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**Combination of brentuximab-vedotin and ifosfamide, carboplatin, etoposide (ICE)
in relapsed/refractory peripheral T-cell lymphoma**

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Summary statement. The combination of brentuximab-vedotin with ifosfamide, carboplatin and etoposide (BV-ICE) has not been reported so far for the treatment of relapse or refractory peripheral T cell lymphoma (R/R PTCL). R/R PTCL patients can achieve complete response with this combination, but unfortunately, few had a sustained response. This association should preferably be used as a bridge to stem cell transplant or be followed by maintenance therapy.

Abstract.

Objectives. Relapsed/refractory peripheral T cell-lymphomas (PTCL) have a poor prognosis. We aimed at assessing efficacy of ifosfamide, carboplatin, etoposide (ICE) regimen, a known therapeutic option, to which we added brentuximab-vedotin (BV).

Methods. In this study, we retrospectively analyzed patients with PTCL treated with BV-ICE in our center between July 2014 and March 2018.

Results. Fourteen patients received BV-ICE. Median age was 62 years (range, 31-73). Main histological subtypes were PTCL not otherwise specified (29%), angioimmunoblastic T-cell (21%), follicular-T helper (21%) or anaplastic large-cell (15%) lymphomas, all were CD30 positive. Overall response was seen in four (29%) patients, and complete response (CR) in two (14%). Most frequent adverse events were infections, and cytopenia. Two-year progression-free and overall survival were 14% and 17.5%.

Conclusion. Patients with relapsed/refractory PTCL treated with BV-ICE can achieve CR, but few had a sustained response. This association should preferably be used as a bridge to stem cell transplant or be followed by maintenance therapy.

Keywords: Brentuximab-Vedotin, ICE, peripheral T-cell lymphoma

Introduction.

Peripheral T-cell lymphoma (PTCL) is uncommon and represents approximately 10% to 15% of all non-Hodgkin lymphomas (1). Nodal subtypes, including PTCL-not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL) are the most frequent among Caucasian patients (1). They are a heterogeneous group of lymphomas with an aggressive clinical course. The T-cell phenotype has a negative impact on overall survival (OS), and PTCLs display worse remission and survival rates in comparison with B-cell lymphomas. Patients frequently have advanced stage and extranodal disease at diagnosis, especially with bone marrow and skin involvement. First-line treatment is usually phosphamide, doxorubicin, vincristine, prednisone (CHOP) or CHOP like chemotherapy, sometimes with addition of etoposide (CHOEP); complete response (CR) rate with this regimen is 64%, and 5-year OS is poor (approximately 30%) (2). However, despite these unsatisfactory results, this remains the standard front-line therapy for CD30-negative PTCL, as other chemotherapy regimens do not seem to yield better results (3).

CD30 is a trans-membrane glycoprotein belonging to the tumor necrosis factor receptor superfamily, and is often expressed by T cell lymphomas (4, 5). It can be targeted by brentuximab-vedotin (BV), an antibody-drug conjugate, which combines a CD30 monoclonal antibody with the microtubule-disrupting agent monomethyl auristatin E. The use of BV in combination with phosphamide, doxorubicin, and prednisone (CHP) was recently approved as a new standard of care in patients with previously untreated CD30-expressing PTCL (6), based on the results of the ECHELON-2 study (7). With this combination, median PFS was 48.2 months for patients treated with BV-CHP *versus* 20.8 months for patients treated with CHOP, resulting in a hazard ratio (HR) of 0.71 (95% CI 0.54–0.93). BV-CHP yielded better CR rate (68% *versus* 56%), and ORR (83% *versus* 72%). The trial also demonstrated improvement in OS (HR 0.66; 95% CI: 0.46–0.95); after a median follow-up of 42 months, the median OS was not reached for either group. The 75th percentile OS was not reached for the BV-CHP group and was 17.5 months for HOP group (7).

Relapsed or refractory (R/R) T cell-lymphomas generally have a very poor prognosis (8). In these patients, the median progression-free survival (PFS) is three months and the median OS is only 5.7

months (9). Therapeutic options at relapse include combination chemotherapy regimens such as DHAP (dexamethasone, high dose cytarabine, cisplatin) or ICE (ifosfamide, etoposide, carboplatin). Early consolidation with autologous stem cell transplantation (SCT) in responsive patients can be an option, but this approach is restricted to fit patients with good performance (9), and has a low success rate.

