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11. Pharmaceutical Information

11.1 Carboplatin

Carboplatin is a second-generation organic platinum and chemotherapeutic agent and is cell cycle non-specific. Like, cisplatin it produces predominantly interstrand DNA cross links, causing DNA lesions and biological effects. Carboplatin exhibits linear pharmacokinetics and is excreted mainly by the kidneys. In patients with creatinine clearances of approximately 60 mL/min or greater, 71% of the dose is excreted within 24 hours. Dosing formulas, which incorporate estimates of glomerular filtration rates (GFR), provide predictable AUC estimates and should be used to calculate doses, especially in elderly patients where renal function may be decreased.

Packaging and Labeling

Investigators should review the approved Package Insert (PI) as per the current version and applicable manufacturer, for full information on storage, handling, preparation and stability.

How Supplied

Carboplatin is commercially available from multiple commercial manufacturers in the United States. Carboplatin may be supplied as a sterile 10 mg/mL aqueous solution or as a sterile lyophilized white powder in 50 mg, 150 mg and 450 mg vials containing equal parts of carboplatin and mannitol by weight.

Handling and Dispensing

Storage Requirements/Stability

Carboplatin may be supplied as a sterile 10 mg/mL aqueous solution and stable to the date on the package when stored at room temperature of 25°C (77°F) [excursions permitted from 15°-30°C (59°-86°F)], and should be protected from light.

Carboplatin may be supplied as a sterile lyophilized white powder in 50mg, 150 mg and 450 mg vials containing equal parts of carboplatin and mannitol by weight. Reconstituted vials do not contain any antimicrobial agents and should be discarded within 8 hours of reconstitution. Unopened vials are stable to the date on the package when stored at room temperature of 25°C (77°F), and should be protected from light. Solutions for infusion should be discarded 8 hours after preparation.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Procedures for proper handling and disposal of anti-cancer drugs should be considered, and several have been published and should be referenced by study sites in internal procedural documents.

Preparation and Administration

Carboplatin should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Solutions can be further diluted to a concentration as low as 0.5 mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride Injection, USP. Administer by continuous infusion over 15 minutes or more.

Needles or IV administration sets containing aluminum parts should not be used for the preparation or administration of the drug as aluminum can interact with carboplatin causing precipitation or loss of potency.

Drug should be disposed of or destroyed as per written institutional policies and per recommendations in the current approved Package Insert.

11.2. Paclitaxel

Paclitaxel (NSC #125973) is commercially available.

How supplied

A concentrated sterile solution, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to infusion.

Reported Toxicities

Myelosuppression, N&V, diarrhea, stomatitis, mucositis, pharyngitis, sinus bradycardia, heart block, ventricular tachycardia, myocardial infarction (MI), hypotension, sensory (taste), peripheral neuropathy, seizures, mood alterations, anaphylactoid and uticarial reactions (acute), flushing, rash, pruritus, alopecia, fatigue, arthralgia, myalgia, light-headedness and myopathy.

Solution Preparation and Administration

The total calculated dose of paclitaxel will be diluted in 500 ml of 5% Dextrose injection, USP (D5W) or 0.9% Sodium Chloride for injection, USP (NSS). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexyl phthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Paclitaxel will be administered as a 1-hour infusion weekly via an infusion control device (pump). Nothing else is to be infused through the line while paclitaxel is being administered.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVP's) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g. IVEX-11, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Storage
The intact vial should be stored at room temperature. Each bag/bottle should be prepared immediately before administration.

Stability
All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 48 hours.

11.3 Bevacizumab (Cohort 1 Only)

Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in vials of two sizes:

Each 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

Each 1000 mg (25 mg/mL – 40 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

Preparation

Opened vials must be used within 8 hours. Vials contain no preservative and are intended for single use only. The calculated dose should be diluted in 100 mL of 0.9% sodium chloride for IV infusion.

Administration

See Section 7.4.2.

Toxicities

The most common adverse events associated with bevacizumab have been hypertension and proteinuria. Other less common events, some of which have been fatal, include bleeding, thrombosis, elevated liver function tests, and bowel perforation, and anastomatic dehiscence. Infusion-related or allergic reactions may also occur. These include fever, chills, rigor, rash, urticaria, and dyspnea. Treatment for such reactions should be done per institutional guidelines.

