In order to provide the most up-to-date and efficacious care to their members, payor executives who are responsible for care management of oncology patients must be aware of the emerging pharmacotherapeutic agents and therapies assessed in clinical trials. The trials reviewed here evaluated investigational agents and regimens for the treatment of squamous-cell carcinoma of the head and neck, breast cancer, colorectal cancer, myelodysplastic syndromes, and chemotherapy-related anemia. The purpose, methods, results, and conclusions of each study are reported and managed care implications are presented.

**Title:** Radiotherapy plus cetuximab (ERBITUX) for squamous-cell carcinoma of the head and neck

**Authors:** Bonner JA, Harari PM, Giralt J, et al.


**Purpose:** To compare the addition of cetuximab to radiation with radiation alone in the treatment of locoregionally advanced squamous-cell carcinoma of the head and neck (SCCHN).

**Methods:** Patients were assigned to receive high-dose radiation alone (n=213) or high-dose radiation plus cetuximab (n=211) for treatment of their locoregionally advanced head and neck cancer. The loading dose of cetuximab was 400 mg/m² intravenously (IV) over 120 minutes 1 week prior to the initiation of radiation therapy, followed by a maintenance dose of 250 mg/m² IV administered weekly for the duration of the radiation therapy. Patients were stratified according to Karnofsky performance status, nodal involvement, and radiation-fractionation regimen. The primary endpoint of the study was the duration of control of the locoregional disease with secondary endpoints being overall survival, progression-free survival, and safety.

**Results:** The median duration of locoregional control of disease was nearly 10 months longer in patients receiving cetuximab (24.4 months vs. 14.9 months; \( P = .005 \)). At 3 years, locoregional control was maintained in 47% of patients treated with the combination therapy and 34% of patients treated with radiation alone (\( P < .01 \)). The median duration of overall survival was 49.0 months in patients treated with combined therapy and 29.3 months in those treated with radiation alone (\( P = .03 \)). Survival at 3 years was improved in the cetuximab-treated patients (55% vs. 45%; \( P = .05 \)). Median progression-free survival also favored the cetuximab-treated patients (17.1 months vs. 12.4 months). Acneiform rash and cetuximab infusion-related toxicity were the only adverse events more common...
Conclusion: Treatment with combined modality therapy (cetuximab and radiation) improves the locoregional control and reduces mortality in patients with SCCHN. The toxicity associated with the addition of cetuximab is acceptable.

Potential Next Step: Additional phase 3 studies utilizing the combination of cetuximab, radiation, and platinum-based chemotherapy.

Managed Care Implications: Cetuximab was recently approved by the FDA for the treatment of locoregional SCCHN and as a single agent in patients with platinum-refractory disease.

Title: Phase 3 study of two different dosing schedules of erythropoietin in anemic patients with cancer.


Purpose: Anemia is a common complication of cancer, and its therapy and its symptoms can profoundly affect a patient's quality of life (QOL). Packed red blood cell (PRBC) transfusions can decrease the symptoms of anemia, but are associated with many adverse reactions. Recombinant human erythropoietin has been used successfully to treat cancer-associated anemia. Administration of epoetin alfa (EPO) (PROCRIT) has primarily been on a 3x/week or weekly basis. These dosing schedules can also be difficult for many patients. The purpose of this study was to compare two maintenance doses of EPO, weekly versus every 3 weeks, in patients with cancer-associated anemia.

Methods: Anemia was defined as hemoglobin (Hgb) <12.0 g/dL in males and <11.0 g/dL in females. The majority of patients had a mild degree of anemia (Hgb>9.0 g/dL) upon entering the study. All patients initially received 3 weekly doses of EPO at a dose of 40,000 units subcutaneously (SC) and were then randomized to 1 of 2 treatment arms: continued weekly administration of EPO (n=183) at a dose of 40,000 units or 120,000 units of EPO administered every 3 weeks (n=182). The duration of therapy after randomization was 18 weeks. The primary endpoint of the study was the proportion of patients receiving PRBC transfusions. Transfusions were administered only for Hgb<8 g/dL unless the treating clinician judged symptoms to be too severe at a higher Hgb level. Secondary endpoints included changes in Hgb and quality of life (QOL) scores from baseline measurements.

