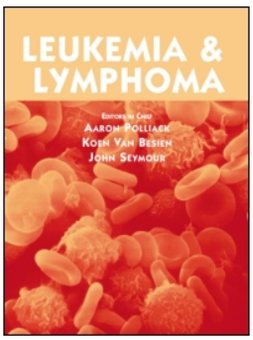


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# Secondary plasma cell leukemia: a multicenter retrospective study of 101 patients

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**ABSTRACT**

This multicenter retrospective study included 101 patients (median age 62 years) with secondary plasma cell leukemia (sPCL). The median time from initial multiple myeloma diagnosis to sPCL was 31 months. Fifty-five out of 72 patients (75%) who received any therapy were treated with immunomodulators (IMiDs) and/or proteasome inhibitors (PIs), and 14/72 (19%) underwent salvage autologous stem cell transplantation (ASCT). The overall response rate in patients who received ASCT or PI (either alone or in combination) was higher than in those who did not (93% vs. 36% and 60% vs. 30%, respectively). The median overall survival (OS) in patients who received therapy was 4.2 months (95% CI: 1.3; 8.0) with a 1-year OS of 19%. Platelet count $\leq 100 \times 10^9$/L at sPCL diagnosis was the only independent predictor of a poorer OS in treated patients (HR = 3.98, $p = .0001$). These findings suggest that patients with sPCL may benefit from salvage ASCT- and PI-based regimens.

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Autologous stem cell transplantation; proteasome inhibitors; secondary plasma cell leukemia

## Introduction

Multiple myeloma (MM), characterized by the neoplastic proliferation of plasma cells (PCs), comprises 1% of all neoplasms and over 10% of all hematological malignancies [1]. Plasma cell leukemia (PCL) is a rare and aggressive disease associated with the malignant accumulation of PCs in the peripheral blood [2]. PCL was first described by Gluziński and Reichenstein [3], more than a century ago. PCL has been defined as the presence of PCs in the peripheral blood at absolute numbers >2000/mm$^3$ or >20% of the total white blood cell (WBC) count [4]. PCL can either develop *de novo* (primary PCL, pPCL) or evolve as a late-stage complication of MM (secondary PCL, sPCL) [5]. The latter, observed in 1% of all MM patients, constitutes approximately 40% of all PCL cases [6], and is associated with a

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particularly unfavorable prognosis. Most of our knowledge regarding the natural history of sPCL and treatment outcomes has been derived from individual case reports and small case series [7–12].

We performed a multicenter retrospective study to analyze the clinical outcomes in patients with sPCL.

## Methods

### Case selection

Between January 2003 and December 2016, all patients with a diagnosis of sPCL established at least 12 weeks after initial anti-MM therapy were identified from the medical records at the participating institutions. PCL was defined as the presence of monoclonal PCs in the peripheral blood at absolute numbers $>2000/mm^3$ or $>20\%$ of the total WBC count. Pathological reports were confirmed by local haematopathologists. The study protocol was reviewed and approved by the Institutional Review Board of each participating institution.

### Data analysis

Clinical data were gathered from the medical records of patients fulfilling the inclusion criteria. The list of analyzed parameters included: age at diagnosis of MM and sPCL, sex, paraprotein isotype, International Staging System at MM diagnosis, number of lines of anti-MM therapy prior to sPCL diagnosis, including autologous stem cell transplantation (ASCT), time elapsed between MM and sPCL diagnoses, peripheral blood PC immunophenotype (CD38/138, CD56, CD20, and CD45 expression) and presence of cytogenetic abnormalities determined by means of fluorescence *in situ* hybridization (FISH; del17p, *t*(11;14), *t*(14;16), *t*(4;14), gain 1q, *t*(14;20) and complex cytogenetics, defined as the presence of at least three cytogenetic abnormalities) at MM and sPCL diagnosis. In addition, WBC count, PC count in peripheral blood, hemoglobin, platelet count and serum lactate dehydrogenase (LDH) level (elevated vs. normal) at sPCL diagnosis, anti-sPCL treatments and therapeutic responses, and overall survival (OS). Treatment outcomes were classified as by the International Myeloma Working Group including: complete response (CR), very good partial response (VGPR), partial response (PR), and no response (NR, both stable and progressive disease) [13]. Overall response rate (ORR), i.e. the proportion of all responses $\geq$ PR, was calculated. OS was defined as the time in months from sPCL diagnosis to last follow-up or death.

