Open Access Library Journal
2024, Volume 11, e11414
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Actual Data on the Efficacy and Safety of Gemcitabine-Docetaxel as Second-Line and Beyond Treatment in Adult Patients with Metastatic Bone Sarcomas: Experience from a Single Institution

Medyouni Hajar[1], Chouef Jihane[1], Siyouri Oumaima[1], Chbihi Chaymae[1], Mhirech Samia[2], Amaadour Lamiae[1], Oualla Karima[1], Benbrahim Zineb[1], Arifi Samia[1], Mellas Nawfel[1]

[1]Department of Medical Oncology, Hassan II University Hospital, Fes, Morocco
[2]Department of Radiotherapy, Hassan II University Hospital, Fes, Morocco
Email: hajarmedyounifmpf@gmail.com

How to cite this paper: Hajar, M., Jihane, C., Oumaima, S., Chaymae, C., Samia, M., Lamiae, A., Karima, O., Zineb, B., Samia, A. and Nawfel, M. (2024) Actual Data on the Efficacy and Safety of Gemcitabine-Docetaxel as Second-Line and Beyond Treatment in Adult Patients with Metastatic Bone Sarcomas: Experience from a Single Institution. *Open Access Library Journal*, **11**: e11414.
http://doi.org/10.4236/oalib.1111414

Received: March 9, 2024
Accepted: April 9, 2024
Published: April 12, 2024

Abstract

Osteosarcoma, the most prevalent primary malignant bone tumor in children, presents significant challenges in treatment, particularly in cases of recurrence or refractory disease. This retrospective study explores the efficacy and safety of gemcitabine-docetaxel (GD) combination therapy as second-line or later treatment in adult patients with advanced bone sarcomas. Twenty-two patients received GD, with 64% showing overall disease control. Median progression-free survival (PFS) was 5 months, and median overall survival (OS) was 8.5 months. Adverse events were manageable, with mainly myelosuppression observed, principally neutropenia followed by anemia and thrombocytopenia, (grade 1 - 2). Despite limitations such as retrospective design and small sample size, GD demonstrated tolerability and modest efficacy, offering a potential treatment option for refractory or recurrent high-grade osteosarcoma where limited alternatives exist.

Subject Areas

Pediatrics

Keywords

Bone sarcomas, Metastatic, Recurrent, Gemcitabine, Docetaxel

1. Introduction

Osteosarcoma is the most common primary malignant bone tumor in children [1] [2]. Despite significant improvements in the overall survival of patients with high-grade osteosarcoma over the past few decades, the recurrent disease still occurs in approximately 30% to 40% of patients with non-metastatic osteosarcoma and 80% of patients with metastatic disease at the time of diagnosis with relapse [3] [4]. Standard multimodal treatment failure in osteosarcoma is associated with a very poor prognosis. Therefore, new drugs or combined therapies are needed for patients with recurrent or refractory high-grade osteosarcoma.

Gemcitabine, a nucleoside antimetabolite, is a deoxycytidine analogue that primarily inhibits DNA synthesis by interfering with DNA chain elongation and depleting deoxynucleotide pools, leading to gemcitabine-induced cell death [5]. Docetaxel is a semi-synthetic analogue of paclitaxel, which promotes microtubule assembly and inhibits disassembly, resulting in cell cycle arrest and apoptosis [6]. *In vitro* studies have shown synergistic antitumor activity of docetaxel and gemcitabine combination in several different cell lines, including osteosarcoma cell lines [7] [8].

Recently, several retrospective clinical studies have been conducted to evaluate the efficacy and toxicity of gemcitabine-docetaxel combination therapy for sarcomas, but the results have been controversial. Furthermore, the pathological histologies of patients included in the studies were diverse, including Ewing's sarcoma, malignant fibrous histiocytoma, osteosarcoma, synovial sarcoma, leiomyosarcoma, and undifferentiated sarcoma [9], Therefore, the role of gemcitabine-docetaxel combination in refractory or recurrent high-grade osteosarcoma is not yet well defined.

There is no agreed-upon single second-line or beyond treatment for recurrent metastatic bone sarcomas. Several treatment regimens have been studied, but only marginal activity has been reported. Therefore, this study examined the tolerability and activity of gemcitabine combined with docetaxel (GD) in patients with progressive metastatic bone sarcomas treated in routine practice.

