**Table S2:** Dose reduction criteria

|  |
| --- |
| **Cardiac toxicity criteria** |
| CHF severe | Withdrawal |
|
| CHF moderately symptomatic orAsymptomatic | LVEF < 45%: withdrawal |
| LVEF decrease 10-20 points and LVEF ≥45%: keep treatment  |
| LVEF decrease > 20 points : withdrawal   |
| **Hematology toxicity criteria**   |
| **PLD+CPM** |
| 0.5x109 /l ≥ *N* < 1.5x109 /l and/or25x109/l ≥ Plat < 75x109/l   | interrupted until *N* < 1.5x109 /l andPlat < 75x109/l  | No dose reduction    |
| *N* < 0.5x109 /l and/or Plat < 75x109/l  | Interrupted until *N* < 1.5x109 /l andPlat < 75x109/l  | Dose reduction of 15% for both drugs    |
| If a patient needs more than 2 weeks to recover normal levels of neutrophils or platelets, PLD plus CO was  withdrawal and patient start PYX treatment or surgery was performed at investigator criteria  |

|  |
| --- |
| **Paclitaxel** |
| *N* < 1.0x109 /l and/or Plat < 75x109/l  | Interrupted until *N* < 1.5x109 /l andPlat < 75x109/l   | Recovery ≤ 1 week: no dose reduction  |
| Recovery ≤ 2 week: rechallenge at a 20 % dose reduction  |
| If a patient needs more than 2 weeks to recover normal levels , paclitaxel was withdrawal and surgery was performed   |
| **Non-hematology toxicity criteria**  |
| **PLD+CPM** | **PTX** |
| Hand foot syndrome (HFS) | Adverse Events |
| G1 | Treatment not interrupted | No dose reduction   | G1 | Treatment not  interrupted  |
| G2  | interrupted until≤ G1  | No dose reduction   | G2  | Treatment not  interrupted   |
| G3  | interrupted until≤ G1  | 15% dose reduction   | G3  | interrupted until ≤ G1   |
| G4  | interrupted until≤ G1  | 25% dose reduction   | G4  | interrupted until ≤ G1   |
| If a patient needs more than 2 weeks to G1, withdrawal PLD+CPtreatment and start with PTX  | If a patient more than 2 weeks to recover to G2, withdrawal PTX treatment and surgery performed  |
| Mucositis | Hypersensitivity |
| G1  | Treatment not interrupted | No dose reduction   | Immediately discontinued the infusion and appropriate symptomatic treatment. Treatment was restarted a lower speed. If tolerated, the infusion may then be completed over the next hour to a total of 90' |
| G2  | interrupted until≤ G1  | No dose reduction   |
| G3  | interrupted until≤ G1  | 15% dose reduction | **PLD+CPM, paclitaxel** |
| Bilirubin > 2x normal lab value |
| G4 | interrupted until≤ G1 | 25% dose reduction  | Treatment interrupted | recovery in 3weeks to G1 | Treatment notinterrupted |
| If patient needs more than 2 weeks to G1, withdrawal PLD+CP treatment and start with PTX | no recovery in 3 weeksto G1  | Interrupted treatment and surgery performed |
| Anaphylactic reaction during infusion   | Creatinine clearance 40-156 ml/min | Normal dose |
| Immediately discontinued the infusion and appropriate symptomatic treatment. Treatment was restarted at a lower speed. If tolerated, the infusion may than be completed over the next hour to a total of 90 '   |
| Creatinine clearance ≤ 40 ml/min  | If ≤ 3 weeks to normal, no interrupted treatment |
| If ≥3 weeks to normal, interrupted treatment and surgery performed |

Abbreviations: CHF: Congestive Heart Failure, LVEF: Left ventricular ejection fraction, N: Neutrophils, Plat: Platelels, G: Grade, PLD: Pegylated liposomal doxorubicin, CPM: Cyclophosphamide, PTX: Paclitaxel,