Bone targeting agents, but not radiation therapy, improves survival in patients with bone metastases from advanced urothelial carcinoma receiving pembrolizumab: results from the ARON-2 study

Bone targeting agents, but not radiation therapy, improves survival in patients with bone metastases from advanced Urothelial Carcinoma receiving Pembrolizumab: results from the ARON-2 study

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Abstract

Background: The ARON-2 study (NCT05290038) aimed to assess the real-world efficacy of pembrolizumab in patients recurred or progressed after platinum-based chemotherapy. This retrospective analysis reports the outcomes of urothelial carcinoma (UC) patients with bone metastases (BM).

Materials and Methods: Medical records of patients with documented metastatic UC treated by pembrolizumab as second-line therapy were reviewed from60 institutions in 20 countries. Patients were assessed for Overall Response Rate (ORR), Progression-Free Survival (PFS), and Overall Survival (OS). Univariate and multivariate analyses were used to explore the association of variables of interest with OS and PFS.

Results: 881 patients were included; of them, 263 (30%) presented BM. Median follow-up time was 22.7 months. Patients with BM showed both shorter median OS (5.9 months vs 13.1 months, $p<0.001$) and PFS (3.5 months, vs 7.3 months, $p<0.001$) compared to patients without BM. Patients who received bone targeted agents (BTAs) showed a significantly longer median OS (8.5 months vs 4.6 months, $p=0.003$) and PFS (6.1 months vs 3.2 months, $p=0.003$), while no survival benefits were observed among patients who received radiation therapy for BM during pembrolizumab treatment compared to those who did not. In multivariate analysis, performance status, concomitant liver metastases, and the lack of use of BTAs were significantly associated with worse OS and PFS.

Conclusions: Bone involvement in UC patients treated with pembrolizumab predicts inferior survival. Poor performance status and liver metastases may further worsen outcomes, while the use of BTAs is associated with improved outcomes.

Keywords:ARON-2 study; Bone metastases; Immunotherapy; NCT05290038; Pembrolizumab; Real-world data; Survival; Tumor Response; Urothelial Cancer.

1. Introduction

Bone is the third most frequent site of metastasis from solid tumors [1]. Bone metastases (BM) are infrequently curable and are associated with poor prognosis [2]. The tendency to occur in multiple sites via hematogenous spread, the difficulties in detecting BM by conventional radiological examinations and the impossibility of obtaining sufficient negative margins are just some of the reasons that explain why carrying out effective and radical surgical treatment of BM is an unrealistic issue. The presence of BM is additionally linked to an increased risk of experiencing skeletal-related events (SREs), such as pain, fractures, spinal cord compression, orthopedic surgery, and disruptions in calcium metabolism. Consequently, this negatively impacts the quality of life for affected patients.

The emergence of immunotherapy has transformed patients' expectations, as they now have the potential for long-lasting tumor responses and, in a selected proportion of cases, the possibility of achieving a cure. Bone metastatic involvement breaks the balance between osteoblasts and osteoclasts and leads to changes in bone unique immune microenvironment. Indeed, bone is characterized by a marked immunosuppressive micro environment, mainly due to the presence in the bone niches of a large number of immature and inhibitory immune cells that hamper the activity of cytotoxic CD8+ T cells [3,4], including myeloid-derived suppressor cells (MDSCs) and M2-phenotype tumor-associated macrophages [5].

In patients with advanced urothelial carcinoma (UC), which accounts for 90% of all bladder cancers and 7% upper tract cancers [6], immunotherapy has become a cornerstone of current therapeutic paradigm, being used as maintenance therapy in patients who are progression-free to platinum-based chemotherapy [7], as first-line therapy for platinum-unfit patients [8,9] and in the second-line setting after progression to platinum-based chemotherapy [10,11,12].

It has been estimated that synchronous and metachronous BM are present in 5% and 30-40% of UC patients, respectively [13]. Approximately 40% of UC patients with BM present as the only

metastatic site with no other metastatic location and in the 33% of all cases BM are present as single lesions [14].

The ARON-2 study (NCT05290038) aimed to assess the real-world efficacy of pembrolizumab in patients who recurred or progressed after platinum-based chemotherapy. In this sub-analysis, we reported the outcome of UC patients with BM.

