Chemotherapy in solitary bone plasmacytoma to prevent evolution to multiple myeloma

Solitary bone plasmacytoma (SBP) is a rare malignancy plasma cell disorder characterized by a proliferation of monoclonal (M) plasma cells localized within a single biopsy-proven lesion without evidence of overt multiple myeloma (MM).[1] Standard of care relies on radiotherapy with a total dose of 40 to 50 grays.[2] Surgery is sometimes combined, mainly in case of neurological compression. Although local disease control is frequent (about 90%), approximately 50% of patients will develop MM within 5 years of diagnosis.[3,4] Some factors have been associated with survival outcomes in several retrospective studies, but these findings are sometimes divergent.[3,5-9] Particularly, the impact of adjuvant chemotherapy has been highly debated, with controversial literature.[3,5,10-13] However, the data mainly rely on small retrospective case series, conducted before the era of novel chemotherapeutic agents. The aim of this study was to describe the characteristics and outcome of patients treated for SBP, to identify factors associated with progression to MM and death, and to assess whether adjuvant chemotherapy improves outcome.

Between 1992 and 2020, patients with histologically confirmed diagnosis of SBP according to the International Myeloma Working Group (IMWG) criteria,[1] identified through a systematic search in the electronic database, were included. All Assistance Publique-Hôpitaux de Paris patients are informed that their clinical data can be used for research and give their consent for the use of their data unless they provide an opposition to it. None of the patients in this study objected to the use of their data. Therapeutic management (including radiotherapy, chemotherapy) was recorded and response to treatment was assessed after radiotherapy and then after chemotherapy. Treatment response was assessed retrospectively according to the IMWG criteria,[14] (adapted to clinical practice, for patients with a detectable M-component on serum or urine immunofixation [IF]) and according to radiological response only for non-secretory SBP. Briefly, complete response (CR) for secretory SBP was defined as the disappearance of the M-component and no evidence of disease progression on imaging assessment when performed. For non-secretory SBP, CR was defined by the absence of an active lesion assessed by magnetic resonance imaging (MRI) or positron emission tomography/computed tomography (PET/CT). Progressive disease (PD) was defined by a significant increase in the size of the M-component or significant imaging progression. Otherwise, patients were considered partial responders (PR). Progression to MM was considered when bone marrow plasmacytosis (BMPC) was ≥10% or when BMPC reached <10% with multiple bone lesions. MM-free survival (MMFS) and overall survival (OS) were determined from the start of radiotherapy. Survival curves were computed using the Kaplan Meier method and compared with the log-rank-test. Cox proportional hazards models were used to identify possible independent predictive factors of MMFS and OS for SBP. All parameters associated with the outcome in the univariate analysis (P<0.2), and the variable of particular interest for this study (chemotherapy), were entered into a multivariate model. All analyses were performed with R software (version 1.2.1578 https://cran.r-project.org/). All P values were two-sided and P<0.05 was considered statistically significant.

Seventy-seven patients with a diagnosis of SBP were included (Table 1). Overall, 21 (27.3%) patients had two bone marrow examinations at two different locations. Cytogenetics, available in 29 (37.7%) patients, detected a t(4;14) translocation in one patient (3.4%). Immunophenotyping of plasma cells, available in eight (10.4%) patients, revealed the presence of monoclonal plasma cells in the bone marrow in one case (12.5%). All patients received radiotherapy at a median dose of 45 grays (range, 30-55). The decision to combine chemotherapy and radiotherapy was left to the discretion of each referring hematologist. Chemotherapy was prescribed in 32 of 77 (41.6%) patients, concomitant to radiotherapy in eight of 32 (25%) patients or adjuvant in 24 of 32 (75%) patients. In these 24 patients, chemotherapy was initiated at a median of 4.3 months (range, 1.6-12.3) after the start of radiotherapy. Chemotherapy included mainly immunomodulatory drug combinations in 28 of 32 (87.5%) (Table 1).

The median follow-up duration was 87.1 months (range, 1.6-306.8). MM occurred in 45 (58.4%) patients. Only one (1.3%) local recurrence of plasmacytoma occurred. Thirteen (16.9%) patients died: ten (76.9%) from MM, two (15.4%) from solid cancer and one (7.7%) of unknown cause. Five-year MMFS and OS were 47.9% and 86.8%, respectively (*Online Supplementary Figure S1*).