### Statistical analysis

The chi-square and the rank-sum tests were used to compare categorical and continuous variables, respectively. OS was defined as the time in months between date of sPCL diagnosis and the date of last follow-up or death. For the survival analysis, the Kaplan–Meier method was used to generate survival curves, which were then compared using the log-rank test. The Cox proportional-hazard regression method was used to fit univariate survival models, the results of which are reported as hazard ratios (HRs) with 95% of confidence intervals (95% CIs). Variables with $>50\%$ of missing data were not included in the survival analyses. All reported *p* values are two-sided, and were considered significant if less than .05. Calculations and graphics were obtained using the statistical software Statistica version 10.0 (StatSoft, Tulsa, OK).

## Results

A total of 101 patients with an established diagnosis of sPCL were included in the analysis. The median age at the time of sPCL diagnosis was 62 years (range 33–80), and the median time from MM diagnosis to sPCL diagnosis was 31 months (range 3–133). There was a female predominance with a female to male ratio 1.2 to 1 (55/45). The median number of MM treatment lines prior to sPCL diagnosis was 2 (range: 1–5), with 45/99 (45%) patients receiving more than two lines, and 54/99 (55%) undergoing ASCT prior to sPCL diagnosis. At the time of sPCL diagnosis, 82/101 (81%) patients had hemoglobin concentrations $\leq$10 g/dL, 53/66 (80%) presented with elevated LDH levels, 80/101 (79%) with platelet counts $\leq 100 \times 10^9$/L, and 59/97 (61%) with $>40\%$ of plasma cells in the peripheral blood. The proportions of patients with IgG and non-IgG isotypes were 49% and 51%, respectively. Other clinical characteristics of the patients, including parameters recorded at the time of MM diagnosis, are listed in Table 1.

At the time of sPCL diagnosis, the malignant cells in all patients had positive expression of CD38/138, and met the criteria for PCL (monoclonal PCs $>2000/mm^3$ or $>20\%$ of the total WBC count). Additionally, 36/51 (71%) patients tested positive for CD56 expression by the malignant plasma cells. As, this is a retrospective multicenter analysis, cytogenetics were not routinely performed in all patients. *t*(11;14) was detected in 7/37 (19%) patients, and complex cytogenetics, i.e. at least three cytogenetic abnormalities, in 2/41 (5%) (Table 2). The number of patients with cytogenetic abnormalities

**Table 1.** Clinical characteristics of 101 patients with secondary PCL.

| Characteristics | Median (range) or number (%) |
|---|---|
| Median age at MM diagnosis (years) | 57.5 (27–80) |
| Male sex | 45/100 (45%) |
| Paraprotein isotype at MM diagnosis[a] | |
| IgG | 49/98 (50%) |
| Non-IgG | 49/98 (50%) |
| Light chain only | 12/98 (12%) |
| IgA | 34/98 (35%) |
| Nonsecretory | 2/98 (2%) |
| ISS staging at diagnosis of MM | |
| ISS stage 1 | 10/80 (13%) |
| ISS stage 2 | 23/80 (29%) |
| ISS stage 3 | 47/80 (59%) |
| Median time from MM diagnosis (months) | 31 (3–133) |
| Median WBC count ($\times 10^9$/L) | 11.5 (1.3–81) |
| Median hemoglobin (g/dl) | 8.3 (3.2–13.1) |
| Median platelet count ($\times 10^9$/L) | 40 (3–500) |
| Median plasma cell count in PB ($\times 10^9$/L) | 4.5 (0.1–64) |
| Plasma cell count in PB $\geq 20 \times 10^9$/L | 11/97 (11%) |
| Median plasma cell percentage in PB | 45 (2.9–92) |
| Plasma cell percentage in PB $\geq$40% | 59/97 (61%) |
| Elevated LDH level | 53/66 (80%) |

WBC: white blood cell; LDH: lactate dehydrogenase; ISS: international staging system; PB: peripheral blood; MM: multiple myeloma.
[a]In 3/34 patients, IgA(+) at the time of MM diagnosis, paraprotein isotype has changed to LC at PCL diagnosis; in another 3/34, the paraprotein status at PCL diagnosis was unknown.

