Stability and compatibility of paclitaxel infusion under replicated clinical use conditions to facilitate dose-banding

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Pharmacotherapy

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cycle use of growth factors. A study of patients with breast cancer receiving docetaxel 100 mg/m² Q3W (expected FN incidence of 20% without growth factor support) demonstrated that patients receiving pegfilgrastim experienced a significant reduction in FN compared with placebo (1% versus 17%; p<0.0001). Additionally, pegfilgrastim significantly reduced the incidence of FN-associated hospitalization and IV antibiotic use. Pegfilgrastim has shown >50% of initial neutropenic events occur in cycle 1 for non- Hodgkin's lymphoma patients. We analyzed our study to determine if breast cancer patients also experience neutropenic events early in therapy.

METHODS: Breast cancer patients (ECOG 0 to 2) received either pegfilgrastim (n=465) or placebo (n=465) on the day after docetaxel for up to 4 cycles. FN was defined as temperature ≥38.2°C and absolute neutrophil count <0.5x10⁹/L (within 1 day after temperature ≥38.2°C).

RESULTS: For patients receiving placebo, most neutropenic events occurred in cycle 1. Patients receiving pegfilgrastim, few FN events occurred and a pattern could not be discerned.

<table>
<thead>
<tr>
<th>Placebo (n=465)</th>
<th>Pegfilgrastim (n=465)</th>
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</thead>
<tbody>
<tr>
<td>Fieber, Neutropenia, % (95% CI)</td>
<td>Cycle 1 11 (95, 14.4) ≤1 (0.1, 1.6)</td>
</tr>
<tr>
<td>FN-associated hospitalizations, % (95% CI)</td>
<td>Cycle 2 to 4 6 (3.7, 8.1) ≤0.2 (0.2, 2.2)</td>
</tr>
<tr>
<td>FN-associated IV anti-infective use, % (95% CI)</td>
<td>Cycle 1 9 (6.8, 12.3) 1 (0.4, 2.5)</td>
</tr>
<tr>
<td>FN-associated hospitalizations, % (95% CI)</td>
<td>Cycle 2 to 4 5 (2.8, 6.8) ≤0.1 (0.1, 1.2)</td>
</tr>
<tr>
<td>FN-associated IV anti-infective use, % (95% CI)</td>
<td>Cycle 1 6 (4.9, 9.1) 0 (0.4, 2.5)</td>
</tr>
<tr>
<td>FN-associated IV anti-infective use, % (95% CI)</td>
<td>Cycle 2 to 4 4 (2.5, 5.6) ≤0.1 (0.1, 1.9)</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Patients receiving moderately myelosuppressive chemotherapy with growth factor support experienced two-thirds of neutropenic events in cycle 1. Patients receiving first and subsequent cycles pegfilgrastim were generally protected from experiencing neutropenic events.

233. Hematologic outcomes and costs in epoetin alfa (EPO) and darbepoetin alfa (DAR) treated cancer patients with anemia: results of the Dosing and Outcomes Study of Erythropoietic Stimulating Therapies (D.O.S.E. Registry). Ali Memisoglu, MD; Cyrus Peake, MS; Radha Vichare, MS; R. Scott McKenzie, MD; Jamie Howell, PharmD, MS; Catherine Talc Poch, MBA; (1)DABM Associates, DABM, Lexington, MA; (2)Ortho-Biotech Clinical Affairs, LLC, Bridgewater, NJ.

PURPOSE: EPO and DAR, two erythropoietic stimulating therapies (ESTs), are FDA approved for the treatment of chemotherapy-related anemia. D.O.S.E. is an ongoing prospective, observational registry collecting data on real-world practice and outcomes associated with these ESIs in cancer patients.

METHODS: Data were drawn from hospital and community-based outpatient practices during 1/06-4/09. Adult patients were required to have diagnosis of a non-myeloid malignancy, baseline hemoglobin (Hb) ≥11 g/dL, and received at least 2 doses of either EPO or DAR. Outcomes assessed included treatment duration; mean weekly and cumulative doses; Hb change from baseline at weeks 4, 8, 12, and proportion of patients receiving transfusions. Cost was based on 2004 wholesale acquisition cost.

RESULTS: 361 patients (149 EPO, 212 DAR) from 24 sites were identified. Baseline characteristics were similar between groups and reported for the entire cohort: median age: 62-77 years, median weight: 74-6 kg, gender: 65% female, and mean baseline Hb 10.0 g/dL. Breast and lung cancer were the most common malignancies in both groups. Both groups had identical mean treatment duration (weeks 4-12), and maximum Hb change from baseline were similar in weeks 4, 8, 12, and 4.9 (0.9).

CONCLUSIONS: Results of this prospective observational study suggest similar hematological outcomes with 16% higher drug cost in the DAR group compared to the EPO group. The similar number of Hb measurements suggest a comparable number of office visits for both treatment groups over the relatively brief treatment duration.

234. Greater area under the hemoglobin change curve is associated with improved outcomes in patients receiving epoetin alfa (EPO) or darbepoetin alfa (DAR) for chemotherapy-related anemia (CRA). Patrick Lefebvre, MA; Mei-Sheng Duh, MPH; Sc.D. D. R. Scott McKenzie, MD; Samir H. Mahy, PharmD, MBA; Richard C. Woodman, MD; Denise Williams, MD; (1)Georges d'Analyse, Lf, Montreal, QC, Canada; (2)Analysis Group, Inc, Boston, MA; (3)Ortho Biotech Clinical Affairs, LLC, Dallas, TX; (4)Johnson and Johnson Pharmaceutical Research and Development, Raritan, NJ.

