Artesunate for Parenteral use

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Abstract

Artemisia based medications are used the world over for anti-malarial activity. Their pharmacology and safety are well studied and published in the scientific literature. The use of these agents in the patient with cancer and their effectiveness against cancer cell lines are newer areas of scientific research, but also published in the literature. Experience in our clinical research of over one thousand parenteral doses of Artesunate have shown this agent to be safe in patients with advanced cancers. While specific human clinical data needs to be collected our experience and the basic pharmacology of artesunate in cancer lead us to the conclusion that this agent is worthy of further investigation in oncology practice.

Safety

Artesunate is a parenteral medication derived from portions of *Artemesia*. This sesquiterpene is widely used in the treatment of malaria in many parts of the world. Administration is generally either via the intravenous or intramuscular route, although rectal and oral dosing are employed.

In adults parenteral artesunate has shown a highly tolerable and low side effect profile [1] when used in typical parenteral doses [2]. Toxicities have been reported in certain Artemisinin derivatives in animal studies but generally not human studies [3]. Toxicity noted in some cases (animal and human) was attributed to the oil based parenterals which are not recommended for use in humans [3,4], but these effects are not generally seen in the artesunate form of the drug [4].

In the pediatric population studies assessing both the efficacy and safety of parenteral artesunate similar positive profiles for safety are noted [5,6]. In one smaller review of artesunate in a total of 274 children [5] no increased risk of adverse events was noted beyond the adult data (when dosed appropriately). In the largest study of safety looking at 2712 children administered parenteral artesunate (AQUAMAT) a similar safety profile was noted [6]. This safety profile in the pediatric population has led to the WHO recommendation of parenteral artesunate use in children infected with malaria [7].

Pharmacology / Mechanism of Action

Multiple cell line studies show positive tumor kill with Artemisinin agents [8,9,10,11]. Many cell line studies (some of which are summarized here) show positive effect of the agent Artemisinin in tumor cell damage and kill while research is ongoing to elucidate all the potential benefits in cancer from this multi-target agent.

Some data indicates Artemisinin having antiangiogenic activity [12] while other data shows VEGF inhibition [16]. Other data elucidates the role of ROS generation via iron and iron transport moieties in the apoptotic effects of Artemisinin [13,14,15]. In a xenograft in vivo model the activity of Artemisinin against pancreatic cancer cells was shown to be similar to that of gemcitabine and proved to have significant tumor regression [15].

Clinical experience in the setting of some bacterial infections as well as chronic Epstein-Barr virus and Cytomegalovirus infections has shown positive therapeutic effect. [17; 20-22]

Recently, growing evidences reveal that artemisinin and its derivatives also possess potent anti-inflammatory and immunoregulatory properties. [23] In other data researchers state "Our results indicated that artesunate could decrease MCP-1, major pro-inflammation cytokine, in serum, urine and kidney. We also found that the level of BAFF, the major B cell activation factor, was decreased in artesunate treated MRL/lpr mice. Its efficacy was comparable with that of cyclophosphamide in this study. Taken together, we have demonstrated that artesunate can inhibit the progression of disease and reverse the pathologic lesion of lupus nephritis." [24] Other data are showing that cytokine manipulation by artesunate provides immune modulation in a direction away from autoimmunity and potentially against some triggers of metastasis. [25,26]

INTRAVENOUS USE GUIDELINES:

Dose:

- Test dose at 60 mg IV on the first day [1]
- Subsequent doses could increase to 120 to 240 mg if tolerated two to three times weekly in combination with doses of intravenous ascorbic acid over 25 grams. Intravenous ascorbate should be given directly after the IV artesunate. [1]
- Doses in animal models have been used safely up to 240 mg/kg [19], and some human clinical use has included dosing to 600 mg – but our experience shows efficacy at the lower doses mentioned above. [17]

Administration:

- Intramuscular administration is appropriate but may cause local tissue irritation.
    - Recommend Deep IM in a large muscle
    - Not more than 120mg in an IM administration
- Intravenous dosing via either a central or peripheral line.
- Carrier solutions:
    - Dextrose 5% in Water (D5W) 20-100 mL carrier solution

- 0.9% normal saline 20-100 mL carrier solution

- Rate of administration: 15 minutes max until tolerance is established then it may be given as a slow push if tolerated.

- Artesunate is stable in room light UV exposure and does not require light abated tubing or IV bags. [18]

- Other IV compatibility:

  - No other additives should be mixed in the IV bag with the Artesunate.

  - High dose IV vitamin C is best given following the Artesunate to continue the ROS activity.

- Other IV incompatibility:

  - Antioxidant treatments – separate by 4 hours if using Artesunate alone and 24 hours if using Artesunate with high dose IV vitamin C.

Screening:

- Intolerance to oral artemisinin or artemesia compounds is a caution and may exclude use in the IV setting

- Iron studies:

  - One mechanism of action for artesumate is cyclic use of transition metals in the body (such as iron and copper) for ROS generation. [13-15] This leads to concerns regarding iron or copper depletion during use. The authors clinical experience [17] with thousands of artesunate administrations leads to the following conclusions in this regard:

    - In the authors clinical experience dosing of artesunate and ascorbate as described above at a dose frequency of once to twice a week anemia occurs in less than 5% of patients.

    - In dose schedules which are more frequent, or use higher doses of artesunate, iron depletion may occur with more frequency.

    - For these reasons CBC and iron studies are indicated as noted below.

- Other lab studies:

  - Prior to administration: CBC, Chemistry panel (Metabolic panel including electrolytes, bilirubin, AST/ALT, eGFR/BUN/CRE), G6PD.

- During therapy: If anemic prior to therapy a CBC and iron studies at 4 weeks and then every 4-8 weeks as indicated. If not anemic prior to therapy CBC and iron studies at 8 weeks and then as indicated for follow up.
- Other lab and imaging studies should be followed as indicated per patient clinical need.

Cautions:

- Artesunate has direct immune and anti-infective effects. Latent infections may cause temperature rise or other cytokine effects following use.
- Use as a push with caution until tolerance is established.
- Use with caution and close monitoring in those with intolerance to wormwood / artemesia products.

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