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Italian real life experience with brentuximab vedotin: results of a large observational study on 40 relapsed/refractory systemic anaplastic large cell lymphoma

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Original Article: **Italian real life experience with brentuximab vedotin: results of a large observational study on 40 relapsed/refractory systemic anaplastic large cell lymphoma**

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Running head: Brentuximab vedotin in ALCL: real life experience

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ABSTRACT

From November 2012 to July 2014, brentuximab vedotin was available in Italy for patients with relapsed systemic anaplastic large cell lymphoma outside a clinical trial context according to the national law 648/96. A large Italian observational retrospective study was conducted on the use of brentuximab vedotin in the everyday clinical practice to check if clinical trial results are confirmed even in a real life context. Primary endpoint was the best response; secondary endpoints were the overall response rate at the end of the treatment, duration of response, survival and the safety profile. A total of 40 heavily pretreated patients were enrolled. Best response was observed after a median of 4 cycles in 77.5%: globally, 47.5% patients obtained a complete response, 64.2% in the elderly subset. Overall response rate was 62.5%. At the latest follow up 15/18 patients are still in complete response (3 with consolidative procedure). Progression free survival was 39.1% at 24 months and disease free survival 54% at 24 months (median not reached). Particularly, all the long term responders were aged <30 years at first infusion. The treatment was well tolerated even in this real life context and no death has been linked to drug toxicity. Brentuximab vedotin induces clinical responses quite rapidly, i.e. within the first 4 cycles in most responder patients, thus permitting the timely application of the transplantation phase. For patients ineligible for transplant or for who transplant failed, brentuximab vedotin may represent a feasible effective therapeutic option in everyday clinical practice.

Introduction

Approximately 40% to 65% of patients with systemic anaplastic large-cell lymphoma (sALCL) develop recurrent disease after front-line therapy.[1] Historically, at relapse the disease is resistant to conventional multiagent chemotherapy regimens, and there is no established standard of care. High-dose therapy and autologous stem cell transplantation (ASCT) may result in long-term remission in 30% to 40% of patients, but the benefit is limited to patients with chemotherapy-sensitive disease.[2-6]

Given that most patients with relapsed and refractory (R/R) sALCL are scheduled to undergo a highly toxic high-dose chemotherapy regimen, any strategy aimed at achieving a minimal disease status, specifically a positron emission tomography (PET)-negative status before ASCT, without severe toxicity would represent a major advance in the overall management of these patients. Furthermore, although the role of ASCT, the outcomes remain poor in those with primary chemorefractory disease, where long-term survival rarely exceeds 15-17%.[1] In fact, disease recurrence still remains the principal cause of ASCT failure, and early disease progression after transplant, i.e. within 6 months from high-dose conditioning, emerges as the most important predictor of unfavorable outcome. No standard treatment options exist for patients showing disease relapse after ASCT or for patients not eligible for ASCT. In fact, while allogeneic stem cell transplantation (alloSCT) may induce a long-term progression-free survival (PFS) in a fraction of patients, only a few are candidates for this procedure, mainly as a result of unsatisfactory pre-transplant cytoreduction and substantial risk of morbidity due to the heavy load of previous therapies. Under this light, the optimization of the outcomes obtained with high-dose regimens and ASCT still remains a current strategic priority, in order to offer the best chance of cure for the largest fraction of patients with R/R disease.

Brentuximab vedotin (BV) is an antibody-drug conjugates targeting CD30 which may represent the optimal candidate among the new developed agents for the treatment of R/R sALCL.[7] In fact, sALCL is characterized by the expression of CD30. In the initial phase 1 study of BV in patients with CD30+ lymphoid diseases, both the 2 sALCL patients achieved a complete response (CR).[7] The favorable activity of this agent in R/R sALCL was clearly documented by Pro et al in a phase 2 study involving 58 patients: 86% obtained a response, which was a CR in 57% of cases.[8] Median PFS for these patients was 13.3 months, and the median overall survival (OS) was not reached (estimation is 64% at 4 years). The same relevant proportion of CR in this subset of patients also emerges from the data collected by Zinzani et al regarding the BV Named Patient Program (NPP) experiences across Europe.[9,11,15-17]

