Leukemia Research Reports 16 (2021) 100281

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Pharmacological dose ascorbic acid administration in relapsed refractory multiple myeloma patients

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ARTICLE INFO

Keywords:
Arsenic
Ascorbate
Intravenous
Oxidative
Reactive oxygen species

ABSTRACT

Objective: High-dose ascorbic acid leads to the formation of highly reactive oxygen species due to the pro-oxidant effect, resulting in cell death; therefore, used as an additive treatment in several malignancies. We present the results obtained by administration of pharmacological dose of ascorbic acid to conventional chemotherapy in relapsed refractory multiple myeloma patients.

Materials-methods: Intravenous ascorbic acid at a pharmacologic dose of 15 gram/week was added to the chemotherapy regimen of relapsed refractory multiple myeloma patients, who received carfilzomib-lenalidomide-dexamethasone treatment and did not respond after the second cycle.

Results: The total of 4 patients who had previously received 6–9 lines of myeloma treatment were included. After 4 cycles of chemotherapy + ascorbic acid combination, 1 patient had a complete response whereas other patients had a very good partial response.

Conclusion: The addition of pharmacological dose ascorbic acid to conventional chemotherapy can be an effective approach in relapsed refractory patients. Clinical studies with a large number of patients will be useful to evaluate the pharmacological dose of ascorbate in plasma cell disorders.

1. Introduction

Multiple myeloma is a malignant neoplasm of clonal plasma cells. There is no consensus regarding the optimal treatment approach for the relapsed refractory multiple myeloma (RRMM) patients. The patients that have been treated with immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies are devoid of further treatment options [1].

Pharmacological dose ascorbic acid (AA) which its anti-cancer effects were discovered thirty years ago can be used as an additive treatment for RRMM patients [2]. AA shows anti-tumor effects via two pathways. One of them is related to DNA methylation, while the other is the pro-oxidant effect. In MM, aberrant DNA methylation is a prominent mechanism. Supporting this, some authors showed DNMT3A promoter hypermethylation [3]. AA is a cofactor and increases the activity of the ten-eleven-translocation (TET) enzymes, which are responsible for the increase of both DNA demethylation and hydroxymethylation [4]. Oxidative stress increase and DNA damage occur while the antioxidant enzyme levels decrease in patients with myeloma [5]. High dose AA leads to the formation of highly reactive oxygen species (ROS) due to the pro-oxidant effect, resulting in cell death [6]. Here, we report the results of pharmacological-dose of AA therapy in addition to Carfilzomib-Lenalidomide-dexamethasone (CRd) regimen in patients with RRMM.

2. Patients and methods

Four patients with RRMM were included. The progressive disease had been observed under previous treatments in all cases. The patients had never been exposed to intravenous AA during their former chemotherapy cycles. None of them had renal failure and all had a glomerular filtration rate above 100 ml/minute/1.73 m^2. Official permission was obtained from the Turkish Drug and Pharmacy Agency for all patients because it was an off-label treatment. In addition to the CRd regimen, intravenous AA 7.5 g/day, for 30 min, two days every week was given after the second cycle for the patients who remained stable or progressed [7]. None of the patients received any AA test dose. The treatment solution was prepared from AA for injection (Ulagay Turkey IE). Each 5 mL of AA ampoules contain 500 mg ascorbic acid, 4 mg methylparaben and 0.5 mg propylparaben. Fifteen ampoules (total 7.5 gram) were given in

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https://doi.org/10.1016/j.lrr.2021.100281
Received 17 May 2021; Received in revised form 20 November 2021; Accepted 21 November 2021
Available online 22 November 2021

50 ml Ringer's lactate solution in 15–30 min. A single starting AA dose of 7.5 g over 30 min at 0.25 g/min was infused. All patients were observed at the time of the infusion and up to 2 h. Antiviral (acyclovir) and antithrombotic prophylaxis (aspirin) were continued to the patients and they were evaluated with hematological and biochemical parameters every week and serum-urine protein/immunofixation electrophoresis every four weeks.

3. Results

The patients had been treated with 6–9 different regimens containing melphalan, bortezomib, ixazomib, thalidomide, cyclophosphamide, lenalidomide, pomalidomide, dexamethasone, and stem cell transplantation (SCT) until CRd treatment. Three patients had an SCT history following first-line treatment and they had received consolidation treatment as two cycles of VTD after SCT, beginning with post-transplantation 100th day. Case 2 was considered as International Staging System (ISS) stage III due to β_2 microglobulin level of 6.3 mg/L, whereas the other three cases were considered as ISS II. Myeloma FISH panel analysis which was performed at diagnosis did not reveal any abnormality for del 17p, t (4,14), t (14,16). At the end of the 4th CRd+AA cycles, complete remission (CR) was achieved in one patient and very good partial remission (VGPR) in three patients (Table 1). Second autologous SCT was performed in case 1, who achieved CR. However, we were unable to perform a second SCT in three patients because of their general status. For the patient with tandem SCT, two more cycles of CRd therapy were administered as a post-transplant consolidation. While she was on lenalidomide maintenance, she experienced a clinical relapse after 11 months, and she died due to progressive disease. Case 2 refused to have treatment after 5 cycles of CRd+AA therapy and left observation. It was learned that he died six months after the last cycle. The other two patients died due to progressive disease at 11 and 13 months. During or after the AA infusion, we have not observed any adverse effects.