2. Patients and Methods

2.1 Study population

Patients aged ≥18 years with a cytological and/or histological confirmed diagnosis of advanced UC progressing(cohort A) or recurring(cohort B) after platinum-based therapy and treated with pembrolizumab between January 1st2016 to April 1st 2023 were included in the ARON-2 study.

The ARON-2 study was conducted among 60 Institutions from 20 countries. The list of variables collected in the study dataset included age, gender, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), tumor histology, type and time of surgery, time and setting of prior chemotherapy, sites of metastases, and response to immunotherapy.Patients with insufficient data on tumor response to therapy were not included in the ARON-2 study.

The follow-up consisted of physical examinations, laboratory analyses, and Computed Tomography (CT) of the chest and the abdomen or Magnetic Resonance Imaging (MRI) scans of the abdomen at baseline and every 2–4 months thereafter, according to physicians' practice, or when PD was clinically suspected.

2.2 Study endpoints

Disease response to treatment was determined in each center, referring to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)[15]. Overall Response Rate (ORR) was calculated by the sum of CR and PR.

Overall Survival (OS) was calculated from the time of first pembrolizumab administration until death. Progression-Free Survival (PFS) was calculated as the time from the first pembrolizumab administration to documented disease progression or death from any cause, whichever occurred first. Patients without disease progression or death or lost at follow-up at the time of the analysis were censored at the last follow-up visit.

2.3 Statistical Analysis

The Kaplan-Meier method with Rothman's 95% confidence intervals (CI) was used to estimate survival curves of OS and PFS. Comparisons between survival curves were performed by using the log-rank test. Cox proportional hazards models were adopted to compare the multivariable effects on patients' survival and to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). The level of significance was set to 0.05,and all *p* values were two-sided.

MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium) was used for the statistical analyses. The study was approved by the ethical committee of the Marche Region.

3. Results

3.1 Baseline characteristics

Eight hundred and eighty-one patients were included in our analysis. BM at diagnosis of metastatic disease were identified in 263 patients (30%), whose 67 patients (8%) presented BM without concomitant metastatic sites; 97 patients (37%) presented with BM at the time of UC diagnosis. The median follow-up time was 22.7 months (95%CI 20.9−76.0). Male predominance was observed (*n*=652 patients; 74%). Patients were of a median age of 71years (range 26−95). ECOG-PS was ≥2 in 165 patients (19%). Upper urinary tract carcinomas accounted for the 26% of all cases. Tumor histology was pure UC in 715 patients (81%).Variant histologies included: squamous in 83 (9%), poorly differentiated in 20 (2%), plasmacytoid in 14 (2%), neuroendocrine in 9 (1%), sarcomatoid in 8 (1%), clear cell in 8 (1%), glandular in 7 (1%), micropapillary in 6 (1%), nested in 5 (<1%),

microcystic in 2 (<1%), lymphoepithelioma-like in 2 (<1%), and giant cell in 2 (<1%).

In our analysis, 571 patients (65%) received pembrolizumab following progression to first-line platinum-based chemotherapy (cohort A) and 310 (35%) after recurring within 12 months since the completion of adjuvant or neoadjuvant chemotherapy (cohort B).

Four hundred and eighty-eight (55%) had died at time of the analysis. Treatment with pembrolizumab was ongoing in 321 patients (37%). Of the 560 patients who progressed following pembrolizumab, 173 (31%) received subsequent systemic therapies. Patients' baseline characteristics are summarized in Table1.

3.2 Survival analysis

In the overall study population, the median OS and PFS were 10.3 months (95%CI 8.9−11.8) and 6.0 months (95%CI 5.1−6.6), respectively. Patients with BM showed both shorter median OS (5.9 months, 95%CI 4.7−6.7, vs 13.1 months, 95%CI 11.3−15.3, p<0.001, Figure 1) and PFS (3.5 months, 95%CI 6.4−8.6, vs 7.3 months, 95%CI 3.2−4.2, p<0.001, Figure 1).

In cohort A, the median OS and PFS were 8.6 months (95%CI 7.3−10.2) and 5.4 months (95%CI 4.3−6.3), respectively. Patients without BM showed statistically longer median OS (11.8 months, 95%CI 9.6−14.6, vs 5.2 months, 95%CI 4.1−6.3, p<0.001, Figure S1) and PFS (6.6 months, 95%CI 5.1−7.9, vs 3.5 months, 95%CI 3.0−4.4, p<0.001, Figure S1).