Novel single agents, such as pralatrexate, an antifolate agent, or histone deacetylase inhibitors romidepsin and belinostat can also be used in R/R PTCL. These drugs are able to induce objective responses ranging from 23% to 38% in R/R PTCL, and rare patients achieve durable remissions (10-12). The combination of romidepsin and ICE regimen has also been used for the treatment of relapsed or refractory T-cell (13). With this combination, the overall response rate (ORR) was 93%, 12 (80%) patients achieved CR and nine (50%) patients proceeded to SCT (five allogeneic, four autologous). The median PFS was ten months (95% confidence interval (CI): 1-21 months) and the median OS was 15 months (95% CI: 10-20 months). Other agents, such as alisertib, bendamustine or lenalidomide, have shown efficacy in treating R/R PTCL and can be a therapeutic option after failure of other agents (14-16). The COMPLETE study suggests that treatment with these new agents can allow greater response and survival at first relapse in PTCL patients, while maintaining the ability to achieve transplantation, compared to multidrug chemotherapy (17). However, this non-randomized study included a small and heterogeneous population, which might have included bias in the analysis. We therefore need other approaches to treat these challenging patients.

As mentioned earlier, the use of BV-CHP is a new standard of care in patients with previously untreated CD30-expressing PTCL. Use of combination of targeted agents and chemotherapy, rather than a single-agent, has also been associated with a more favorable outcome in relapsed or refractory PTCL (9). Furthermore, the addition of BV to the ICE regimen is being evaluated prospectively in an on-going study including patients with relapsed or refractory Hodgkin's disease (NCT02227199), with good results and no excessive cumulative toxicity. We chose to evaluate this combination among patients with relapsed/refractory PTCL, as CD30 is often expressed by T-cell lymphomas. In this study, we retrospectively analysed all patients treated with the combination of BV-ICE in the setting of CD30⁺ relapsed/refractory PTCL.

Patients and Methods.

Population. Inclusion criteria were diagnosis of PTCL; treatment with the combination of BV and ICE; age >18 years old. Diagnosis was carried out according to the World Health Organization classification. Expression of CD30 was assessed by immunohistochemical staining, and CD30 positivity was defined by any detectable CD30 expression with this method and quantified either by percentage or semi-quantitative measure of all tumor cells.

otherapy regimens. ICE consisted of ifosfamide IV 5 g/m² on day 1, carboplatin IV with an area under the curve (AUC) of five on day 1, and etoposide IV 100 mg/m² on days 1-3. Cycles were repeated every 21 days. BV was given at a dose of 1.8 mg/kg (maximum dose, 180 mg) as an intravenous infusion over 30 minutes, on day 1 and day 8 of a 21-day treatment cycle. Granulocyte-Colony Stimulating Factor (G-CSF) was used to prevent febrile neutropaenia. All patients were given herpes zoster prophylaxis with valaciclovir and pneumocystis prophylaxis.

Outcome. This is a retrospective, monocentric study. Data collected as part of routine care were retrospectively analysed. Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Response to treatment was assessed with positron emission tomography with 18F-fluorodeoxyglucose after two and four cycles, or earlier according to physicians' judgement.

Statistics. Continuous variables were recorded as median and range. Qualitative variables were recorded as frequency and percent. OS (OS) was defined as the time from BV-ICE chemotherapy initiation to death from any cause; PFS as the time from BV-ICE initiation to relapse or progression or death from any cause, whichever came first. OS, PFS and follow-up were calculated by the Kaplan-Meier method. Baseline statistics were performed using Microsoft Excel v12.2.8 for data analysis, and Graphpad prism software v7.0 for response to treatment and survival analysis.

Ethics. This study was conducted in accordance with the guidelines of the Declaration of Helsinki of 1975, as revised in 2008. No informed consent was required as this study was retrospective. Patients signed a non-opposition form for the use of their clinical data.

Results.