Results: There was no difference in the percentage of patients requiring PRBC transfusions during the entire study (23% receiving 40,000 units weekly vs. 18% receiving 120,000 units every 3 weeks; P=.22). The same result was seen when comparing patients only during the maintenance phase of the study (13% vs. 15%; P=.58). The total number of PRBC units transfused during the study was 135 in the 40,000-unit arm and 109 in the 120,000-unit arm. Patients enrolled in the 40,000-unit arm had a higher mean end-of-study Hgb (12.0 vs. 11.5 g/dL; P=.0006) and greater mean increase in Hgb from baseline (1.8 vs. 1.4 g/dL; P=.01). With regards to QOL, patients in the 40,000-unit arm had a higher global QOL score at baseline, whereas patients in the 120,000-unit arm had greater global improvement in QOL during the study. The end-of-study QOL scores were equivalent.

Conclusion: The authors concluded that following 3 weekly doses of...
Comparison of the Hepatic arterial infusion versus Docetaxel of trasuzumab therapy may prove to be more effective and better tolerated than trastuzumab therapy in patients with HER2-positive breast cancer.

**Purpose:** The administration of trastuzumab with chemotherapy in patients with HER2-positive breast cancer has improved survival. This has been particularly true when the drug is combined with paclitaxel (TAXOL), docetaxel, vinorelbine, cisplatin, or carboplatin. However, some combinations have led to an increased risk of heart failure as determined by a decrease in left ventricular ejection fraction. A shorter course of trastuzumab therapy may prove to be equally effective and be better tolerated.

**Methods:** One thousand ten (1010) women with axillary-node positive or high-risk node negative breast cancer were assigned at random to receive 3 cycles of docetaxel (100 mg/m² IV every 21 days) or vinorelbine (25 mg/m² IV on Days 1, 8, and 15, every 21 days) followed by 3 cycles of FEC (fluorouracil 600 mg/m², epirubicin 60 mg/m², and cyclophosphamide 600 mg/m² every 21 days). Two-hundred-and-thirty-two women who had HER2-positive disease were further randomized to receive 9 weekly infusions of trastuzumab (4 mg/kg IV loading dose followed by 2 mg/kg IV weekly) or placebo. Trastuzumab was not administered during the FEC chemotherapy. The primary endpoint of the study was recurrence-free survival.

**Results:** Recurrence-free survival at 3 years was better in the docetaxel arm (n=390) than the vinorelbine arm (n=388) (91% vs. 86%; P=.005). Overall survival did not differ between the two groups.

**Recurrence-free survival at 3 years was better in the docetaxel arm (n=390) than the vinorelbine arm (n=388) (91% vs. 86%; P=.005). Overall survival did not differ between the two groups.**

**Managed Care Implications:** Future studies will allow for choice between the two available products. Treatment with a red cell growth factor could then coincide with the schedule of chemotherapy administration. This would make for fewer patient office visits and injections, which should also enhance QOL.

**Title:** Adjuvant docetaxel (TAXOTERE) or vinorelbine (NAVELBINE) with or without trastuzumab (HERCEPTIN) for breast cancer.

**Authors:** Joensuu H, Kellokumpu-Lehtinen P, Bono P, et al.

**Reference:** J Clin Oncol. 2006;24:1395-1403.

**Purpose:** Patients with colon cancer often develop liver metastases as the sole site of metastatic disease. Since these lesions derive a majority of their blood supply via the hepatic artery, direct infusion of drug by this route may lead to improved survival. Previous studies comparing hepatic arterial infusion (HAI) versus systemic chemotherapy have shown improved response rates in patients treated with HAI. However, due to the crossover design of those studies, a survival advantage for the HAI-treated patients has been difficult to assess. This study was designed to treat patients with either systemic chemotherapy or
Patients with histologically confirmed colorectal cancer with unresectable liver metastases and no evidence of extrahepatic disease were eligible for this multi-institutional study. Prior adjuvant therapy with fluorouracil (FU) and leucovorin (LV) was allowed if therapy had been completed at least 12 months before study initiation. Systemic therapy consisted of intravenous (IV) LV 20 mg/m² followed immediately by FU 425 mg/m², both given as IV infusions for 5 consecutive days every 4 weeks. The drugs administered via HAI pumps were floxuridine (FUDR) (0.18 mg·kg·30 mL)/(pump flow rate mL/d); LV (4 mg·m²·30 mL)/pump flow rate mL/d) and dexamethasone 25 mg. The primary endpoint of the study was survival with secondary endpoints being tumor response, toxicity, quality of life (QOL), and cost effectiveness.