This high response rate is important not only in pretreated patients showing a poor prognosis, but also in first-line R/R patients because a CR obtained before transplant is one of the stronger predictors for long-term survival.[10] BV can represent an optimal therapeutic option as a bridge to both ASCT and alloSCT program in patients achieving a suboptimal response after salvage treatment.[11,12] Recent updates on the pivotal study have shown that BV can induce long lasting CR in sALCL pretreated cases either without additional consolidation therapies, suggesting that BV may be curative for some patients.[13,14] The pooled overall response rate (ORR) and CR rate reported for R/R sALCL patients (globally 46) in NPP cohorts were 69.5% for both rates.[9,11,15-17]

After accelerated approval by US Food and Drug Administration, eligible patients in Italy were granted early access through a NPP. After the closure of NPP, between 2012 BV was available in Italy for patients with R/R sALCL, based on a local disposition of the Italian Drug Agency (AIFA) issued according to a national law (Law 648/96: “medicinal products that are provided free of charge on the national health service”): a boundary zone

in the passage from clinical trials to marketing and free use phases where patients can be treated in any case.

On the basis of our previous explorative study,[18] a large Italian observational retrospective study was conducted on the use of BV in R/R sALCL patients in the everyday clinical practice to check if clinical trial results are confirmed even in a real life context.

Methods

An observational retrospective study was conducted among patients with sALCL treated from November 2012 to July 2014 with BV in 38 Italian centers outside of clinical trials, according to the national law no. 648/96.[19] The study was approved by our institutional board (Azienda Ospedaliera di Bologna, Policlinico S.Orsola-Malpighi, coordinating center) and by all involved Ethical Committees and registered in the Italian Registry of Observational Studies. All participants gave written informed consent in accordance with the Declaration of Helsinki. A shared database was used after the approval of all the co-investigators and variables were strictly defined to avoid bias in reporting data.[19] We obtained a special permission (for scientific purpose) from our Ethical Committee to collect even data of patients who were deceased or lost to follow up.

BV is administered as a 30-minute infusion of at the dose of 1.8 mg/kg of body weight every 3 weeks for a maximum of 16 cycles. Dose reduction to 1.2 mg/kg is recommended in case of grade 3 toxicity and the treatment has to be interrupted in case of grade 4 toxicity.

The primary endpoint of the study was the best response achieved during BV therapy; secondary endpoints were the ORR at the end of the treatment, duration of response (DoR), OS, PFS, disease free survival (DFS), and the drug safety and tolerability. Duration of therapy was defined as the number of cycle performed.

Effectiveness was also evaluated through the occurrence of long term responder (LTR) patients, defined as patients who have response (CR or partial response [PR]) duration ≥12 months. Response is assessed by PET/CT scan after cycle 4, 8, 12 and at drug discontinuation by each investigator using the International Working Group revised response criteria for malignant lymphoma.[20] Safety and tolerability were evaluated by recording incidence, severity, and type of any adverse event (AE) according to the National Cancer Institute Common Terminology Criteria for AEs v4.0.

OS was defined as the time from initiation of therapy to death from any cause and was censored at the date of the last available follow up. PFS was measured from initiation of therapy to progression, relapse, or death from any cause and was censored at the date of the last available follow up. DFS was calculated for CR patients from the first documentation of response to the date of relapse or death due to lymphoma or acute toxicity of treatment. DoR was calculated from the first objective tumor response (CR or PR) to first documentation of progression or death.[20] Lost to follow up patients (N=2). were censored at the latest available date.

Demographics and patients' characteristics as well as AEs were summarized by descriptive statistics. Survival functions were estimated by using the Kaplan-Meier method and were compared using log-rank test. Statistical analyses were performed with Stata 11 (StataCorp LP, TX) and p values were set at 0.05.

Results

Of the estimated 40 patients who received BV under the Law 648/96, all participated in this observational study. All had histologically confirmed CD30+ disease. The median age at BV was 47 years (range, 17-80 years) with 14 (35.0%) elderly (age> 60 years) patients; 28 were males and 12 were females. Eleven (27.5%) had systemic symptoms at baseline (Table 1).