Population. Between July 2014 and March 2018, 14 patients with relapsed or refractory PTCL were treated with BV and ICE at our center. Patients' characteristics are described in **Table 1**. Median age was 62 years (range, 31-73). Most frequent histological subtypes were PTCL-NOS, AITL, follicular-T helper (FTH) lymphoma and ALCL. All patients had positive CD30 immunohistochemical staining, but level of positivity varied among patients (Supp. Table 1). CD30 positivity was high in four (29%) patients, and low or intermediate in seven (50%) patients. Level of positivity was not available in three (21%) patients (Table 1). Most patients had aggressive disease: all except one had Ann-Arbor stage III-IV disease, median International Prognostic Index (IPI) score was two (range, 1–3). Median Eastern Cooperative Oncology Group (ECOG) status was one (range, 0-3). All patients had refractory disease at treatment initiation and had received a median of two therapeutic lines (range, 1-3) before treatment initiation. Median time from diagnosis was 7.7 months [interquartile range IQR, 3.1 – 11.1].

BV-ICE regimen. Median number of cycles of BV-ICE regimen received was one (range, 1-4). Chemotherapy was stopped in 11 patients because of progressive disease (nine patients, 64%) or toxicity (two patients, 14%). Full-dose chemotherapy was administered in seven patients (50%); dose-reduction was decided for the others, because of age, ECOG status and/or comorbidities, according to physician's judgment.

Adverse events. Adverse events (AEs) observed in the BV-ICE cohort are described in **Figure 1**. We observed 28 (68%) grade III-IV AEs and two (5%) grade V AEs, one septic shock and one encephalopathy (status epilepticus). Most frequent AEs were infections (n=15, 37%), and were mostly fever of unknown origin. We also observed cytopenias, mostly anaemia (n=7, 17%) and thrombocytopenia (n=6, 15%). Neutropenia was less frequent (n=3, 7%); G-CSF was systematically used. Haematological toxicity was significant, as 94% of cytopenias were grade III-IV (n=15). We observed three cases of encephalopathy, including one fatal status epilepticus. Only one patient experienced peripheral neuropathy.

Response. Overall response (OR) was seen in four (29%) patients. Two (14%) patients achieved a durable CR, of 29 and 42 months, respectively, as noted in outcomes. Partial response (PR) was seen in two patients. One patient had stable disease. Disease progression was seen in the other

nine patients. To note, among three of these patients, clinical or metabolic response was seen after one or two cycles (two had PR and one had CR) but had then progressive disease.

As indicated in Supp. Table 1, the two patients who achieved CR had better ECOG status, had received fewer treatment lines before BV-ICE; age, comorbidities, Ann-Arbor stage, or chemotherapy dose reduction did not seem to influence the response to BV-ICE. One patient had ALCL, the other had PTCL-NOS; both patients had high CD30⁺ expression (100% of tumor cells) on immunohistochemical staining. Achievement of CR allowed these patients to receive consolidation treatment: one patient received two cycles of BV-ICE, followed by one cycle of BV alone, as a bridge to allogeneic SCT; the other patient received four cycles of BV-ICE followed by maintenance with 11 cycles of BV as a single agent, given every three weeks. Neither of them relapsed at last follow-up.

Outcome. Median follow-up was 29.5 months. Median PFS was 36.5 days. Median OS was 103 days. The two-year PFS and OS were 14% and 17.5%, respectively. Only the two patients who achieved CR remained alive at last follow-up, 29 and 42 months after treatment initiation. Nine (64%) patients died of progressive disease. Three (21%) patients died of other causes, one from cardiogenic shock, and one from status epilepticus; the third patient had progressive disease after one cycle of BV-ICE, underwent salvage chemotherapy and allogeneic SCT, and died from septic shock occurring four months after BV-ICE treatment. Survival data is shown in **Figures 2a and 2b.**

Discussion.

Relapsed or refractory T cell-lymphomas have a very poor prognosis. In our study, the OR for patients treated with BV-ICE was 29%, but only 14% had sustained CR. Median PFS was 36.5 days, and median OS was 103 days.