In order to study the impact of adjuvant chemotherapy, the eight (10.4%) patients treated with concomitant chemotherapy were excluded from this analysis, since response to radiotherapy alone was not assessable and the indication of concomitant chemotherapy might reflect a more aggressive disease. Compared to patients not treated with chemotherapy, patients treated with adjuvant chemotherapy had more frequent detectable M-component at diagnosis (95.8% *vs*. 73.3%, respectively; P=0.03; *Online Supplementary Table S1*). Absence of CR

Table 1. Characteristics of 77 patients with solitary bone plasmacytoma.

	Overall population N=77
Baseline demographic, clinical and biological characteristics	
Median age in years (range)	59.0 (27.0-89.0)
Male sex, N (%)	47 (61.0)
Site of plasmacytoma, N (%)	
Spine	42 (54.5)
Limb	13 (16.9)
Pelvis	8 (10.4)
Rib	4 (5.2)
Sternum	2 (2.6)
Skull	8 (10.4)
Symptoms at diagnosis (76 evaluated), N (%)	
Local pain	66 (86.8)
Local swelling	3 (3.9)
Incidental discovery	7 (9.2)
Neurological compression syndrome	12 (15.8)
Positive IF (serum and/or urine), N (%)	62 (80.5)
Serum, N/N (%)	57/77 (74.0)
IgG κ	33/57 (57.9)
IgG λ	18/57 (31.6)
IgA λ	4/57 (7.0)
Light chain λ	1/57 (1.8)
Light chain κ	1/57 (1.8)
Urine (60 evaluated), N (%)	12 (20.0)
Median serum M-spike, g/L (range) (74 evaluated)	4.3 (0-36.0)
Median FLC ratio, (range) (51 evaluated)	1.5 (0-118.0)
Abnormal FLC ratio (<0.26 or >1.65) (51 evaluated), N (%)	30 (58.8)
Bone marrow involvement	
Median BMPC, % (range)	2.0 (0-8.0)
BMPC ≥5%, N (%)	12 (15.6)
Aberrant and/or immature PC on BM aspiration (72 evaluated), N (%)	25 (34.7)
Clonal PC by immunophenotyping on BM aspiration (8 evaluated), N (%)	1 (12.5)
Clonal PC infiltration by immunohistochemistry on BM biopsy (11 evaluated)	0
Imaging procedure performed to exclude other location	
X ray, N (%)	40 (51.9)
WB-CT, N (%)	5 (6.5)
All spine and pelvis MRI or WB-CT, N (%)	50 (64.9)
^{18}F-FDG PET/CT, N (%)	63 (81.8)
Therapeutic management	
Median radiotherapy dose, grays (range) (72 evaluated)	45.0 (30.0-55.0)
Radiotherapy alone, N (%)	45 (58.4)
Radiotherapy + chemotherapy, N/N (%)	32/77 (41.6)
Adjuvant chemotherapy	24/32 (75.0)
Concomitant chemotherapy	8/32 (25.0)
Regimen (32 evaluated), N (%)	
Edx-Dex	1 (3.1)
TD	16 (50.0)
RD	3 (9.4)
VD	2 (6.3)
MPT	1 (3.1)
VTD	3 (9.4)
VRD	4 (12.5)
VCD	1 (3.1)
VRD auto-SCT VRD	1 (3.1)
Median duration of chemotherapy in months, N (range)	7 (2.5-21.3)
Surgery, N (%)	22 (28.6)

auto-SCT: auto-stem cell transplantation; BM: bone marrow; Edx-Dex : cyclophosphamide + dexamethasone; FLC: serum free light chain; IF: immunofixation; Ig: immunoglobulin; M: monoclonal; MPT: melphalan + prednisone + thalidomide; PC: plasma cell; RD: lenalidomide + dexamethasone; TD: thalidomide + dexamethasone; VD: bortezomib + dexamethasone; VCD: bortezomib + cyclophosphamide + dexamethasone; VRD: lenalidomide + bortezomib + dexamethasone; VTD: thalidomide + bortezomib + dexamethasone; WB: whole body; X-ray: whole skeleton plain radiography; CT: computed tomography, PET: positron emssion tomography; MRI: magnetic resonance imaging.