PURPOSE: Previous research with erythropoetin-stimulating therapies has shown area under the 16-week Hb change curve (Hb AUC16) to be a more sensitive and comprehensive efficacy measure versus traditional single time-point or threshold-based measurements such as hematopoietic response. To date, Hb AUC16 has not been validated within a randomized controlled trial of anemia treatment.

METHODS: Data were retrospectively analyzed from a randomized controlled clinical trial (n=380) designed to compare the hematopoietic effect of EPO and DAR in solid tumor patients with CRA. Inclusion criteria were a baseline Hb ≤11 g/dL and receiving chemotherapy. Hb AUC16 was calculated using sequential trapezoidal methodology based on Hb changes over 16 weeks of treatment and was stratified into quartiles to assess correlation with clinical and drug utilization outcomes. Trend tests were performed on the individual EPO and DAR groups, as well as the combined group, to determine if the following outcomes had significant linear trends across the Hb AUC16 quartiles: proportions of patients meeting hematopoietic response (Hb rise ≥2 g/dL from baseline or Hb ≥12 g/dL during study), and average weekly EPO or DAR dose.

RESULTS: Mean Hb AUC16 values were higher for the EPO group versus the DAR group (EPO: 14±2g/dL; DAR: 7±2g/dL, p<0.001). Greater Hb AUC16 values had a strong linear association with decreasing proportions of patients transfused (p<0.0001), decreasing time to red blood cell transfusions, and decreasing average weekly EPO or DAR doses (p<0.001). These results were observed in the EPO and DAR groups separately, as well as in the two groups combined.

CONCLUSIONS: Hb AUC16 is associated with clinical outcomes and drug utilization benefits in patients with CRA receiving either EPO or DAR. These features should make it a preferred comprehensive efficacy measure in the assessment of comparative treatment responses.

235. Stability and compatibility of paclitaxel infusion under replicated clinical use conditions to facilitate dose-handling. Asha Kattige, Ph.D; Graham J. Sewell, Ph.D.; (1)University of Bath, Bath, United Kingdom; (2)Kingston University, Kingston-upon-Thames, United Kingdom.

PURPOSE: To investigate the stability and compatibility of paclitaxel infusion at concentrations 0.1 mg/ml (for 1mg/ml and 1.2mg/ml, in Freeline infusion bags containing 0.9% sodium chloride or 5% glucose under refrigerated storage and clinical use conditions to facilitate an outpatient chemotherapy dose-handling scheme.

METHODS: Dose-handling is widely used in UK and offers advantage of patient convenience but needs stability data to permit batch manufacturing. Stability and compatibility of paclitaxel infusion stored in Freeline infusion bags was evaluated by in-cubating at 2-8°C or 25°C to represent refrigerated storage and clinical use conditions. Samples were withdrawn at selected time intervals and analysed for physical stability (visible and sub-visible particulates, pH, % weight loss) and chemical stability using a validated stability-indicating HPLC method.

RESULTS: Results indicated that in all cases, paclitaxel is chemically stable with variation in assay values within a 3% but exhibited precipitation on prolonged storage at 2-8°C and 25°C. The stability of 0.1 mg/ml, 0.75 mg/ml and 1.2 mg/ml paclitaxel infusions at 2-8°C in 5% glucose was 28, 16 and 12 days respectively. There was a negligible change in pH and the variation over 28-day study period was less than 0.6 pH units. Similarly, moisture diffusion across the infusion bag was minimal with less than 1% weight loss.

CONCLUSION: Stability in-cubate for various paclitaxel infusions varied and was a function of paclitaxel concentration in the infusion, diluents used and the storage temperature. In all cases, physical stability of the infusion was the limiting factor influencing the stability of the infusion. Maximum stability period of 28 days was observed for paclitaxel (0.3mg/ml) infusion prepared in 5% glucose and stored at 2-8°C. Given the increased popularity of the 90mg/ml weekly regimen in the UK, the 0.3mg/ml concentration would be appropriate for most patients and the 28-day shelf life would facilitate a dose-handling scheme.

236. Determination of paclitaxel in rabbit plasma using liquid chromatography tandem mass spectrometry: comparison of liquid liquid extraction (LLE) with solid phase extraction (SPE). Ansgar Böhm, Pharm.D. Ph.D; D. Noble Nemelko, B.S.; Kenneth B. Bauer, Pharm.D., Ph.D.; (1)Department of Pharmacy Practice and Science, School of Pharmacy, University of Maryland, Baltimore, Baltimore, MD; (2)University of Maryland Greenspring Cancer Center, Baltimore, MD.

PURPOSE: Clinical application of a continuous low dose of paclitaxel as an anti-angiogenic agent has been recommended for treatment of cancer. Liquid chromatography tandem mass spectrometry (LC-MS/MS) has been used for the quantification of low concentration of paclitaxel in plasma samples. Both solid phase extraction (SPE) and liquid-liquid extraction (LLE) have been used in sample preparation protocols. We have compared SPE and LLE as methods of sample extraction to quantify low concentration of paclitaxel based on the use of small sample volumes (200μl plasma).

METHODS: Rabbit plasma spiked with known amounts of paclitaxel was...