**Table 2.** Cytogenetic characteristics of 101 patients with secondary PCL.

| Cytogenetic abnormalities | At MM diagnosis positive/tested (%) | At sPCL diagnosis positive/tested (%) |
|---|---|---|
| del17p | 17/59 (29) | 22/48 (46) |
| *t*(11;14) | 9/53 (17) | 7/37 (19) |
| *t*(14;16) | 2/49 (4) | 1/38 (3) |
| *t*(4;14) | 13/58 (22) | 10/43 (23) |
| Gain 1q | 7/46 (15) | 11/46 (24) |
| *t*(14;20) | 0/41 (0) | 2/37 (5) |
| Complex cytogenetics[a] | 8/53 (15) | 2/41 (5) |

[a]Defined as 3 or more cytogenetic abnormalities. MM: multiple myeloma.

was too low to derive an accurate analysis of the impact on outcomes.

Among 72 patients who received any therapy for sPCL, 55 (75%) patients were treated with novel agents, such as immunomodulators (IMiDs) and/or proteasome inhibitors (PIs) or monoclonal antibodies (Mabs), 14/72 (19%) patients underwent salvage ASCT, and 2/72 (3%) patients received allogeneic stem cell transplantation. Patients who received a PI, either alone or in combination with conventional chemotherapy, IMiD or both, had higher ORR than those treated with other regimens (60% vs. 30%, $p = .01$). The ORR increased with the number of agents from various groups included in the first-line treatment, from 39% for a single therapy to 49% and 67% for doublet and triplet therapy, respectively ($p = .46$). ORR in patients who underwent salvage ASCT was substantially higher than in those who did not receive ASCT (93% vs. 36%, $p < .001$). Importantly, at least partial response was documented in all eight patients who received both salvage ASCT and PI therapy alone or in combination as part of the treatment for sPCL (Table 3).

**Table 3.** Salvage treatment for secondary PCL with responses in 72 patients who received the therapy and were evaluable for response.

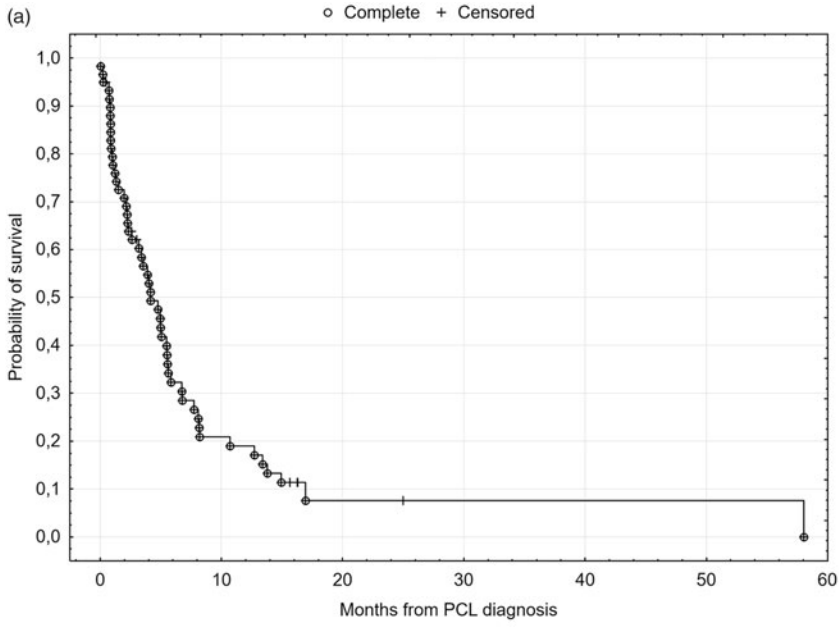
| Treatment | Number (%) | CR (%) | VGPR (%) | PR (%) | NR (%) |
|---|---|---|---|---|---|
| Chemo only | 17 (24) | 2 (12) | 2 (12) | 2 (12) | 11 (65) |
| PI/IMID/MA only | 6 (8) | 0 (0) | 1 (17) | 2 (33) | 3 (50) |
| Chemo-PI | 26 (36) | 5 (19) | 1 (4) | 10 (38.5) | 10 (38.5) |
| Chemo-IMID | 11 (15) | 0 (0) | 0 (0) | 3 (27) | 8 (73) |
| PI-IMID | 6 (8) | 1 (17) | 0 (0) | 1 (17) | 4 (67) |
| Chemo-PI-IMID | 6 (8) | 1 (17) | 1 (17) | 2 (33) | 2 (33) |
| PI mono-/combination | 42 (58) | 7 (17) | 3 (7) | 15 (36) | 17 (40) |
| Bortezomib[a] | 35 (48) | 7 (20) | 3 (9) | 13 (37) | 12 (34) |
| Carfilzomib[a] | 7 (10) | 0 (0) | 0 (0) | 2 (29) | 5 (71) |
| Other regimen | 30 (42) | 2 (7) | 2 (7) | 5 (17) | 21 (70) |
| Single therapy | 23 (32) | 2 (9) | 3 (13) | 4 (17) | 14 (61) |
| Doublet therapy | 43 (60) | 6 (14) | 1 (2) | 14 (33) | 22 (51) |
| Triplet therapy | 6 (8) | 1 (17) | 1 (17) | 2 (33) | 2 (33) |
| Doublet or triplet therapy | 49 (68) | 7 (14) | 2 (4) | 16 (33) | 24 (49) |
| ASCT | 14 (19) | 6 (43) | 2 (14) | 5 (36) | 1 (7) |
| Non-ASCT | 58 (81) | 3 (5) | 3 (5) | 15 (26) | 37 (64) |
| PI[a] + ASCT | 8 (11) | 4 (50) | 1 (12.5) | 3 (37.5) | 0 (0) |
| Other | 64 (89) | 5 (8) | 4 (6) | 17 (27) | 38 (59) |