Hypertension is among the most common adverse events associated with bevacizumab to date. Both new hypertension and worsening of existing hypertension have been reported. Hypertension may require treatment; ACE inhibitors, calcium channel blockers, beta blockers (note alternatices to metoprolol are suggested as there are interactions with hydroxychloroquine, see Section7.6) and diuretics have all been reported to be effective in this setting. Although most hypertension can be controlled by medication, hypertensive crises have been reported in several studies, and the end organ consequences included CNS bleeding and ischemia, and congestive heart failure

Proteinuria, ranging from asymptomatic abnormal urinalysis to nephrotic syndrome, has been described in 10% or more of patients receiving bevacizumab. Proteinuria is managed with dose modifications as described in the dose modification section.

Bleeding, including fatal CNS hemorrhage, has been reported. DIC has been described in a few patients receiving bevacizumab in combination with oxaliplatin, fluorouracil and leucovorin. Bleeding at tumor sites or at sites of other pre-existing abnormalities (e.g., diverticulosis, hemorrhoids) has also been described. Further toxicity observed in a Phase III study included fatal hemoptysis in 2 of 55 patients with non-small cell lung cancer, both of whom had a history of hemoptysis. Although most episodes of epistaxis were short-lived and resolved without treatment, some required medical intervention.

Thrombosis/embolism Both arterial and venous thromboses (including pulmonary embolism, mesenteric vein thrombosis, ischemic bowel, and cerebral vascular accident) have been described in patients receiving bevacizumab. Fatal pulmonary embolus has also been described.

Hepatic Dysfunction: Reversible and marked elevations of liver function tests (total bilirubin and/or transaminase and AP) have been rarely reported when bevacizumab is used in combination with chemotherapy or concurrently with other drugs that are potentially hepatotoxic. The mechanism of such hepatic toxicities is unclear. It is possible that in rare occasions, bevacizumab may potentiate the liver side effect of a concurrent medication, although it is unclear at this time whether bevacizumab alone can cause LFT derangement.

Bowel perforation and bowel anastomotic dehiscence have been reported in clinical trials using bevacizumab alone or in combination with chemotherapy. Although these events were likely related to co-existing factors such as tumor involvement, chemotherapy, recent invasive procedures or bowel inflammation, contribution of bevacizumab to these events cannot be excluded. A fatal bowel perforation has been described. Partial delay in wound healing has been demonstrated in animal models treated with anti-VEGF antibodies and it is possible that bevacizumab may delay or compromise wound healing in patients.

Other toxicities Other reported or potential toxicities associated with bevacizumab include:

Constitutional—Headache, infection without neutropenia, asthenia;

Cardiovascular—Hypotension, pericardial effusion Skin—Rash, urticaria;

Gastrointestinal—Nausea, vomiting, stomatitis/pharyngitis, colitis, intestinal obstruction;

Pulmonary—Pulmonary infiltration, dyspnea;

Musculoskeletal—Arthralgia, chest pain.

11.4 Hydroxychloroquine

Product Description: Hydroxychloroquine is a colorless crystalline solid, soluble in water to at least 20 percent; chemically the drug is 2-[[4-[(7-Chloro-4-quinolyl) amino]pentyl]ethylamino]ethanol sulfate (1:1). Hydroxychloroquine sulfate tablets contain 200 mg Hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration.

Product Name: hydroxychloroquine

Product Dosing: 1200 mg per day

How Supplied: Hydroxychloroquine tablets, USP of 200 mg (equivalent to 155 mg of base), white, unscored, film-coated, capsule-shaped tablets debossed "93" and "9774" on one side and plain on the other side in bottles of 100 and bottles of 500.

Storage Requirements/Stability: Tablets are stable at room temperature. Storage temperatures should be between 20° and 25°C. Store away from light and moisture. Dispense in a tight, light-resistant container.

Route of Administration:
The dose of hydroxychloroquine will be 600 mg PO BID as determined by protocol 030801. Hydroxychloroquine should be taken at the same time each day. Hydroxychloroquine may be given orally or via NG tube. The dose may be given with a meal or milk. For patients that can't swallow capsules or tablets, the tablet may be removed and be dissolved in 5 ml of water or mixed in a small amount of liquid or food. However, the drug may be bitter-tasting. The drug may be dissolved in 5 ml of water for NG administration. Patients receiving antacids, sucralfate, cholestyramine, and/or bicarbonate should have the study drug dose at least 1 hour before or 2 hours after these medications.

Drug Interactions: There are known drug interactions with the following medications: penicillamine, telbivudine, botulinum toxins, digoxin, and propafenone. Depending on the specific drug, hydroxychloroquine increases the levels of these other drugs, or interferes with the activity of the agent (specifically with botulinum toxin).