Data for efficacy of ICE chemotherapy for relapsed or refractory PTCL are scarce; most studies are retrospective, and study populations are heterogeneous, making comparison between studies difficult. A study compared DHAP *versus* ICE among patients with relapsed and/or refractory lymphoma (18). Results were slightly better within the ICE group (n=22), with CR and OR rates of 27% and 68%, respectively, versus 18% and 48% in the DHAP group (n=27). Of note, is that this study included both Hodgkin's disease and non-Hodgkin lymphoma. In another study aimed

at defining the best salvage regimen for patients with refractory or relapsed PTCL, DexaBEAM (dexamethasone, carmustine, etoposide, cytarabine, and melphalan) was compared to ICE, both followed by autologous SCT (19). The OR and CR in the DexaBEAM group were 69% and 38%, respectively, versus 20% and 7% with the ICE regimen. Interestingly, for all patients proceeding to autologous SCT, the 3-year OS was 50 % and was not different irrespective of first-line salvage therapy.

The toxicity profile for the combination of BV and ICE was good in the current study. Few peripheral neuropathies were seen, probably because our patients received a low cumulative dose of BV. Haematological toxicity was significant, but easily manageable in an outpatient setting. Infectious complications, however, were frequent, and need to be carefully monitored and managed.

In our study, we used BV-ICE as a salvage therapy for very advanced patients, all of which had refractory disease at treatment initiation. Two of 14 patients (14%) who achieved CR are alive; one had BV maintenance after induction, and the other one underwent allogeneic SCT. Two (14%) other patients achieved PR, but duration of response was short, and patients rapidly had progressive disease. This underlines that this association should be used as a bridge to either autologous or even allogeneic SCT or be followed by maintenance therapy. Interestingly, we observed that CD30 expression assessed by immunostaining was positive in 100% of the tumor cells for the two patients who achieved CR. This has to be verified on larger series, but this could be a predictor of response to BV-ICE in patients with PTCL. To note, age or comorbidities did not seem to strongly influence response, in our small series of patients.

In conclusion, few patients with R/R PTCL had a sustained response with the combination of BV with ICE chemotherapy, although it appeared safe, with no excessive cumulative toxicities. This regimen might be more efficient in patients with high CD30 expression on immunostaining. Responses were short among our patients, and this combination should be used as a bridge towards autologous or allogeneic SCT in eligible patients, and/or be followed by maintenance therapy, whenever possible.

Using the combination of BV-CHP as first line therapy, according to the ECHELON-2 study, will probably allow more durable responses, along with better OS, in patients with CD30-expressing PTCL. We could therefore expect, in the near future, fewer patients needing salvage therapies; however, relapsed or refractory patients might become less responsive to a second treatment with BV. New approaches and agents will be needed to treat these challenging cases.

nowledgements: none

lict of interests: The authors report no conflict of interest.

Data availability statement. The data that support the findings of this study are available on request from the corresponding author.

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Table 1.
Patients
,
charact
eristics

| Patients' characteristics (n=14) | N (%) | Median (range) or [IQ] |
|---|--------------|-----------------------------------|
| Females, n (%) | 4 (29) | |
| Age, years | - | 62 (31 - 73) |
| rison Comorbidities Index | - | 3 (0 – 6) |
| gnosis, n (%) | | |
| PTCL NOS [†] | 4 (29) | - |
| AITL [†] | 3 (21) | - |
| TH lymphoma [†] | 3 (21) | - |
| ALCL [†] | 2 (15) | - |
| Transformed mycosis fungoides | 1 (7) | - |
| ATLL [†] | 1 (7) | - |
| 30 status, n (%) | | |
| Positive | 14 (100) | - |
| Low | 6 (43) | - |
| Intermediate | 1 (7) | - |
| High | 4 (29) | - |
| Unknown | 3 (21) | - |
| Negative | 0 | - |
| Unknown | 0 | - |
| -Arbor stage, n (%) | | |
| I - II | 1 (7) | - |
| III - IV | 13 (93) | - |
| IPI score [‡] | - | 2 (1 - 3) |
| ECOG [§] status | - | 1 (0 - 3) |
| Previous treatments lines, n | - | 2 (1 - 3) |
| utologous SCT [¶] | - | 1 |
| Allogeneic SCT [¶] | - | 0 |
| Time from diagnosis, months | - | 7.7 [3.1 – 11.1] |

| | | |
|--|-------|-----------|
| Number of cycles received | - | 1 (1 - 4) |
| Treatment received after BV-ICE ^{††} , n (%) | | |
| BV maintenance | 1 (7) | - |
| Autologous SCT [¶] | 1 (7) | - |
| Allogeneic SCT [¶] | 1 (7) | - |
| <p>PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; FTH: follicular-T helper; ALCL: anaplastic large-cell lymphoma; ATLL: adult T-cell leukemia/lymphoma; ‡international prognostic index ; §eastern cooperative oncology group ; ¶ stem cell transplant; ††BV-ICE: brentuximab-vedotin, ifosphamide, etoposide, carboplatin</p> | | |

Figure legends.