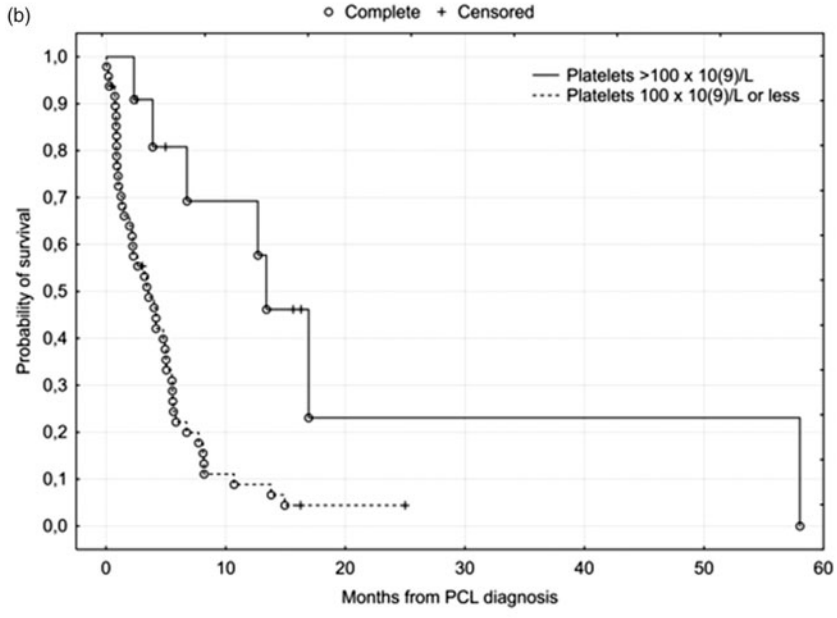
CR: complete response; VGPR: very good partial response; PR: partial response; ORR: overall response rate; NR: no response; PI: proteasome inhibitor; IMID: immunomodulator; MA: monoclonal antibody; ASCT: autologous stem cell transplantation; sPCL: secondary plasma cell leukemia.
[a]Alone or in combination therapy. The terms 'single therapy', 'doublet therapy', and 'triplet therapy' refer to the use of chemotherapy and/or PI and/or IMID, regardless dexamethasone was included or not.