after radiotherapy was the main reason for prescribing chemotherapy, as none of the 24 patients treated with adjuvant chemotherapy were meeting CR criteria after radiotherapy, compared to 12 of 45 (26.7%) patients treated with radiotherapy alone (*P*=0.002; *Online Supplementary Table S1*). Nevertheless, 5-year MMFS was 62.9% for patients treated with adjuvant chemotherapy compared to 41.7% for patients treated with radiotherapy alone (*P*=0.2) (Figure 1A). In multivariate analysis, adjuvant chemotherapy was associated with a reduced risk of progression to MM (hazard ratio [HR]=0.30; 95% confidence interval [CI]: 0.14-0.64), as well as achieving CR after radiotherapy (HR=0.16; 95% CI: 0.05-0.56), while BMPC ≥5% at diagnosis was associated with an increased risk of developing MM (HR=2.81; 95% CI: 1.20-6.57) (Table 2).

In sensitivity analyses performed in the entire study population, 5-year MMFS was significantly higher in patients achieving CR whatever treatment was (radiotherapy alone or combined with chemotherapy) (73.3% *vs.* 32.9%; *P*=0.0004). Five-year MMFS was 56% in patients treated with radiotherapy plus chemotherapy (adjuvant or concomitant) compared to 41.7% in patients treated with radiotherapy alone (*P*=0.2) (Figure 1B). In multivariate analysis, achieving CR compared to PR or PD was associated with a lower risk of progression to MM (HR=0.25; 95% CI: 0.11-0.59; *Online Supplementary Table S2*). In this model, chemotherapy (adjuvant or concomitant) and BMPC ≥5% were no longer associated with the risk of MM but were close to significance (HR=0.50; 95% CI: 0.25-1.00; and HR=2.40; 95% CI: 1.00-5.74, respectively; *Online Supplementary Table S2*).

All deaths were observed in patients with detectable M-component at baseline (*P*=0.04). Age was associated with the risk of death (HR=1.06; 95% CI: 1.00-1.11) whereas chemotherapy was not (*P*=0.45). Achieving CR after complete treatment was associated with improved survival (HR=0.22; 95% CI: 0.05-0.99) (*Online Supplementary Table S2*).

In this retrospective study of 77 patients with SBP, we confirmed that about half of the patients develop MM within 5 years. Also, we found that chemotherapy, although frequently prescribed in patients with poorer prognosis, was associated with a lower risk of evolution to MM. Furthermore, we observed that response to the first line of treatment (radiotherapy +/- chemotherapy) was the main factor associated with the risk of MM and death. In the present study, the 5-year risk of developing MM was 52.1%, which is similar to previous data in the literature.[3,4] However, this risk may differ depending on prognosis factors. Indeed, we observed that patients in CR after treatment had better outcomes in terms of MMFS and OS. Comparable results have been described in MM.[15] In SBP, persistence of M-protein or abnormal serum free-light chain ratio after treatment was associated with an increased risk of MM in several publications.[7,9] Thus, it appears that the treatment goal should be to obtain a CR. However, response after radiotherapy alone is often incomplete leaving an important place for adjuvant chemotherapy in the therapeutic management of SBP. Many retrospective series did not find benefit of chemotherapy,[3,5,13] but these series were mainly performed before the era of novel agents. Nevertheless, a series of 46 patients with solitary plasmacytoma showed improved outcomes for the concomitant lenalidomide-dexamethasone group compared to the radiation therapy-alone group (5-year disease-free-survival, 81.7% *vs.* 48.4%; *P*=0.047).[10] Also, ad-