The median number of prior lymphoma-related systemic regimens was 2 (range, 2-10) including high dose chemotherapy and autologous stem cell transplantation (ASCT) (in 13, 32.5% of the patients). Eight patients (20%) had received prior radiation therapy. Eighteen were anaplastic lymphoma kinase negative (ALK+) and 22 anaplastic lymphoma kinase positive (ALK-) status. For each patient the status after both frontline therapy and most recent therapy was collected: 24 (60%) patients had disease that was refractory to frontline therapy and 25 patients (62.5%) had disease that was refractory to last therapy before BV.

Response to treatment

Best response was observed after a median of 4 cycles in 31 (77.5%) patients: 19 (47.5%) obtained a CR and 12 (30%) achieved a partial response (PR). Overall responses rate at the end of the treatment was 62.5% (25 patients) represented by 18 (45%) CR and 7 (17.5%) PR; among the remaining patients, one had stable disease (SD), and 14 patients showed progression of disease (PD), respectively.

The best response rate was higher in the elderly subset (>60 years): 9 (64.3%) CR and 3 (21.4%) PR with an overall response rate of 85.7%. Four patients who were in CR at first restaging relapsed during further BV courses; 2 patients who were in PR at first restaging converted to CR status after the 4 subsequent infusions.

All patients who were in SD or PD at first restaging did not improve their status at the end of therapy. The median number of cycles administered was 8 (range 1-16).

With a median follow up of 18 months global OS was 56.9% at 24 months (Figure 1) and median not reached yet. PFS at 24 months was 39.1%, median achieved at 12.5 months (Figure 2). DFS was 54% at 24 months (Figure 3); 4 out of 19 (21%) CR patients relapsed and 15 patients were in continuous CR (CCR) at the last follow up with a median DoR of 12 months (range, 9-24 months). After controlling for confounding variables, no differences in any time to point endpoints between ALK- and ALK+ patients were observed.

Among the CRs, 3 patients had consolidation with transplant (1 ASCT and 2 alloSCT). Currently, 15 patients are still in CR and, in particular, the 3 with consolidative procedure; among elderly patients, 6 out of 9 (66.7%) patients are still in CCR without any consolidative procedure after a median of 14 months. There are 5 LTR patients and all of them are still in CCR at the last available follow up. To note, they were all aged <35 years at BV therapy and only 1 of them had a subsequent consolidative transplant. At the latest follow-up, 27 (67.5%) patients were alive and 13 deceased (11 due to lymphoma, 2 for complications after alloSCT: one for respiratory insufficiency related to graft-versus-host-disease and 1 for pneumonia).

Safety

All patients who received at least one BV infusion were included in the safety analysis. In general, the treatment was well tolerated and the toxicity profile was very similar to the previously published data. Twelve patients had at least one toxicity. All hematologic toxicities but one were grade 1-2. In fact, we registered a grade 3 neutropenia. The extra-hematologic side effects were mostly represented by peripheral sensorial neurological toxicity (15/20) and, among them, 3 were grade 3. The other AEs were by nausea grade 1-2 (two patients), erythema grade 2 (two patients), hyposthenia grade 2 (one patient). Neurological toxicity always reversed completely after end of treatment. No long-term toxicity related to BV was observed during the follow-up period, even in patients later subjected to transplant consolidation.

Discussion

This retrospective large multicenter Italian study on 40 patients with R/R sALCL treated with BV outside a clinical trial represents the largest ever reported in a real world context. Our results are in accordance to the pivotal phase II study and its updates and to

the other national experience studies with an ORR of 77.5% and a CR rate of 47.5% in terms of best response.[8,9,11,14-18]

In addition, we extrapolate some interesting consideration about the role of BV in everyday clinical practice. First, both the best response rate and ORR were higher in the elderly setting: 85.7% vs 77.5% and 64.3% vs 62.5%, respectively.