The median follow-up for the 72 patients who received any treatment for sPCL was 16.3 months (95% CI: 15.1; 23.9), with a median OS of 4.2 months (95% CI: 1.3; 8.0), and a 1-year OS rate of 19% (95% CI: 8.5; 29.5) (Figure 1(a)). In the univariate analysis, including only treated patients (Table 4), platelet count $\leq 100 \times 10^9$/L was the only factor associated with poorer survival (HR = 3.98, 95% CI: 1.98; 7.98, $p = .0001$). The median OS in patients with platelet count $\leq 100 \times 10^9$/L was 3.5 months (95% CI: 1.0; 5.6) compared to 13.2 months (95% CI: 5.3; 16.6) in patients with platelet count $> 100 \times 10^9$/L (log-rank $p < .001$; Figure 1(b)).

## Discussion

This multicenter study showed that salvage therapy with novel agents, especially PIs, and ASCT might improve the outcomes in patients with sPCL. These observations are clinically relevant since sPCL, a rare complication of MM, is associated with particularly unfavorable prognosis, with median OS of 1–2 months [7,10], and there are no standard treatment recommendations for this condition. The available published evidence regarding treatment of sPCL is sparse and




| | Platelets 100 x $10^9$/L or less | Platelets >100 x $10^9$/L |
|---|---|---|
| Median Follow-Up (months) | 15.4 (8.4; 20.4) | 15.9 (7.0; -) |
| 1-Year OS (%) | 8.9 (0.6; 17.1) | 69.3 (39.9; 98.6) |
| Median OS (months) | 3.5 (1.0; 5.6) | 13.2 (5.3; 16.6) |

**Figure 1.** Overall survival estimates in 72 treated patients with secondary plasma cell leukemia for the entire cohort (a) and stratified by platelet count (b).

originates primarily from individual case reports and small case series.

Although small numbers, more than 90% of our patients subjected to salvage ASCT responded to the salvage treatment, and nearly half of them achieved CR. The effectiveness of ASCT has been also confirmed in pPCL. Drake et al. [14] reported on 272 patients with pPCL treated with ASCT. The CR rate was 41%, and median OS was over 2 years. In a study conducted by the Center for International Blood and Marrow Transplant Research, 61% out of 97 pPCL patients who underwent ASCT survived at least 3 years [15]. However, when interpreting these results, one should remember that prognosis in pPCL is substantially better than in sPCL, with median OS of 7–12 months utilizing conventional chemotherapy [16].

**Table 4.** Univariate analysis for overall survival in 72 patients with secondary SCL who received a salvage therapy.

| Variable | HR (95% CI) | *p* value |
|---|---|---|
| Male sex | 1.31 (0.75–2.28) | .33 |
| Time from MM diagnosis ≥24 months | 0.83 (0.48–1.44) | .51 |
| Age at PCL diagnosis ≥60 | 1.71 (0.96–3.05) | .071 |
| WBC $\geq 15 \times 10^9$/L | 1.14 (0.66–1.99) | .63 |
| Hemoglobin ≤10 g/dL | 1.39 (0.73–2.68) | .32 |
| Platelets $\leq 100 \times 10^9$/L | 3.98 (1.98–7.98) | .0001 |
| Plasma cells $\geq 20 \times 10^9$/L | 1.75 (0.87–3.54) | .12 |
| Plasma cells ≥40% | 1.23 (0.68–2.24) | .49 |
| Elevated LDH level | 1.02 (0.39–2.64) | .96 |
| Non-IgG isotype | 0.77 (0.43–1.35) | .36 |
| CD56 expression | 0.75 (0.27–2.03) | .57 |
| CD45 expression | 2.12 (0.65–6.94) | .21 |
| CD20 expression | 0.76 (0.29–2.00) | .58 |
| Del17p | 1.25 (0.62–2.53) | .53 |
| *t*(11;14) | 0.36 (0.10–1.27) | .11 |
| *t*(4;14) | 0.95 (0.38–2.37) | .92 |
| Gain 1q | 0.60 (0.18–2.02) | .41 |

HR: hazard ratio; MM: multiple myeloma; PCL: plasma cell leukemia. *t*(14;16) and *t*(14;20) are not included in the survival analysis.

We observed a beneficial effect of salvage ASCT and initial PI salvage therapy implying that combination of these two treatments may improve prognosis in sPCL. Indeed, although this subset was too small for any definitive conclusions, all eight patients with sPCL who underwent salvage ASCT following PI therapy showed at least a partial response to initial salvage treatment. Also, the results obtained previously in pPCL patients support the notion that consolidation with ASCT following PI may result in deep responses and contributes to a relatively prolonged remission [10,17–19].