4. Discussion

Oxidative stress is a result of the excessive production of reactive oxygen species (ROS) and/or their insufficient elimination by antioxidants. ROS detoxification occurs via two major systems, glutathione (GSH) and thioredoxin. Some authors have described antioxidant depletion in patients with MM [8,9]. With selective action on myeloma cells, AA has the potential to reduce GSH in these patients [10]. AA can selectively kill KRAS and BRAF mutant colorectal cancer cells by targeting glyceraldehyde3-phosphate-dehydrogenase (GADPH). It is not known that this pathway could be a mechanism of AA-mediated plasma cell growth inhibition in MM [11].

Because oral ascorbate at 1 g produces plasma saturation, many clinical studies utilize 1 g AA in combination with arsenic trioxide (As_2O_3), which activates caspase cascade and increases the release of ROS from the mitochondria as a potentiating effect of As_2O_3 [12]. Bahlis et al. showed the efficacy of As_2O_3 and AA combination in six patients with RRMM [13]. There is only one study that suggests AA inhibits the antitumor activity of bortezomib in vivo, which was suggested to be related to the boron group activity of bortezomib [14].

Berenson et al. administered bortezomib, melphalan, and AA (BAM) to 25 patients with RRMM in a single-arm phase 2 study [15]. AA and melphalan were given in the evening while bortezomib in the morning because of the possible inactivation of bortezomib with AA. The overall response rate and median response duration were 74% and 17 months, respectively in this study. Other studies also reported synergistic effects of As_2O_3 and AA combination in patients with RRMM [16,17,18]. As_2O_3 and AA, in addition to bortezomib and dexamethasone combination can be an effective treatment strategy in these patients [19]. Pharmacological doses of AA describe very high doses of AA administration and generally accepted as 15–100 gr. Pharmacologic dose AA depletes glutathione levels, increases H_2O_2, and generates ROS [20,21,22]. Mitochondrial damage and apoptosis occur in malignant cells without any effect on normal cells [4].

Our four patients have received a CRd regimen, with no obvious response at the end of 2 months. The response after adding AA (VGPR: three patients, CR: one patient) supported that AA increased the efficacy of the CRd regimen. There was no opportunity to use monoclonal antibodies such as daratumumab in our country due to financial restrictions. In addition to chemotherapy, we preferred to give 15 g/week of AA to our patients, because the initiation of the pro-oxidant effect was possible at doses of 15 g or more based on prior in vivo and in vitro studies [22, 23]. We did not prefer the oral route; considering that tight control of AA concentration from oral ingestion avoids reaching adequate levels of AA at plasma and extracellular fluid concentrations [24]. We believe that addition AA to combination chemotherapy was clinically additive since prior therapy without AA showed no clinical improvement in these four patients. The importance of our study is the first administration of pharmacological AA without As_2O_3 in patients with RRMM.

Table 1
Demographic and clinical characteristics of the patients.

Factors	Case 1	Case 2	Case 3	Case 4
Age /gender	64/female	75/male	61/male	73/male
Previous treatment and duration (m)	VCD:2, VTD:4, VTD (post-SCT): 4, Rd:12, IRd: 24, PomDex:10, PomCycDex: 8	VMP:12, Rd:48, VRD:63, PomDex:2, PomCycDex:4	VCD:2, VTD:3 VTD (post-SCT):4, Rd:22	VCD:2, VTD:2, VTD (post-SCT):4, Rd:41, PomDex:28, IRd:3
ISS at diagnosis	2	3	2	2
Time interval from diagnosis to AA treatment (m)	66	131	33	82
CRd + AA cycles (n)	4	4	5	5
Plasmacytomas	Yes, multiple	No	No	No
Response to CRd plus AA	CR	VGPR	VGPR	VGPR

AA: Ascorbic acid, **CR:** Complete remission, **CRd:** Carfilzomib-Lenalidomide-dexamethasone, **IRd**: Ixazomib-lenalidomide-dexamethasone, **ISS:** International staging system, **m**: month(s), **n:** Number, **PomCycDex**: Pomalidomide-cyclophosphamide-dexamethasone, **PomDex:** Pomalidomide-dexamethasone, **Rd**: Lenalidomide-dexamethasone, **SCT**: Stem cell transplantation, **VCD**: Bortezomib-cyclophosphamide-dexamethasone, **VGPR:** Very good partial remission, **VTD**: Bortezomib-thalidomide-dexamethasone.

5. Conclusion

Pharmacologic dose AA administration is inexpensive, easily applicable, tolerable without drug interaction. The effectiveness of combining pharmacological doses of AA and conventional chemotherapy should be demonstrated with further clinical studies.

6. Study limitations

Our study has some limitations. The most important limitation is the restricted number of patients. In addition, previous treatment lines and combination regimens were different among the patients. Also, the pharmacologic dose of AA was initiated after 2 cycles of CRd chemotherapy and it can be delayed until the evaluation of the results, after completion of 4 cycles CRd chemotherapy.

7. Ethics

7.1. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

7.2. Ethics

All procedures were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

7.3. Informed consent

Consent forms for participation and publication have been taken from all patients.

Declaration of Competing Interest

None

Acknowledgements

We thank Prof. Dr. Serhan Alkan for language editing.

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