To be in CR after 4 cycles is confirmed very important for classifying the patient as a real good responder; at the same time, the right number of cycles to be performed for evaluating the potential consolidation with transplant (in the major part allogeneic transplant) or the continuation with BV until the cycle 16 remains an open issue, mainly because in case of CR the choice between the two options is at the physician discretion. According to the recent update by Pro et al. on the pivotal phase II study, the 5-year PFS was 68% in CR patients submitted to alloSCT versus 47% in patients who continued BV treatment even though they had obtained CR after the first 4 cycles.[8,14] In this update the authors reported that 27.6% of the whole study population has achieved long-term remission exceeding 5 years in response to single agent BV without any additional anticancer therapy, other than transplant. In our study the estimated DFS at 2 years was 54% and 15 patients (37.5%) are in CCR with a median DoR of 12 months (range 9-24 months). As only 3/15 patients had transplant consolidation, comparison between them and patients who did not received SCT procedure was not possible. Thus, also in the real life experience as in the in the pivotal study, DoR and DFS indicate that, among R/R sALCL, a substantial subset of patients who obtained CR with single agent BV either obtained a long-term disease control and may potentially be cured. An important question remains unclear: among the patients in CR, which may benefit from the transplant consolidation? In our series there are 5 LTR patients and all of them are still in CCR at the latest follow-up and, in particular, only 1 with a consolidative alloSCT procedure. Update on pivotal study and our data could indicate that it is possible to obtain long disease

control also without transplant consolidation with the real chance to cure a subset of R/R sALCL only with BV.[14] Physicians are still divided on whether or not offer a consolidative transplant to CR patients as solid clinical trial data are lacking on this issue. A large, well-designed randomized control study is needed, but ALCL is so rare that we are unlikely to ever have a definitive answer.

Differences in survival outcomes between ALK+ and ALK- patients have been often reported: no statistical significance in our sample was observed between the two subgroups.[21]

Our study indicated that for patients who obtained a SD or PD after 4 cycles of BV the potential conversion rate to PR or CR with further administrations is close to zero. The final message is that when patients show SD or PD at first restaging, they have to be shifted rapidly to another treatment. On the other hand, for patients who achieved PR after first restaging it could be important to continue the treatment: in our series 2/12 (16.7%) patients showed a conversion from PR to CR status.

In conclusion, the results of this large retrospective study on 40 R/R sALCL in the daily practice support the efficacy of single agent BV with manageable toxicity without evidence of cumulative toxic effects with previous regimens. We acknowledge that this kind of reports carry potential bias as the lacking of predictable and calculated sample size and the risk of toxicity underreporting. ALCL represents approximately 2% to 3% of all lymphoid neoplasms, thus it is a very rare disease. The phase II study who lead to an FDA accelerated approval of BV enrolled globally 58 patients, thus 40 ALCL patients from a single nation is a substantial sample related to this pathology. However, we could not analyze prognostic features due to the small sample and we reported the raw observed data. Observational studies may better identify clinically important AEs when compared with randomized controlled trials, for several reasons. Those reasons include longer follow-up times, the inclusion of patients with concomitant illnesses who may be more

likely to experience drug interactions or other side effects and to detect infrequent or rare complications. Regarding the retrospective nature of this specific study, AIFA has a strict monitoring on drugs prescribed under the law 648/96 and physicians have to report any AE occurring during treatment: thus, all the safety data are already in the patients' chart at the time our retrospective study starts.

In particular, our report confirms the activity in elderly patients, the duration of the clinical response independently by the transplant consolidation, and the relevance of the CR status after 4 cycles in term of final response. BV is the first drug which led to a drastic management change in ALCL, entailing an ORR of 80%. Next research efforts could be aimed at developing combination regimens with BV to reach the 100% of response in R/R ALCL patients.

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Table 1: Patient demographics and characteristics at baseline.