Results: One hundred thirty-five (135) patients were enrolled in the study. Sixty-eight (68) were randomly assigned to HAI and 67 to systemic therapy. Only 3% had received adjuvant chemotherapy. Eighteen patients never received the protocol treatment; nine patients in each group for a variety of reasons. The overall survival was 24.4 months in the HAI group and 20.0 months in the systemically treated group (P= .0034). Response rate (47% vs. 24%; P = .012) and time-to-hepatic progression (9.8 months vs. 7.3 months; P = .034) also favored the HAI-treated group. Time-to-extrahepatic progression was shorter in the HAI-treated patients (7.7 months vs. 14.8 months; P = .029). QOL measurements were taken at baseline, 3, 6, 9, 12, 15, and 18 months. Results showed improved physical functioning in the HAI-treated group at 3-(P = .038) and 6-(P = .024) month followup. No differences were found in social functioning, role functioning-emotional, or general health perceptions. Treatment-associated toxicity such as neutropenia (Grade ≥ 3), diarrhea, and stomatitis were greater in the systemically treated group while liver toxicity was higher in the HAI treatment group.

Conclusion: HAI increased overall survival, response rate, and time-to-hepatic progression compared with systemic chemotherapy. Newer chemotherapeutic regimens containing irinotecan and oxaliplatin need to be evaluated either in comparison to or in combination with HAI.

Potential Next Steps: Newer drug combinations need to be evaluated.

Managed Care Implications: Additional trials may prove HAI to be the treatment of choice in those patients with liver-only disease following resection of the primary colorectal lesion.
best supportive care (BSC) (blood and platelet transfusions +/- growth factor support; n=81). Decitabine infusion was repeated every 6 weeks. The median patient age was 70 years and an International Prognostic Scoring System (IPSS) score of intermediate-2 or high-risk MDS was noted in nearly 70% of all patients enrolled. The primary endpoints of the study were overall response rate (ORR) and time to conversion to AML.

**Results:** The intent-to-treat (ITT) analysis showed an overall response rate (complete plus partial response) of 17% (15/89) in the decitabine-treated patients versus a 0% ORR in the supportive care group (P<.01). Eight patients achieved a complete response (normalization of peripheral blood counts and bone marrow blasts <5% without dysplastic changes, hemoglobin (Hgb) >11 gm/dL, neutrophil count ≥1.5x10⁹/L, and platelet count ≥100x10⁹/L, while 7 achieved a partial response. The median time to first response was 3.3 months or following 2 cycles of decitabine. If hematologic response (response of at least one cell line, but less than a PR or CR) is included, the decitabine-treated arm had a response rate of 30% versus 7% in the BSC arm (P<.001). Responses to decitabine were noted in all IPSS risk groups and similar responses were seen at a similar rate in patients who had seen previous therapy for their MDS (versus no previous therapy) or had de novo or secondary MDS. Patients treated with decitabine had a longer median time to the development of AML or death (12.1 months vs. 7.8 months; P=.16). However, subgroup analysis showed patients on the decitabine arm experienced a longer median time to the development of AML or death if they were treatment-naïve (12.3 months vs. 7.3 months; P=.08), had an IPSS score of intermediate-2/high risk (12.0 months vs. 6.8 months; P=.03) or had de novo MDS (12.6 months vs. 9.4 months; P=.04).

**Conclusion:** Decitabine is effective in the treatment of MDS. Responses are durable and there is an improved time-to-AML transformation and death. An increase in the duration of decitabine therapy may lead to improved results.

**Decitabine is effective in the treatment of MDS.**

Responses are durable, and there is an improved time-to-AML transformation and death. An increase in the duration of decitabine therapy may lead to improved results.

**Potential Next Steps:** Additional trials with decitabine remain to be completed. A comparison to azacitidine (VIDAZA) would be beneficial in determining the role of these two agents.

**Managed Care Implications:**

Decitabine is the second agent of this class to be approved by the FDA for the treatment of MDS. Alternative dosing schedules are being approved to allow for out-patient administration.

This dosing can be reviewed in:
**Blood.** 2004;104:1437.

**Title:** Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa (ARANESP) for the treatment of chemotherapy-induced anemia

**Authors:** Canon J-L, Vansteenkiste J, Bodoky G, et al.


**Purpose:** Anemia is a frequent complication of cancer treatment and effects patient’s quality of life. Darbepoetin is a long-acting erythropoiesis-stimulating protein that is administered by a variety of different schedules. This study compares the efficacy and safety of weekly versus an every-3-week regimen.