Figure 1. Adverse events in patients treated with BV-ICE combination.

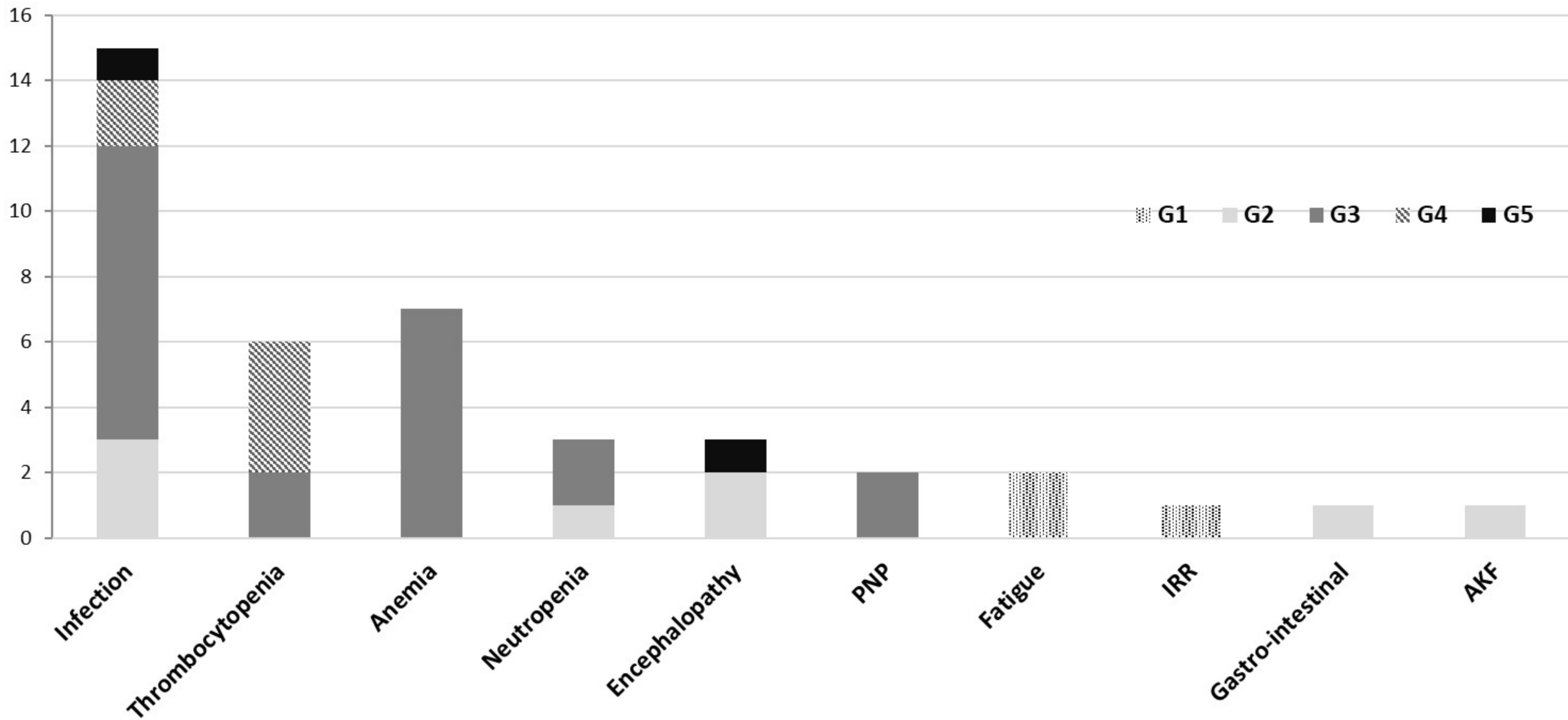
Gx stands for grade, according to CTCAE v5.0. PNP: peripheral neuropathy; IRR: infusion-related reaction; AKF: acute kidney failure