2. Patients and Methods

Setting and type of study: This is a descriptive, monocentric retrospective study of 22 consecutive cases of advanced bone sarcoma managed at CHU Hassan II Fes, MOROCCO, over a 10-year period from 2010 to 2020. A thorough search of the PubMed and Google Scholar databases was carried out to find the bibliographic sources that will enable us to discuss the results found and write up this study.

Study participants: Data were collected from the patient files of the medical oncology department, CHU HASSAN II FES, for all cases included during the study period. For each patient, we collected the following data: age at diagnosis, sex, location, anatomopathological and immunohistochemical characteristics, therapies received and evolutionary aspects of the disease. An evaluation form

was used to collect data from each of the included files.

Inclusion criteria: All patients over 18 years of age, followed for histologically confirmed metastatic bone sarcoma, managed within the department during this period, who had received at least one line of therapy, were progressing, had received the Gemcitabine-docetaxel combination as salvage treatment for refractory or recurrent high-grade osteosarcoma was administered as follows: gemcitabine at 675 mg/m^2 was given on days 1 and 8, and docetaxel at a dose of 75 to 100 mg/m^2 was administered on day 8. The combined use of these drugs was repeated every 3 weeks, and each 3-week treatment schedule was designated as one cycle.

Exclusion criteria: All patients admitted to the department for tumors other than sarcomas, age less than 18 years, having received a protocol other than Gemcitabine docetaxel, incomplete files, patients without histological evidence,

The primary endpoints were objective response, progression-free survival, and toxicity.

3. Results

Twenty-two adult patients with bone sarcomas received gemcitabine 675 mg/m^2 on days 1 and 8 and docetaxel 100 mg/m^2 on day 8 every 3 weeks, as second-line (n = 11) or third-line (n = 11) treatment for metastatic osteosarcomas (n = 11), Ewing's sarcomas (n = 10), or chondrosarcomas (n = 1). [Figure 1]

The median age was 20.5 years (range, 18 - 45). The majority of patients had PS = 1 (n = 19), and 77% of patients were male [Figure 2]. All patients received growth factors as primary prophylaxis for neutropenia. Gemcitabine was administered over 90 minutes. The median number of cycles delivered was 4 (range, 1 - 8).

Overall disease control of 64% (95% CI: 49% - 78%) was observed with 2 CR

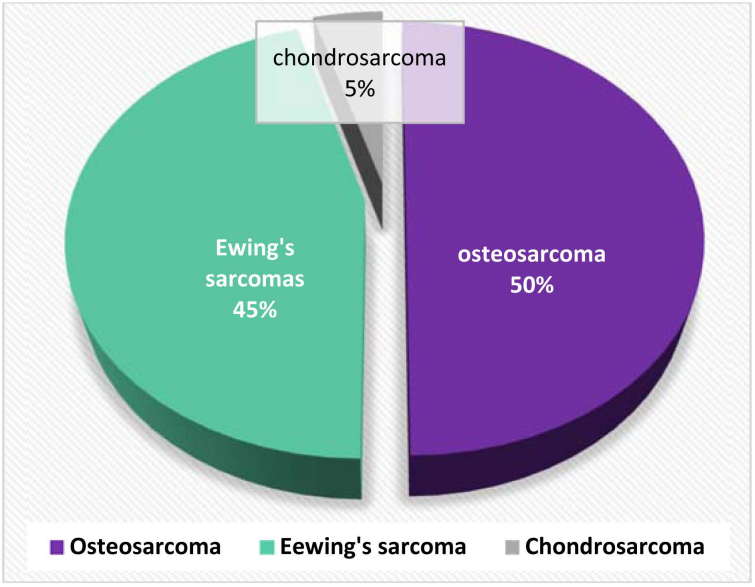

Figure 1. Histological type.

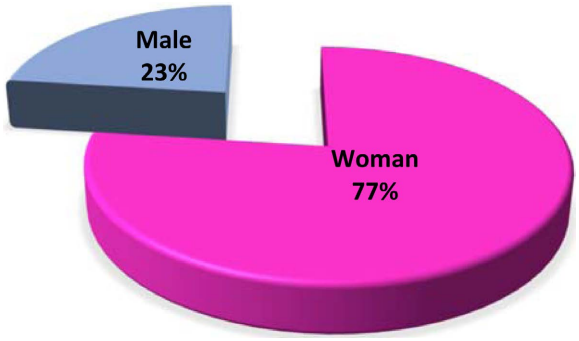

Figure 2. Gender breakdown.