In cohort B, the median OS and PFS were 17.0 months (95%CI 11.7−30.0) and 9.0 months (95%CI 5.4−16.0), respectively. Patients without BM showed statistically longer median OS (17.0 months, 95%CI 11.7−30.0, vs 9.0 months, 95%CI 5.4−16.0, p=0.015, Figure S1) and PFS (10.0 months, 95%CI 6.8−13.7, vs 3.7 months, 95%CI 3.0−5.3, p<0.001, Figure S1).

3.3 Survival analysis in patients with BM

In patients with BM, no statistically significant differences were found between males and females (5.9 months, 95%CI 4.8−7.0 vs 5.7 months, 95%CI 3.2−6.8, p=0.369) as well as between patients

aged<65 years vs ≥65years (6.6 months, 95%CI 4.1−9.0 vs 5.8 months, 95%CI 4.6−6.7, *p*=0.911) or between current or former smokers and no-smokers (5.8 months, 95%CI 4.6−7.0, vs 5.9 months, 95%CI 3.7−6.8, *p*=0.195).

Patients with BM stratified by ECOG-PS (0-1 vs≥2) showed a median OS of 6.7months (95%CI 5.8−8.6) vs3.6 months (95%CI 2.5−4.6, *p*<0.001, Figure 2).

Patients with pure UC histology showed a median OS of 6.0 months (95%CI 4.8−6.8), while in patients with mixed variant histology was 4.8 months (95%CI 3.9−16.0, *p*=0.908). Interestingly, no statistically significant differences were found between patients with tumors of the upper tract (5.2 months, 95%CI 4.1−8.5) vs lower tract (5.9 months, 95%CI 4.6−6.7, *p*=0.756).

Synchronous metastatic disease was associated with shorter median OS (4.3 months, 95%CI 3.2−5.9, vs 6.7 months, 95%CI 5.5−9.0, *p*=0.018, Figure 2). By stratifying patients according to concomitant sites of metastasis, patients with exclusively BM reported a median OS of 7.7 months (95%CI 5.0−11.7). Statistically significant differences were observed between patients with or without liver metastases (3.9 months, 95%CI 2.9−5.8, vs 6.3 months, 95%CI 5.4−7.2, *p*=0.012, Figure 2), while no significant differences were found between patients with or without metastases to the lungs (5.8 months, 95%CI 3.6−6.8, vs 5.9 months, 95%CI 4.6−7.0, *p*=0.481)or to the lymph nodes (5.2 months, 95%CI 4.1−6.6, vs 6.7 months, 95%CI 5.0−9.0, *p*=0.289).

No statistically significant differences were found between patients treated or not by radiation therapy during pembrolizumab treatment (6.0 months, 95%CI 4.3−6.8, vs 5.7 months, 95%CI 4.6−8.0, *p*=0.783), while the use of bone-targeted agents (BTAs) was associated with a significantly longer median OS (8.5 months, 95%CI 6.3−14.1 vs 4.6 months, 95%CI 3.8−5.9, *p*=0.003, Figure 3).

ECOG-PS≥2 was associated with shorter median PFS compared to ECOG PS 0-1(2.8 months, 95%CI 1.9−3.4, vs 4.0 months, 95%CI 3.3−6.0, *p*<0.001, Figure 4).No statistically significant differences were observed between males vs females (3.5 months, 95%CI 3.0−4.2 vs 3.6 months, 95%CI 2.3−6.4, *p*=0.589), patients aged <65years vs ≥65years (3.5 months, 95%CI 2.8−5.3 vs 3.5

months, 95%CI 3.2−4.5, *p*=0.547), smokers vs non-smokers (3.7 months, 95%CI 3.2−5.2, vs 3.2 months, 95%CI 2.6−4.4, *p*=0.205), pure vs mixed UC histology (3.7 months, 95%CI 3.2−4.5, vs 3.2 months, 95%CI 2.0−4.8, *p*=0.803), upper vs lower urinary tract (3.8 months, 95%CI 2.6−5.3, vs 3.5 months, 95%CI 3.1−4.4, *p*=0.793), synchronous vs metachronous metastatic disease (3.1 months, 95%CI 2.3−3.7, vs 3.8 months, 95%CI 3.3−5.2, *p*=0.217). By stratifying patients according to concomitant sites of metastasis, patients with exclusively BM showed a median PFS of 3.8 months (95%CI 3.3−6.7). Patients with concomitant liver metastases showed a significantly shorter median PFS compared to those without liver metastases, (2.7 months, 95%CI 2.1−3.6, vs 3.8 months, 95%CI 3.2−4.8, *p*=0.020, Figure 4).