Total population, N	40
ALK+ ALK-	22 18
Median age, years (range)	51.4 (22.6-80.7)
Median time from diagnosis-BV, years (range)	2 (1-16)
Male, N (%)	28 (70.0)
Stage, N (%) - I/II - III - IV	 9 (22.5) 5 (12.5) 26 (65.0)
Systemic symptoms, N (%)	11 (27.5)
- Refractory to most recent therapy, N (%) - Refractory to first line therapy, N (%)	24 (60.0) 25 (62.5)
Median number of previous therapies (range)	2 (2-10)
Prior autologous stem cell transplant, N (%)	13 (32.5)
Prior radiotherapy, N (%)	8 (20)

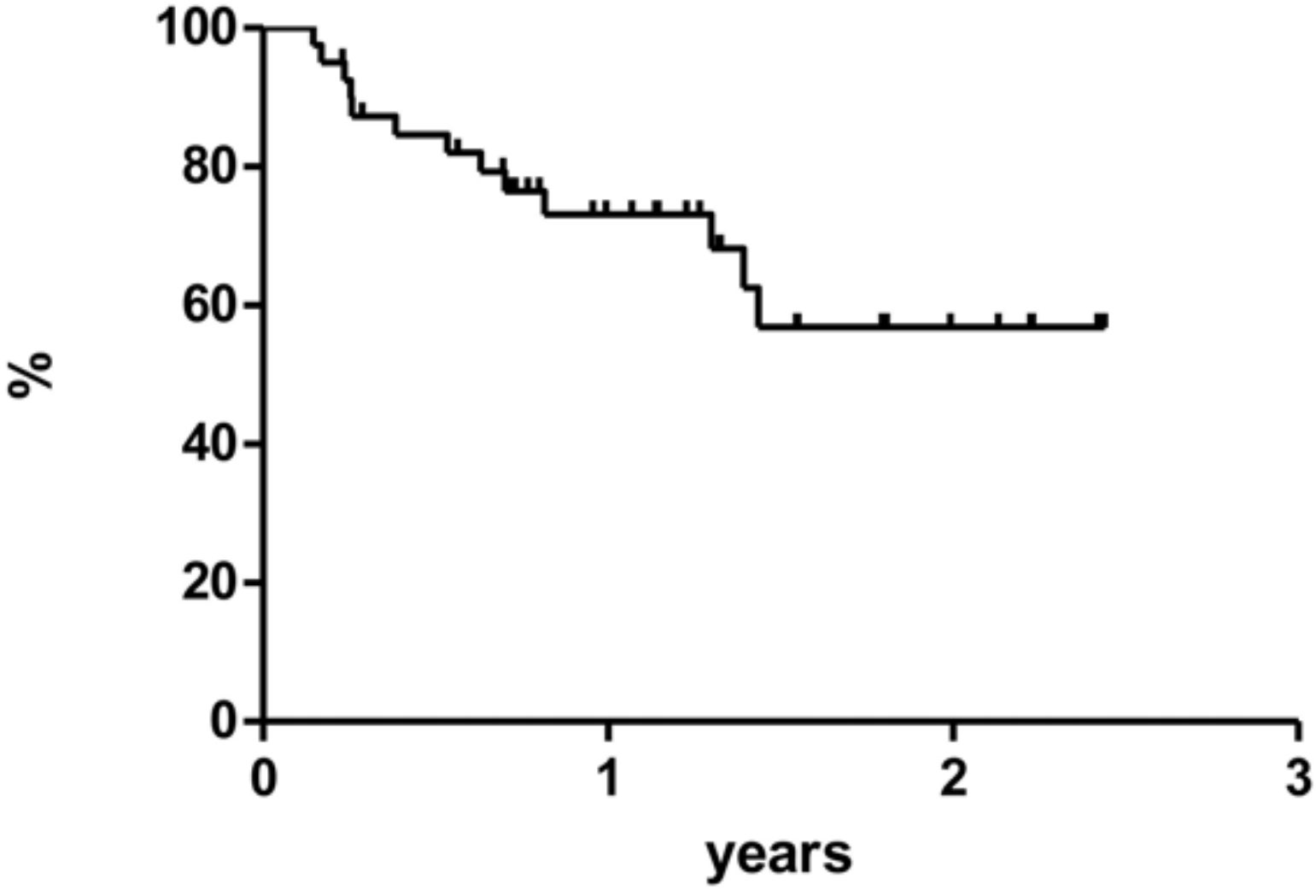
ALK: anaplastic lymphoma kinase; BV: brentuximab vedotin; ECOG: Eastern Cooperative Oncology Group.