e 2. Survival data

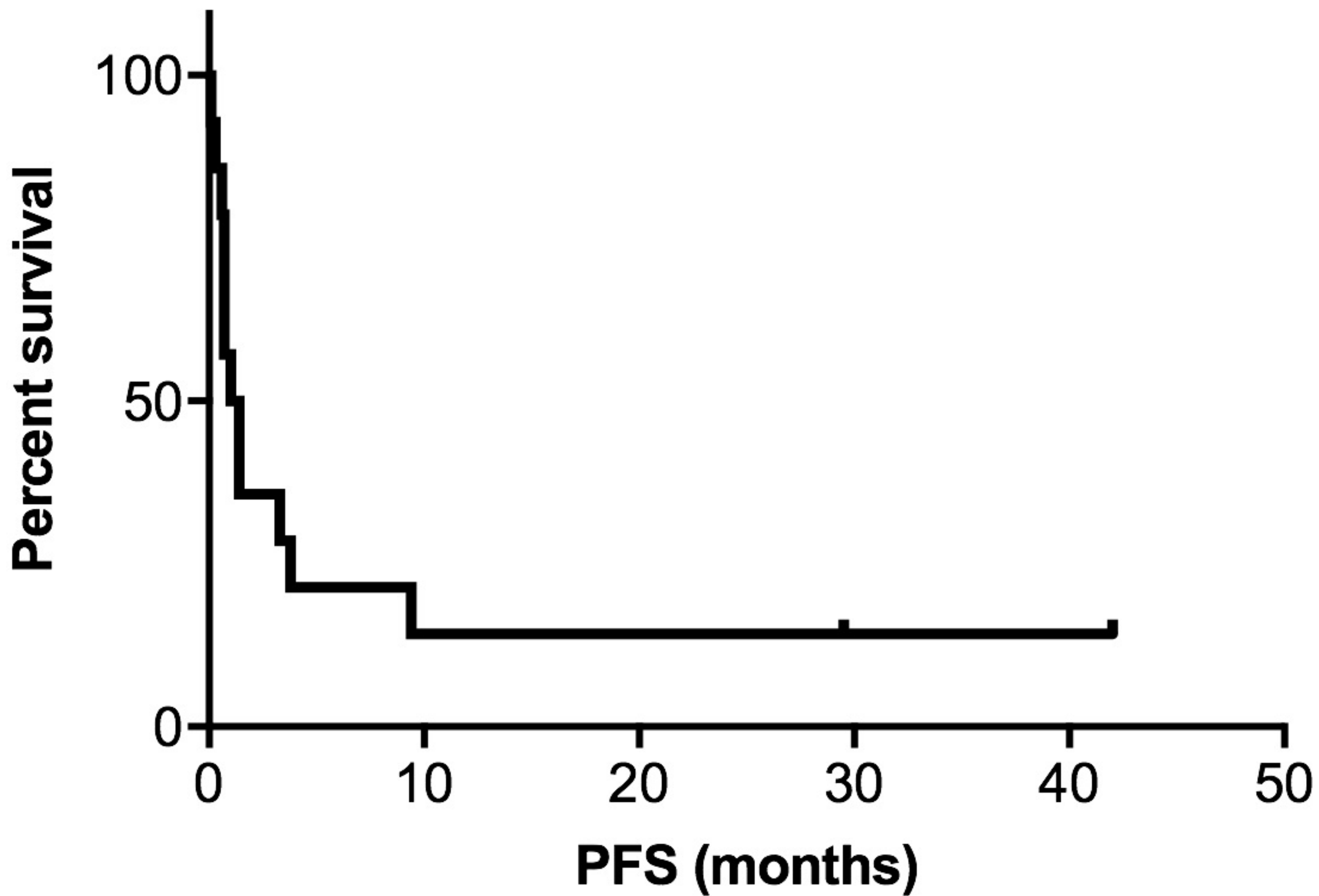
Figure 2a. Progression-free survival

e 2b. Overall survival

Adverse events



Progression-free survival



Overall survival