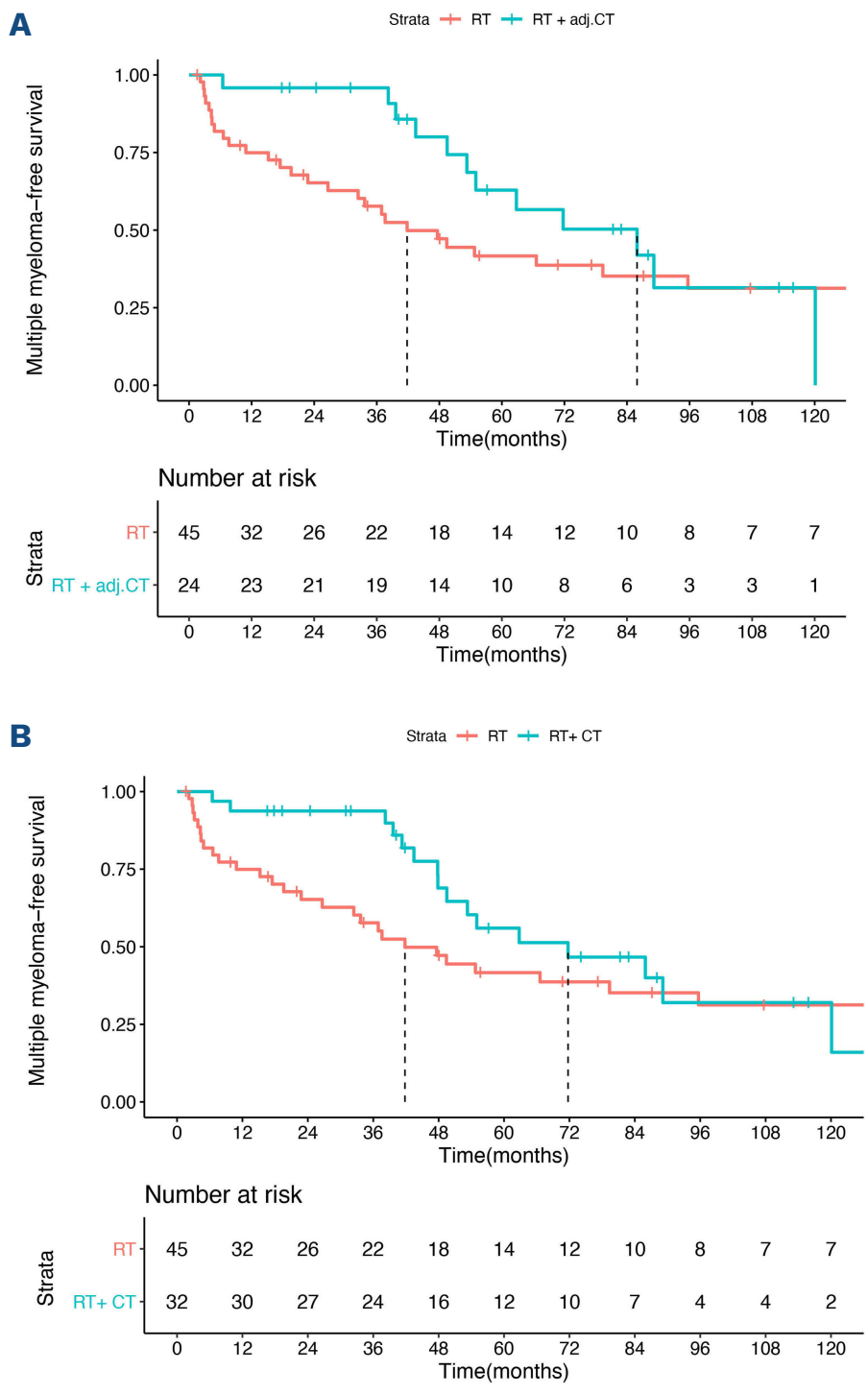

Figure 1. Comparison of the impact of treatment regimen on survival of multiple myeloma-free patients. Multiple myeloma-free survival in patients treated with radiotherapy alone (RT) compared with (A) patients treated with radiotherapy and adjuvant chemotherapy (RT + adj.CT) and (B) patients treated with radiotherapy and chemotherapy (adjuvant or concomitant) (RT + CT).

Table 2. Factors associated with progression to multiple myeloma: univariate and multivariate analysis in 69 patients with solitary bone plasmacytoma treated with radiotherapy alone or combined with adjuvant chemotherapy.