Toxicity:
Anorexia, nausea, vomiting, diarrhea, abdominal cramps, alteration of retinal pigmentation, visual scotoma (visual field defects), disturbance of accommodation with symptoms of blurred vision, halos around light, photophobia, corneal deposits, rash, hemolysis in patients with G6PD deficiency.

Extraocular muscle palsy, skeletal muscle weakness, absent or hypoactive deep tendon reflexes.

Irritability, nervousness, emotional changes, nightmares, psychosis, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia. Neuromyotoxicity is rare. Weight loss, lassitude, exacerbation or precipitation of porphyria, and nonlight-sensitive psoriasis. Cardiomyopathy has been rarely reported and the relationship with hydroxychloroquine is unclear.

12. Data Collection and Records to be Kept

12.1 Data Reporting to Coordinating Center

A subset of the NCI's CTMS case report forms, in electronic format (e-CRFs) will be utilized. Completion of the e-CRFs will be done in accordance with the instructions provided by the [redacted] center in a study-specific data capture plan. Electronic CRFs will be submitted to the OHRS via the On-line Clinical Oncology Research Environment (OnCore). The e-CRFs are found in the study specific calendar that has been created in OnCore. The system will prompt the user to the forms that are required based upon the patient's enrollment and treatment dates.

The Principal Investigator at each institution will be responsible for assuring that all the required data is entered onto the e-CRFs accurately and within 2 weeks of the date in which the previous cycle was completed.

Periodically, monitoring and/or auditing visits will be conducted by staff from the Coordinating Center. The Principal Investigator at each participating center will provide access to his/her original records to permit verification data entry.

12.2 Research Charts

A research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Copies of the most significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment and documents that verify Grade 3-4 adverse events and response. This information will be updated on a prospective basis and will be confidentially maintained at the OHRS.

12.3 Reports

Publications and annual reports for submission to the IRB and FDA will be written by the Principal Investigator using the data captured on the CRFs. Study progress reports will be provided to participating institutions for submission to local IRBs.

13. Data and Safety Monitoring

Monitoring of this study will occur in accordance with the [redacted] approved Data and Safety Monitoring Plan (DSMP). An "initiation audit" will be conducted by OHRS Quality Assurance staff in accordance with the DSMP following enrollment of the first two (2) or three (3) patients. Subsequent audits will occur on an annual basis if the findings from the initiation audit were satisfactory. More frequent audits of patient data and study conduct will occur if necessary. [redacted]

14. Multi-Institutional Guidelines

14.1 IRB Approvals

[redacted]

14.3 Initiation Meetings

A study initiation meeting will be conducted with each participating institution prior to enrollment of patients from the institution. OHRS staff will conduct the study initiation meeting in close proximity to IRB approval of the study at the participating center. In most situations the study initiation meeting will be conducted via teleconference. Web-based training regarding e-CRF completion will be utilized as appropriate.

14.4 IRB Continuing Approvals

Investigators from participating institutions must provide to the OHRS, a copy of the institution's approved continuing review documentation. Registration will be halted at any participating institution in which a current continuing approval is not on file. [redacted]

[redacted] and Consents

The OHRS will maintain a copy of all amendments, consent forms and approvals from each participating institution. Consent forms will be reviewed and [redacted] as soon as possible.

14.6 Patient Registration

All patients from participating institutions must register patients with the OHRS central registration desk, as described in Section 5.7 of this protocol.

14.7 Data Collection and Toxicity Reporting

The PI at each institution will be responsible for assuring that all the required data is collected and entered onto the eCRFs accurately and completed eCRFs submitted as described in Section 13.

14.8 Data Monitoring and Source Document Verification

Each site participating in the accrual of patients to this protocol will be audited for protocol and regulatory compliance, data verification and source documentation.