Similarly to OS, the use of BTAs was associated with a significantly longer median PFS (6.1 months, 95%CI 4.1−10.8 vs 3.2 months, 95%CI 2.8−3.6, *p*=0.003, Figure 3), while no statistically significant differences were found between patients treated or not by radiation therapy during pembrolizumab treatment (3.5 months, 95%CI 3.1−5.3, vs 3.5 months, 95%CI 2.9−4.2, *p*=0.879).

3.4 Response to therapy

In the overall study population, 79 patients (9%) experienced CR, 192 (22%) PR, 214 (24%) SD and 396 (45%) PD, with an ORR of 31%. In patients with BM, we reported CR=4%, PR=17%, SD=22% and PD=57%,with an ORR of 21%.

The median OS was significantly different according to the best response to pembrolizumab, being NR (95%CI NR−NR), NR (95%CI NR−NR), 8.6 months (95%CI6.2−16.8) and 3.3 months (95%CI 3.1−3.9) in patients with CR, PR, SD, and PD, respectively (*p*<0.001, Figure 5). In the same view, in patients with CR, PR, SD, and PD, median PFS was NR (95%CI NR−NR), 18.8 months (95%CI 12.8−18.8), 7.5 months (95%CI 5.8−14.8) and 2.0 months (95%CI 1.8−14.1), respectively (*p*<0.001, Figure 5).

3.5 Role of prognostic factors in patients with BM

At univariate analysis, ECOG-PS, synchronous metastatic disease, liver metastases and the use of bone targeted agents were significant predictors of OS (Table 2). As for PFS, the univariate analysis showed a prognostic role of ECOG-PS, liver metastases and the use of bone targeted agents. At multivariate analysis, ECOG-PS, liver metastases and the use of bone targeted agents proved to be significantly associated with both OS and PFS(Table 2).

4.Discussion

The role of immune checkpoint inhibitors for the treatment of bone metastases from different malignancies has been elusive for years while, more recently, evidence has increased supporting their activity and efficacy. Our study confirms the negative prognostic role of BM in UC patients receiving pembrolizumab and confirms that pembrolizumab is effective in the real-world context, showing an ORR of 21%, although the evaluation of bone response to anticancer agents still remains challenging. Furthermore, our data support the importance of the extent of best tumor response to pembrolizumab reported according to RECIST 1.1, which indeed was associated with both OS and PFS (Figure 5).

In the phase III trial led by Bellmunt*et al.* [10], the HRs for pembrolizumab vs chemotherapy in patients with or without BM were 0.85 and 0.67, respectively, with a ratio of 1.27, which appears as bad as the HR=1.45 associated with liver metastases in our analysis. Similarly, our data confirm the prognostic role of ECOG-PS in UC patients treated by pembrolizumab, with a HR=1.65, which is comparable with the ratio of 0.74/0.43=1.72 reported the phase III trial [10].

The management of patients with BM often requires a multidisciplinary approach that involves specialists in oncology, radiotherapy, endocrinology, palliative care, neurosurgery,and orthopedics to avoid serious SREs causing impairment in quality of life and survival. In our study,radiation therapy during pembrolizumab treatment was not associated with improved OS. Of note, to the best of our knowledge, our study for the first time showed in a real-world context that the use of bone targeted agents was associated with a significantly advantage in terms of both OS and PFS in UC

patients treated by pembrolizumab and was confirmed as an independent prognostic factor at multivariate analysis for both OS and PFS. The evidence that only 31% of patients with BM included in our analysis received BTAs strongly emphasize the necessity to carefully evaluate patients' bone health status and the risk of SREs in our daily clinical practice. In addition, interestingly, in our analysis there was no statistical difference among patients with BM originating from upper versus lower tract tumors, even though upper tract primary appear to be less responsive to immunotherapy, probably correlated to a higher presence of FGFR3 alterations.