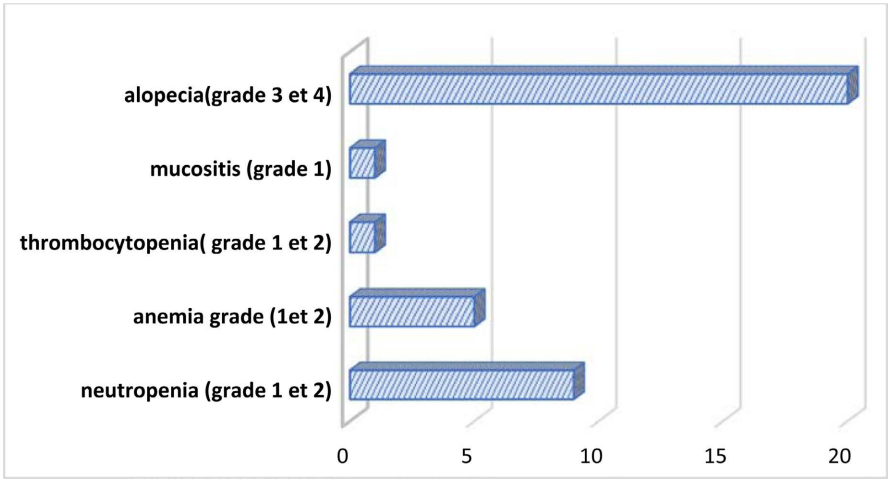

Figure 3. Breakdown by side effects.

(1 osteosarcoma and 1 Ewing sarcoma), 2 PR, and 10 SD. Median PFS was 5 (2 - 12) months and median OS was 8.5 (2 - 24) months. No febrile neutropenia or treatment-related deaths occurred. The main toxicities were neutropenia (grade 1 - 2; n = 9), anemia (grade 1 - 2; n = 5), thrombocytopenia (grade 1 - 2; n = 1), mucositis (grade 1; n = 1), and alopecia (grade 3 - 4; n = 20). [**Figure 3**]

Regarding antiemetic treatment, ondansetron and dexamethasone were used in accordance with ASCO guidelines. Granulocyte colony-stimulating factor was used when patients with febrile neutropenia or grade 4 neutropenia were deemed to require its administration by the attending.

4. Discussion

Patients with recurrent or refractory osteosarcoma have a very poor prognosis, and new strategies are, therefore, necessary to improve the prognosis of this subgroup of patients. In the last decades, several clinical studies have been conducted to evaluate the efficacy of the gemcitabine-docetaxel regimen in recurrent or refractory osteosarcoma. McTiernan and Whelan [10] did a Phase II study, which showed that single-agent docetaxel was inactive in patients with relapsed osteosarcoma, and Mora *et al.,* [11]. reported that the gemcitabine–docetaxel regimen showed antitumor activity against Ewing sarcoma but not osteosarcoma,

while Navid *et al.,* [12] did a retrospective study to find that gemcitabine-docetaxel combination therapy was well tolerated and showed antitumor activity in children and adolescents with recurrent or refractory osteosarcoma, with an overall response rate of 30% and a disease control rate of 40%. Based on these results, the efficacy of the gemcitabine–docetaxel combination regimen in recurrent or refractory osteosarcoma patients was controversial, partially due to the relatively small number of patients included in the trials. As a result, we took this retrospective study to investigate the efficacy and toxicity of the gemcitabine-docetaxel regimen for Maroccan patients with recurrent or refractory high-grade osteosarcoma.

Among the 22 patients evaluated for response in this retrospective study, we found that the tumor control rate was 64%. Two patients achieved partial response, two patients achieved complete response (1 osteosarcoma and 1 Ewing sarcoma), and ten patients achieved stabilization

Similar to what had been observed in other studies; the main adverse events of gemcitabine and docetaxel combination therapy were myelosuppression, but the incidence rates of Grade III and IV myelosuppression in our study were lower than those reported by other studies, which also partially due to the low dose of drugs. The Grade III and IV gastrointestinal disorders and myelosuppression including anemia, leucopenia and thrombocytopenia were tolerable by using 5-hydroxytryptamine-3 receptor blockers (as anti-emetics), adequate hydration and steroids (to relieve gastrointestinal disorders) and supportive treatments such as granulocyte colony-stimulating factor, interleukin-11 and low-dose steroids to help in recovery from myelosuppression.