Figure Legends

Figure 1: Overall survival.

Figure 2: Progression free survival.

Figure 3: Disease free survival.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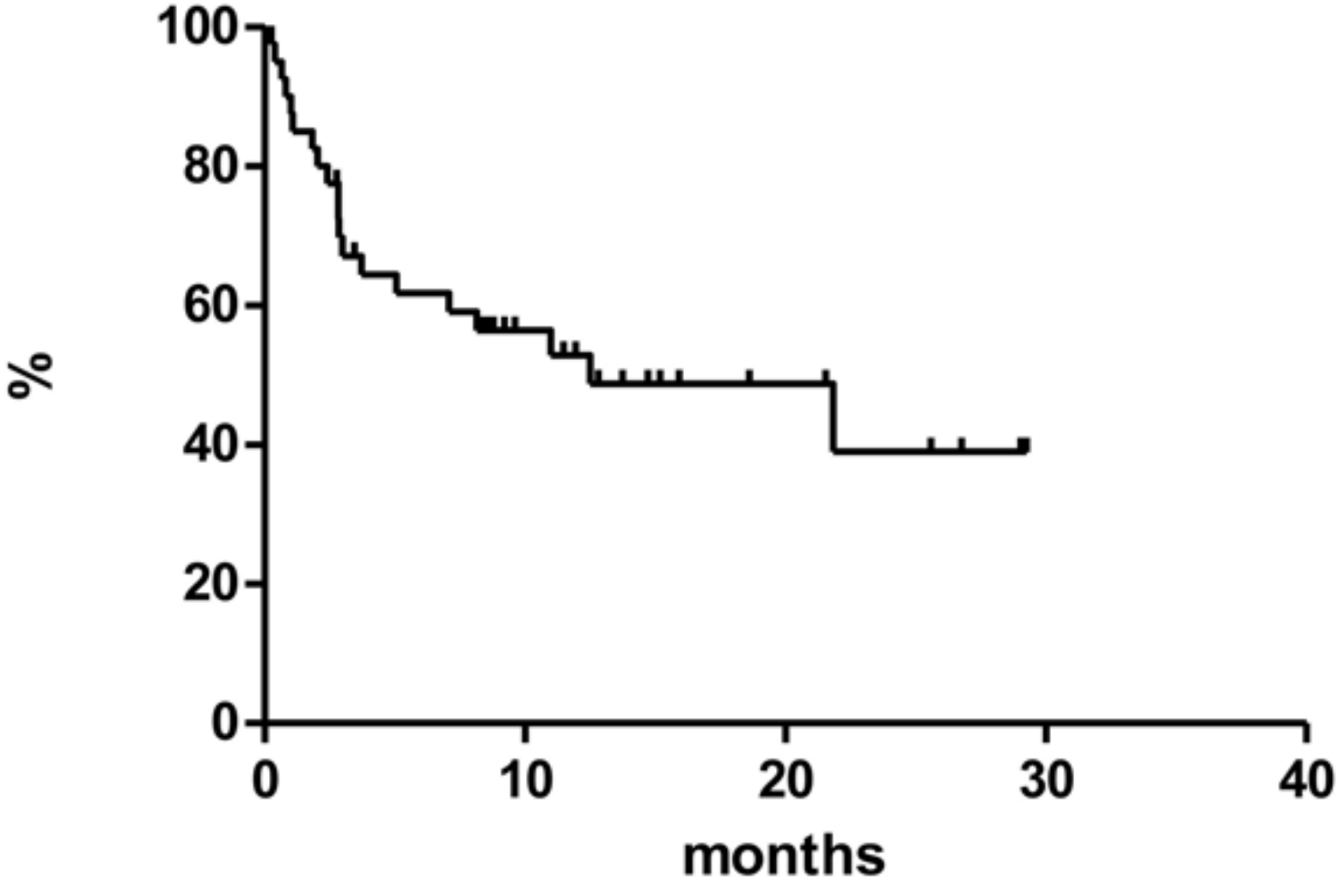
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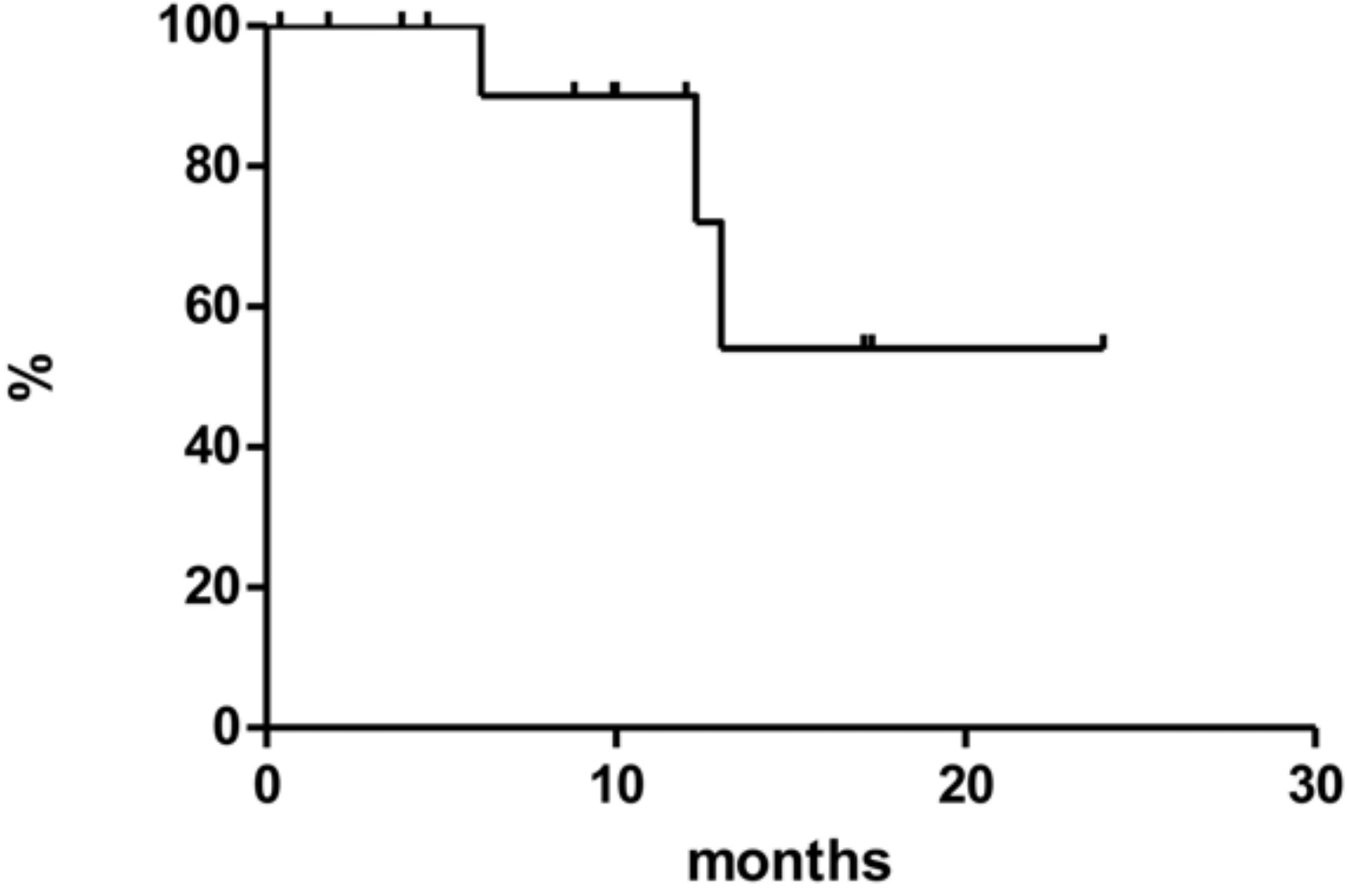
40
months


100
80
60
40
20
0
%
0
10
20
30
months