Of note, the performance status in pPCL patients is usually better than in individuals with sPCL resulting not only from the more aggressive character of the latter, but also a consequence of previous anti-MM treatment [7]. As a result, many patients with newly diagnosed sPCL do not receive any salvage treatment or are treated conservatively, as 29 patients (29%) included in our series.

In our cohort, responses to either mono- or combination therapy with PIs were markedly better than to other regimens (ORR: 60% vs. 30%, $p = .013$). This observation is consistent with sparse published data regarding treatment outcomes in sPCL patients. In a study conducted by Katodritou et al. [10], ORR in 17 sPCL patients was only 24%; however, a higher ORR of 36% was observed on a subgroup analysis of patients treated with bortezomib. The OS in the bortezomib-treated patients was 7 months, and therapy with this agent was identified as an independent predictor for improved survival [10]. Similarly, high ORR values (44%) were also documented in a small series of nine patients with sPCL, treated with lenalidomide, bortezomib and dexamethasone, and a median OS of 5 months [11].

We observed that ORR rates to the initial salvage treatment for sPCL increased with the number of agents from various groups (conventional chemotherapy, immunomodulators, and PIs) included in the therapeutic protocol, as long as one of them was a PI. In contrast to pPCL, where studies demonstrate a clear advantage of combination therapy with a PI and IMID [9,19–21], the available evidence in sPCL is limited. Unfortunately, our sample population was too heterogeneous in terms of the therapeutic protocols, and patients treated with IMIDs were generally underrepresented, so we were not able to verify potential benefits of a PI and IMID combination.

Our study identified platelet count $\leq 100 \times 10^9$/L as an independent biological predictor of worse OS. Both the median OS and 1-year OS rate were compromised in patients with platelet count $\leq 100 \times 10^9$/L (median OS: 3.5 vs. 13.2 months, 1-year OS: 8.9% vs. 69.3%, log-rank $p = .0001$). The unfavorable effect of thrombocytopenia on OS in sPCL was also reported by Katodritou et al. [10]. However, thrombocytopenia is a common finding in sPCL (79% of our patients presented with platelet counts $\leq 100 \times 10^9$/L), which may negate its applicability as a clinically relevant prognostic factor. Surprisingly, we found no prognostic value of elevated LDH level, but it should be emphasized that information about this parameter was missing in 35% of patients.

Probably, more accurate prognostic information would be obtained from the profile of cytogenetic abnormalities, but available evidence is too limited. In our study, the presence of *t*(11;14) was associated with a survival benefit on univariate analysis, but due to a large proportion of missing data (63%), this finding should be treated with caution. In some retrospective studies of pPCL patients, *t*(11;14) predicted more favorable outcomes, whereas del(13q), del(17p), del(1p), ampl(1q+), and a complex karyotype were associated with reduced OS [22,23]. Other studies did not find a link between cytogenetic profile and prognosis in pPCL [19,24]. Thus, larger prospective studies with uniform treatment are needed to further examine the prognostic role of cytogenetic abnormalities in pPCL and sPCL.

We acknowledge limitations of this study. Our study is retrospective, lacks protocol standardization, and has a number of incomplete variables. This refers primarily to incompleteness of some clinical and laboratory data, especially cytogenetic characteristics. As a result, we were unable to include all potential predictors of OS in multivariate prognostic model, and to formulate any firm conclusions regarding cytogenetic profiles of sPCL. Another inherent weakness of a retrospective study is selection bias as our survival analyses included only patients who received treatment, excluding

persons who were too ill or frail to be treated. Thus, if one included all patients, the prognosis of the sPCL patients would be even graver.

In conclusion, this study suggests that patients with sPCL have a poor overall prognosis, but sPCL patients may benefit from implementation of salvage multidrug PI-based regimens and ASCT. However, given the poor outcomes seen in these patients, novel agents with higher efficacy are needed.

***Potential conflict of interest:*** Disclosure forms provided by the authors are available with the full text of this article online at https://doi.org/10.1080/10428194.2018.1473574.

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