The current study was limited by its retrospective nature, the small number of patients and possible patient selection bias. In addition, the staging and timing of imaging evaluations were not uniform in our patient population. However, we conducted this study to explore a completely different strategy in a rare sarcoma for which there were no other therapeutic options, though the combination therapy showed marginally effective for relapsed or refractory high-grade osteosarcoma.

Future research may be directed towards other prospective studies, exploring the mechanisms of drug resistance and preclinical studies focusing on optimizing the tumor activity of this combination and possibly adding a biological agent.

5. Conclusion

Our study has certain limitations; the retrospective nature of the study, the small sample size, and the heterogeneity of the evaluated population. However, these results stem from routine practice and demonstrate a good tolerance profile of GD and better efficacy outcomes than those observed in clinical trials

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Nagarajan, R., Weigel, B.J., Thompson, R.C. and Perentesis, J.P. (2003) Osteosarcoma in the First Decade of Life. *Medical and Pediatric Oncology*, **41**, 480-483. https://doi.org/10.1002/mpo.10403

[2] de Pinieux, G., Karanian, M., Le Loarer, F., *et al.* (2021) Incidence nationale des sarcomes et des tumeurs du tissu conjonctif de malignité intermédiaire sur quatre ans à l'aide d'un réseau d'experts en pathologie. https://doi.org/10.1371/journal.pone.0246958

[3] Bramwell, V.H., Burgers, M., Sneath, R., *et al.* (1992) Comparaison de deux régimes de chimiothérapie adjuvante intensive de courte durée dans l'ostéosarcome opérable des membres chez l'enfant et le jeune adulte: La première étude de l'intergroupe européen sur l'ostéosarcome. *Journal of Clinical Oncology*, **10**, 1579-1591.

[4] Fuchs, N., Bielack, S.S., Epler, D., *et al.* (1998) Résultats à long terme du protocole COSS-86 du groupe d'étude coopératif germano-austro-suisse sur l'ostéosarcome de chimiothérapie et de chirurgie multimédicamenteuses intensives pour l'ostéosarcome des membres. *Annals of Oncology*, **9**, 893-899.

[5] Gandhi, V., Legha, J., Chen, F., Hertel, L.W. and Plunkett, W. (1996) Excision des résidus de 20, 20-difluorodésoxycytidine (gemcitabine) monophosphate de l'AND. *American Association for Cancer Research*, **56**, 4453-4459.

[6] Ringel, I. and Horwitz, S.B. (1991) Études avec RP 56976 (taxotere): Un analogue semi-synthétique du taxol. *JNCI*: *Journal of the National Cancer Institute*, **83**, 288-291. https://doi.org/10.1093/jnci/83.4.288

[7] Leu, K.M., Ostruszka, L.J., Shewach, D., *et al.* (2004) Preuves en laboratoire et cliniques de la cytotoxicité synergique d'un traitement séquentiel par gemcitabine suivi de docétaxel dans le traitement du sarcome. *Journal of Clinical Oncology*, **22**, 1706-1712.

[8] Ricotti, L., Tesei, A., De Paola, F., *et al.* (2003) Interaction *in vitro* dépendante du calendrier entre le docétaxel et la gemcitabine dans les lignées cellulaires de cancer gastrique humain. *Clinical Cancer Research*, **9**, 900-905.

[9] Ebeling, P., Eisele, L., Schuett, P., *et al.* (2008) Le docétaxel et la gemcitabine dans le traitement du sarcome des tissus mous: Une expérience monocentrique. *Onkologie*, **31**, 11-16.

[10] McTiernan, A. and Whelan, J.S. (2004) Une étude de phase II du docétaxel pour le traitement de l'ostéosarcome récidivant. *Sarcoma*, **8**, 71-76. https://doi.org/10.1155/2004/762736

[11] Mora, J., Cruz, C.O., Parareda, A. and de Torres, C. (2009) Traitement des sarcomes pédiatriques récidivants/réfractaires avec gemcitabine et docétaxel. *Journal of Pediatric Hematology/Oncology*, **31**, 723-729. https://doi.org/10.1097/MPH.0b013e3181b2598c

[12] Navid, F., Willert, J.R., McCarville, M.B., *et al.* (2008) Association de la gemcitabine et du docétaxel dans le traitement des enfants et des jeunes adultes atteints de sarcome osseux réfractaire. *Cancer*, **113**, 419-425.