Our study presents several limitations, mainly due to its retrospective nature.Furthermore, beyond the fact that it is often difficult to evaluate the response of bone metastases, a centralized review of radiological imaging was not performed. Moreover, we had no available data on the concomitant medicationsor comorbidities that could affect the efficacy of pembrolizumab and on the role of bone targeted agents in preventing bone pain and fractures and spinal cord or nerve compressions. And finally, we do not have data on the possible incidence of bone targeting agents-related adverse events (e.g. osteonecrosis of the jaw, hypocalcemia, acute kidney injury) from our case series. As a consequence, our results should be interpreted with caution and are in need of a larger prospective validation, although the efficacy of bone targeting agents in this specific setting, in our opinion, looks enough.

5. Conclusions

Our data clearly suggest thatpembrolizumab is effective in UC patients with BM in the real-world context, proving able to improve both PFS and OS, thus supporting the use of concomitant bone targeted agents in this setting.

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Author contributions

Conceptualization: MS, FM, SS, DS; Data curation: MS, FM, SS, DS; Formal analysis: MS, FM, SS, DS; Investigation: MS, FM, SS, DS; Methodology: MS, FM, SS, DS; Project administration: MS, FM, SS, DS; Resources: all authors; Software: MS, FM, SS, DS; Supervision: all authors; Validation: all authors; Visualization: all authors; Roles/Writing - original draft: MS, FM, SS, DS; Writing - review & editing: all authors.

Funding

This research received no external funding.

Declarations

Conflict of interest

Enrique Grande has received honoraria for speaker engagements, advisory roles or funding of continuous medical education from Adacap, AMGEN, Angelini, Astellas, Astra Zeneca, Bayer, Blueprint, Bristol Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA-Pharma, IPSEN, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, and Thermo Fisher Scientific. EG has received research grants from Pfizer, Astra Zeneca, Astellas, and Lexicon Pharmaceuticals

Fernando Sabino Marques Monteiro has received research support from Janssen, Merck Sharp Dome and honoraria from Janssen, Ipsen, Bristol Myers Squibb and Merck Sharp Dome.

R. Kanesvaran has received fees for speaker bureau and advisory board activities from the following companies; Pfizer, MSD, BMS, Eisai, Ipsen, Johnson and Johnson, Merck, Amgen, Astellas and Bayer.

Camillo Porta has received honoraria from Angelini Pharma, AstraZeneca, BMS, Eisai, General Electric, Ipsen and MSD and acted as a Protocol Steering Committee Member for BMS, Eisai and MSD.

Joaquim Bellmuntreports institutional and personal, paid and unpaid support for research, advisory boards, consultancy, and honoraria (all outside this work) from: AstraZeneca, Bristol Myers-Squibb, EMD Serono, Merck, Pfizer, Roche, Sanofi/Aventis, Up-To-Date, CME events (Peerview, OncLive,), outside the submitted work. No speaker's bureau.

Matteo Santoni has received research support and honoraria from Janssen, Bristol Myers Squibb, Ipsen, MSD, Astellas and Bayer, all unrelated to the present paper.

The other authors declare to have no conflicts of interest.

No writing assistance was utilized in the production of this manuscript.

Acknowledgments

We want to sincerely thank the ARON Working Group for the support received in this analysis and for the continuous efforts in the creation of a global network aimed to share our clinical experiences in the use of new drugs for patients with genitourinary tumors.

Ethics approval

The study was approved by the ethical committee of the Marche Region.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Table Legends

Table 1. Patients' characteristics. Statistically significant values were reported in bold.

Table 2. Univariate and Multivariate analyses in UC patients with BM treated by pembrolizumab. Statistically significant values were reported in bold.

Figure Legends

Figure 1. Median Overall Survival and Progression-Free Survival in the overall ARON-2 study population stratified by the presence of BM.

Figure 2. Median Overall Survival in patients treated with pembrolizumab stratified by ECOG Performance Status, synchronous or metachronous metastatic disease and liver metastases.

Figure 3. Median Overall Survival and Progression-Free Survival in patients treated with pembrolizumab and concomitant bone targeted agents.

Figure 4. Progression-Free Survival in patients treated with pembrolizumab stratified by ECOG Performance Status and liver metastases.

Figure 5. Overall Survival and Progression-Free Survival in patients stratified by type of response to pembrolizumab according to RECIST. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.