially curative therapy; such patients are candidates for palliative trans-arterial or systemic therapies. Sorafenib is the only systemic therapy to demonstrate modest survival benefit over supportive care in the context of randomized controlled trials. However, many cytotoxic chemotherapeutics have achieved a range of tumor responses, but so far without convincing survival benefits in smaller phase II studies.

Petrelli and colleagues (2014) stated that advanced HCC, for which loco-regional treatment is not an option, is a candidate for palliative systemic therapy, but an accepted chemotherapy regimen does not exist. These researchers conducted a systematic literature review and meta-analyses to quantify the benefits of oxaliplatin (OXA)-based chemotherapy in advanced HCC in patients not exposed to sorafenib. Studies that enrolled advanced HCC patients treated with 1st-line OXA-based chemotherapy were identified using PubMed, Web of Science, SCOPUS, The Cochrane Register of Controlled Trials and EMBASE. A systematic review was conducted to calculate the pooled response rate and 95 % CI. The pooled median progression-free survival (PFS) and overall survival (OS), weighted on the number of patients of each selected trials, were also calculated. These investigators tested for significant heterogeneity by Cochran’s chi-squared test and I-square index. A total of 13 studies were included in this review, with 800 patients analyzed. The pooled response rate was 16.8 %. The median PFS and OS were 4.2 and 9.3 months, respectively, with a 1 year OS of 37 %. The weighted median PFS/OS and response rate were 4.5/11 months and 20 % in Western patients. Conversely, in Asiatic studies, the median PFS/OS and response rate were 2.43/6.47 months and 13.2 %, respectively. The authors concluded that OXA-based chemotherapy is effective in advanced HCC and represents a viable option in these patients. Moreover, they stated that a head-to-head comparison with sorafenib or a 2nd-line agent should be verified in prospective trials.
In a phase I study, Tsimberidou et al (2014) examined the effect of oxaliplatin with cytarabine and fludarabine therapy for patients with relapsed or refractory acute myeloid leukemia (AML). Between January 2008 and November 2009, a total of 27 patients were registered in the study. Patients had histologically confirmed disease, performance status 0 to 2, and adequate organ function. The treatment regimen consisted of increasing doses of oxaliplatin (25, 30, or 35 mg/m²/day) on days 1 to 4 (escalation phase), and fludarabine (30 mg/m²) and cytarabine (500 mg/m²) on days 2 to 6, every 28 days for less than or equal to 6 cycles. The dose-limiting toxicity was defined as any symptomatic grade greater than or equal to 3 non-hematologic toxicity lasting greater than or equal to 3 days and involving a major organ system. Of 27 patients, 12 were treated in the dose-escalation phase and 15 at the maximum tolerated dose for oxaliplatin (30 mg/m²; expansion phase). All patients were evaluable for toxicity and response. Only 1 patient received the 2nd cycle; the remaining patients received no further study treatment, owing to slow recovery from toxicities or physician decision. Grade 3 to 4 drug-related toxicities included diarrhea (grade 4) and elevated levels of bilirubin (grade 3) and aspartate transaminase (grade 3). In all, 3 patients had a complete remission and 2 patients complete response without platelet recovery. The authors concluded that oxaliplatin, cytarabine, and fludarabine therapy had anti-leukemic activity in patients with poor-risk AML, but it was associated with toxicity. Different schedules and doses may be better tolerated.

The NCCN’s clinical practice guideline on “Acute myeloid leukemia” (Version 2.2014) does not mention oxaliplatin as a therapeutic option.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96401 -
96450

HCPCS codes covered if selection criteria are met:

J9263 Injection, oxaliplatin, 0.5 mg

Other HCPCS codes related to the CPB:

Q0083 - Chemotherapy administration
Q0085

ICD-9 codes covered if selection criteria are met:

150.0 - 150.9 Malignant neoplasm of esophagus
151.0 - 151.9 Malignant neoplasm of stomach [gastric carcinoma]
152.0- 152.9 Malignant neoplasm of small intestine, including duodenum
153.0 - 154.1 Malignant neoplasm of colon and rectum
154.8
155.1  Malignant neoplasm of intrahepatic bile ducts
156.0  Malignant neoplasm of gallbladder
156.1  Malignant neoplasm of extrahepatic bile ducts
156.2  Malignant neoplasm of Ampulla of Vater
157.0 - 157.9  Malignant neoplasm of pancreas
158.0 - 158.9  Malignant neoplasm of retroperitoneum and peritoneum
183.0  Malignant neoplasm of ovary [epithelial carcinoma]
183.2  Malignant neoplasm of fallopian tube
186.0 - 186.9  Malignant neoplasm of testis
199.1  Malignant neoplasm without specification of site [unknown primary site]

200.00 - 200.28, 200.40 - 200.88  Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue [angioimmunoblastic T-cell lymphoma]
200.88
202.00 - 202.98  Other malignant neoplasms of lymphoid and histiocytic tissue
204.00 - 204.02  Acute lymphoid leukemia [adult T-cell leukemia/lymphoma]
204.10 - 204.12  Chronic lymphoid leukemia
V10.05 - V10.06  Personal history of malignant neoplasm of large intestine, rectum, rectosigmoid junction, and anus

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

140.0 - 149.9,  Malignant neoplasms [other than those listed as covered]
152.0 - 152.9,
154.2 - 154.3,
155.0 - 156.1,
156.8 - 156.9,
158.0 - 182.8,
183.2 - 199.0
200.30 -  Marginal zone lymphoma
200.38
201.90 â€™s disease, unspecified
201.98
209.00 - Neuroendocrine tumors
209.79

Other ICD-9 codes related to the CPB:

042 Human immunodeficiency virus [HIV] disease
079.51 Human T-cell lymphotrophic virus, type I
V58.11 - Encounter for antineoplastic chemotherapy and
V58.12 immunotherapy

The above policy is based on the following references:

Oxaliplatin for Colorectal Cancer:

11. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in
18. Comella P. Randomized trial comparing the addition of oxaliplatin or irinotecan to high-dose leucovorin and 5-Fluorouracil intravenous bolus every two weeks in metastatic colorectal carcinoma: Southern Italy Cooperative Oncology Group 0103. Clin Colorectal Cancer. 2003;3(3):186-189.
Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); 2004.


Oxaliplatin for Esophageal Cancer:


Oxaliplatin for Pancreatic Cancer:


10. Ducrêux M, Mitry E, Ould-Kaci M, et al. Randomized phase II study evaluating oxaliplatin alone, oxaliplatin combined with infusional 5-FU, and


Oxaliplatin for Epithelial Ovarian Cancer:


Oxaliplatin for Testicular Cancer:


Oxaliplatin for Non-Hodgkin's Lymphoma:


**Oxaliplatin for Small Bowel Cancers and Other Indications:**


22. De Los Santos JF, Straughn JM. Management of early stage cervical cancer. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2013b.

23. Wright JD. Management of recurrent or metastatic cervical cancer. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2013.