[redacted]

14.9 Data and Center Audits

[redacted]

15. Statistical Considerations

The primary objective of this study is to assess the antitumor activity, as measured by tumor response rate, of paclitaxel, carboplatin, Bevacizumab (for eligible patients) and hydroxychloroquine in patients with advanced or recurrent NSCLC cancer. The null hypothesis of response rate for the paclitaxel, carboplatin, Bevacizumab combination therapy for lung cancer is 30%. Based on the previous study "Modulation of autophagy with hydroxychloroquine in patients with advanced/recurrent non-small cell lung cancer – a Phase I/II study", we would like to determine if the addition of hydroxychloroquine can increase this response rate to 60%. We will use a Simon's two-stage minimax design with a 5% significance level and 80% power. This procedure calls for 10 patients in the first stage and 7 in the second, so that the maximum sample size is 17. If 2 or fewer responses are observed in the first stage, the trial will be stopped and the addition of hydroxychloroquine to the paclitaxel, carboplatin, Bevacizumab combination will be deemed not worthy of further study. If the trial continues to the second stage, and 8 or fewer responses are observed out of the total of 17, addition of hydroxychloroquine will not be considered worthy of further study in these patients. But if 9 or more responses are observed, future study is warranted.

For the above two-stage minimax design, if the true response rate is 30%, the expected sample size is 14.32, and the probability of early termination is 0.38. In the event that other updated information during the study monitoring may affect the study's design, we will use the method of Wu and Shih[37] as a guide when necessary.

The patients accrued in the Phase I dose escalation study (protocol 030801) will be included in final results of this Phase II study. Evaluable patients for the Phase II portion are those who have received at least two cycles of treatment.

The secondary endpoints of this study are to assess time to progression and one-year survival, and overall survival in patients receiving this regimen. Time to progression will be calculated based on the time between the first day of treatment and the date of disease progression. Overall survival will be calculated based on the time between the first day of treatment and the date of death from any cause.

The one-year survival rate will be estimated with the presentation of its 95% confidence interval. For the assessment of progression free survival and overall survival, Kaplan-Meier estimates of survival function and the standard errors will be calculated. The median survival times and 95% confidence intervals will be presented. In addition, toxicity of this regimen will be assessed. Any relationship between baseline beclin-1 and p62 expression, changes in LC3-II protein expression, and tumor response will be studied based on descriptive analyses.

For the added cohort of 20 patients to be treated with 600 mg bid:
The null hypothesis response rate will be taken to be 30%, as for the previous cohort. This is the response rate for the therapy without hydroxychloroquine. We would like to determine if the addition of the higher dose of hydroxychloroquine will increase this response rate to 60%. We will use a Simon's two-stage minimax design with a 5% significance level and 85% power. This procedure calls for 8 patients during the first stage and 12 patients in the second, so that the maximum sample size is 20. If 2 or fewer responses are observed during Stage I, then the trial will be stopped early for futility. If there are 3 or more responses, the trial will continue to Stage II. If a total of 9 or fewer responses are observed by the end of Stage II, out of a total of 20 patients, then no further investigation of the combination will be considered. If there are 10 or more responses out of 20, the combination including hydroxychloroquine will be considered for further study.

A secondary objective will be to assess the duration of response among responders. This will be assessed by computing a Kaplan Meier survival curve.

[redacted]

16. Human Subjects

16.1 Patient Population

See Section 5.

16.2 Potential Risks

The major risk to the patients involved in this study is that the hydroxychloroquine may decrease the effectiveness or increase the toxicity of the standard regimen of paclitaxel, carboplatin and bevazicumab. In addition, patients may experience unpleasant and potentially fatal side effects from the medications used.

16.3 Consent Procedures

Informed consent must be obtained prior to commencing any research procedures. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the patient or representative. The informed consent document may not include any exculpatory language through which the patient or representative is made to waive any of the patient's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

16.4 Potential Benefits

Patients may experience improved response rates of their disease as well as a chance to increase their overall survival.

16.5 Risk-Benefit Ratio

The major risk of participating in this study versus receiving standard care is that there may be increased toxicity of the regimen or decreased effectiveness. Alternative therapies include standard chemotherapy with bevacizumab or observation

16.6 Gender and Minorities

Female patients accounted for 58% of cancer patients seen within the Cancer Institute of New Jersey's clinical programs within the last year. African-Americans comprised 7%, Hispanics 8%, and Asians 3% of female patients, respectively. For all patients entering clinical trials, the percentages were 52% women, 6% African-American, 5% Hispanic, and 3% Asian.

No person shall, on the grounds of age, race, color, or national origin, be excluded from participation in, or be denied the benefits of, enrollment in this protocol.

17. Economic/Financial Considerations

Patients and/or their insurance carriers will be expected to pay for all costs of therapy, monitoring, and follow-up. Patients will not be charged for the cost of laboratory correlate testing performed. Laboratory correlate testing will be funded by [redacted]

18. Publication of Research Findings

[redacted]

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Appendix A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B

New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.