Parameter	N	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Baseline characteristics					
Age in years	69	1.01 (0.98-1.03)	0.61	-	-
Male sex	69	1.13 (0.60-2.13)	0.70	-	-
Spine location	69	1.08 (0.58-2.01)	0.82	-	-
Positive IF (serum and/or urine)	67	1.58 (0.68-3.68)	0.29	-	-
Serum M-spike size, g/L	69	1.03 (0.99-1.07)	0.13	0.99 (0.95-1.04)	0.83
BMPC, %	69	1.00 (0.86-1.17)	0.96	-	-
BMPC ≥5%	64	1.78 (0.87-3.65)	0.11	2.81 (1.20-6.57)	0.02
Aberrant and/or immature PC on BM aspiration	69	0.96 (0.50-1.85)	0.91	-	-
Modern imaging for diagnosis (PET/CT or WB-MRI)	69	1.19 (0.50-2.85)	0.69	-	-
Treatment regimen					
Radiotherapy dose, grays	64	1.03 (0.96-1.10)	0.46	-	-
Radiotherapy dose ≥45 grays	64	1.15 (0.59-2.23)	0.68	-	-
Surgery	69	0.93 (0.48-1.80)	0.84	-	-
Adjuvant chemotherapy	69	0.65 (0.33-1.29)	0.22	0.30 (0.14-0.64)	0.002
Response after radiotherapy					
Positive IF	66	2.89 (1.35-6.15)	0.006	-	-
Serum M-spike size, g/L	66	1.06 (1.02-1.11)	0.001	-	-
Complete response	63	0.29 (0.10-0.83)	0.02	0.16 (0.05-0.56)	0.004

HR: hazard ratio; CI: confidence interval; BMPC: bone marrow plasma cell; IF: immunofixation (serum and/or urine); M: monoclonal; CT: computed tomography, PET: positron emission tomography; WB: whole body; MRI: magnetic resonance imaging.

juvant chemotherapy was associated with a decreased risk of progression in a retrospective study of 61 patients with SBP (HR=0.2; 95% CI: 0.04-0.97 for combined treatment *vs*. radiotherapy alone).[12] A randomized therapeutic trial (IDRIS Trial, *clinicaltrials gov. Identifier: NCT02544308)* is on-going to evaluate whether adjuvant lenalidomide can improve progression-free survival compared to radiotherapy alone in patients with high-risk SBP. This study will definitively show the room of adjuvant therapy in SBP.

Our study presents several limitations. Due to the rarity of SBP, inclusion time was very long and the number of patients was relatively small, but in line with existing large series. Thus, the treatment procedures were not standardized. Still, our results suggest a benefit of adjuvant chemotherapy used between 1992 and 2020 and it is likely that with the arrival of now available new drugs with even better efficacy, the positive impact of chemotherapy might be even higher. Finally, some data were missing and we could not rigorously use the IMWG response criteria which are, however, not totally adapted to SBP, particularly in non-secretory SBP.

In conclusion, our results highlight the importance of achieving CR after treatment of SBP, which appears to be the main risk factor for progression to MM. They also suggest a benefit of adjuvant chemotherapy, especially for patients at high risk of progression, i.e., with persistent disease after radiotherapy. These observations need to be confirmed and justify a prospective trial.

Authors

Sophia Ascione,[1*] Stéphanie Harel,[2*] Florent L. Besson,[3,4] Rakiba Belkhir,[1] Julien Henry,[1] Bruno Royer,[2] Bertrand Arnulf,[2] Xavier Mariette[1,5] and Raphaèle Seror[1,5]

[1]Department of Rheumatology, AP-HP, Hôpital Bicêtre, Le Kremlin Bicêtre; [2]Department of Immunohematology, AP-HP, Hôpital Saint-Louis, Paris; [3]Department of Biophysics and Nuclear Medicine-Molecular Imaging, AP-HP, Hôpital Bicêtre, Le Kremlin Bicêtre; [4]Université Paris-Saclay, CEA, CNRS, INSERM, BioMaps, Orsay and [5]Center of Immunology of Viral Infections and Auto-immune Diseases (IMVA), INSERM UMR1184, Université Paris-Saclay, Le Kremlin Bicêtre, France

**SA and SH contributed equally as co-first authors.*

Correspondence:
R. SEROR - raphaele.seror@aphp.fr

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Disclosures

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Contributions

All authors contributed to the manuscript. SA, SH, FB, RB, JH, BR, BA, XM, and RS were responsible for conception and design. SA, SH and RS were responsible for data collection and analysis. All authors were responsible for the interpretation of data. SA, SH and RS wrote the first version of the manuscript. All authors critically revised and approved the final version of the manuscript.

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Data-sharing statement

Data are available on request by emailing the corresponding author.

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