**Methods:** Patients with a diagnosis of a nonmyeloid malignancy, undergoing at least 12 weeks of cytotoxic chemotherapy and were anemic (hemoglobin [Hbg] <11 g/dL) within 24 hours of randomization, were eligible for the study. Patients were randomly assigned in a 1:1 ratio to receive darbepoetin alfa at a fixed dose of 500 mcg every 3 weeks or a weight-based dose of 2.25 mcg/kg weekly for 15 weeks. All injections were administered subcutaneously. Doses of the drug were held if the Hbg >13 g/dL or if the Hbg concentration increased by 1 g/dL or greater over a 14-day period. When the Hbg dropped to ≤12 g/dL, the study drug was decreased to 60% of

Continued on p. 55
the previous dose. The primary objective of the trial was to evaluate the efficacy of the every-3-week dosing and prove it was not inferior to the weekly administration of the drug. The primary endpoint of the study was the incidence of red blood cell (RBC) transfusions from week 5 to the end of treatment. Transfusions were permitted for Hbg < 8 g/dL in symptomatic patients or as recommended by the treating physician.

**Results:** Seven hundred five (705) patients were randomly assigned to darbepoetin 500 mcg every 3 weeks (n=353) or weekly darbepoetin (n=352). The percentage of patients requiring a RBC transfusion was lower in the group treated on an every 3-week basis (23% vs. 30%). The frequency of patients achieving a target hemoglobin of ≥ 11 g/dL were 84% in the treatment group receiving therapy every 3 weeks and 77% in the weekly treatment group. Dose modification primarily resulted from a > 1 g/dL increase in hemoglobin within any 14-day period, resulting in a 40% dose reduction. This was noted in 74% of the patients treated every 3 weeks and in 75% of those treated on the weekly schedule. The safety profile of both regimens was comparable.

**Conclusion:** Patients with chemotherapy-induced anemia can be safely and effectively treated with darbepoetin alfa administered every 3 weeks.

**Potential Next Step:** Another large study has suggested that the benefits of T may be limited to hormone-receptor negative breast cancer since its effect may be attenuated in the hormone-receptor positive breast cancer patient by the addition of tamoxifen. Additional studies may be needed to clarify this issue.

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**Clinical Trial Update (Continued from p. 31)**

**Title:** Sequential preoperative or postoperative docetaxel (TAXOTERE) added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27

**Authors:** Bear HD, Anderson S, Smith RE, et al.


**Purpose:** Systemic chemotherapy has been used for operable breast cancer to increase the likelihood of breast conservation. Previous studies have reported that disease-free survival (DFS) and overall survival (OS) were identical when doxorubicin and cyclophosphamide (AC) were administered preoperatively or postoperatively. This study was designed to determine the effect of adding docetaxel (T) to preoperative AC on breast cancer response rates, DFS, and OS. Previous studies have shown improved DFS and OS when taxanes are added to anthracycline-based chemotherapy.

**Methods:** Women with operable breast cancer were randomly assigned to one of three treatment arms. Group 1 (n=768) received 4 cycles of AC (60 and 600 mg/m²) every 21 days for 4 cycles. Patients then underwent surgical tumor removal. Patients in Group 2 (n=767) were assigned to the same AC therapy as the first group, followed by T (100 mg/m²) every 21 days for 4 cycles and then surgery. Group 3 (n=776) received the 4 cycles of AC preoperatively, followed by surgery and then 4 cycles of postoperative T. All patients received tamoxifen (20 mg/d for 5 years) initiated on the first day of chemotherapy regardless of receptor status. The primary endpoints of the study were OS and DFS.

**Results:** There were no significant differences in OS or DFS based upon treatment group. Five-year DFS showed a non-significant trend toward improved DFS in the groups treated with T (Group 1, 67.7%; Group 2, 71.1%; Group 3, 70.0%). There was a significant decrease in the cumulative incidence of all local recurrences as first events in the T treated women. However, there were no significant differences in the cumulative incidence of regional or distant recurrences as first events. The Kaplan-Meyer curves for OS were superimposable.

**Conclusion:** The addition of T, either preoperatively or postoperatively, following preoperative AC did not significantly affect OS or DFS. Concurrent use of tamoxifen may have limited the impact of adding T.

**Potential Next Step:** Another large study has suggested that the benefits of T may be limited to hormone-receptor negative breast cancer since its effect may be attenuated in the hormone-receptor positive breast cancer patient by the addition of tamoxifen. Additional studies may be needed to clarify this issue.

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