Toxicity assessment of concurrent gabapentin/pregabalin administration with high-dose melphalan in autologous hematopoietic cell transplant recipients

Jonathan Angus1 · Aaron Cumpston1,2 · Lauren Veltri2 · Kelly G. Ross2 · Sijin Wen3 · Megan Dillaman1,2✉

Received: 21 April 2021 / Accepted: 21 June 2021 / Published online: 30 June 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract
A theoretical pharmacokinetic interaction mediated through l-amino acid transporter 1 and 2 exists between gabapentin (GP) and pregabalin (PG) with melphalan. Peripheral neuropathy is a common toxicity of various multiple myeloma regimens commonly utilized prior to autologous hematopoietic cell transplant (auto-HCT) with high-dose melphalan (HD-Mel). Therefore, it is likely concurrent administration of either GP or PG will occur in patients receiving HD-Mel conditioning for auto-HCT, which could potentially increase cellular uptake and worsen the mucosal injury. A retrospective chart review of adult patients from January 2012 to July 2016 who received HD-Mel (140–200 mg/m²) at West Virginia University Medicine was performed to assess toxicity and outcomes in these patients. A total of 80 patients were included in the study, with 30 patients receiving GP or PG and 50 control patients. There were no significant differences in grade 2 or higher mucositis, admissions for nausea/vomiting/diarrhea, intravenous opioid requirements, oral topical therapies, antidiarrheal medication use, rescue anti-emetics, days of nausea or vomiting, pain scores, neutrophil or platelet engraftment, treatment-related mortality, progression-free survival, or overall survival. Our data suggest that it is safe to continue GP/PG therapy throughout HD-Mel therapy, with no negative transplant outcomes. Prospective studies or evaluations of larger databases are necessary to better characterize the clinical effect of concomitant therapy.

Keywords Gabapentin · Pregabalin · Melphalan · Autologous hematopoietic cell transplant · Myeloma · Nausea · Vomiting · Mucositis · Neuropathy

Introduction
l-Type amino acid transporter 1 (LAT1) and 2 (LAT2) are responsible for the transportation of large neutral amino acids across the intracellular membrane [1]. These transporters appear to have specific drug-carrying functionality with certain medications, which are structurally similar to amino acids, such as gabapentin (GP), pregabalin (PG), melphalan, levodopa, methyldopa, and baclofen [1, 2]. LAT1 is primarily found in the brain, placenta, certain tumors, and it may also play a role in the transport of molecules into growing cells. LAT2 is primarily found in the kidney, colon, intestine, and may be responsible for the basolateral efflux of molecules (transport in the direction of the lumen to extracellular fluid) [1]. LAT1 overexpression has been documented in various malignancies and is thought to aid in tumor growth, migration, and invasion [3]. In cell-line pharmacokinetic studies, GP significantly inhibited the uptake of amino acids by LAT1 and LAT2 [4]. GP transport into cells has previously been demonstrated to be inhibited by the amino acid l-phenylalanine [2].

Melphalan, a phenylalanine derivative of nitrogen mustard, is an alkylating antineoplastic agent used at high doses as a conditioning agent prior to autologous hematopoietic cell transplantation (auto-HCT) primarily in patients with multiple myeloma [5]. High-dose melphalan (HD-Mel) is associated with significant toxicity including oral mucositis,
nausea, vomiting, and diarrhea [4]. Toxicities can be severe enough to warrant inpatient admission which may increase treatment costs, burden the healthcare system, decrease patient satisfaction, and compromise patient outcomes.

Pharmacokinetic analysis of the interpatient variability in melphalan sensitivity has identified pretreatment hematocrit, fat-free mass, and estimated creatinine clearance as potential sources of this disparity [6, 7]. Uptake of melphalan into cells is primarily mediated by LAT1 and LAT2, which are encoded by the solute carrier family 7 member 5 (SLC7A5) and solute carrier family 7 member 8 (SLC7A8) genes, respectively [8]. A single-nucleotide polymorphism in SLC7A5 (rs4240803) has been shown to have a significant effect on melphalan distribution within the peripheral compartment [7]. SLC7A5 is responsible for melphalan uptake into cells and polymorphisms have previously been shown to be associated with increased toxicity following HD-Mel [7].

Chemotherapy-induced peripheral neuropathy is a common toxicity of multiple myeloma treatment options [9]. GP and PG are anticonvulsant medications useful in the treatment of neuropathic pain due to their ability to bind the neuronal α-2/δ subunits of voltage-gated calcium channels and decrease the transmission of afferent pain signals [10]. It is likely concurrent administration of either GP or PG will occur in patients receiving HD-Mel conditioning for auto-HCT which could theoretically result in changes in cellular uptake, affect mucosal injury, and contribute to other HD-Mel toxicities [8].

Pre-clinical research has demonstrated that L-phenylalanine affects GP transport presumably through competitive inhibition [2]. This finding suggests that GP uptake may be mediated via a L-phenylalanine sensitive transporter. It has previously been demonstrated that a competitive LAT1 inhibitor, 2-amino-2-norbornanecarboxylic acid (BCH), reduced sensitivity to melphalan with simultaneous incubation [11]. Therefore, there is a theoretical concern that co-administration of both melphalan and GP may also lead to competitive inhibition of the agents to their active sites and subsequently lower drug levels of either or both agents. However, it is unknown whether a clinically significant interaction actually does exist. To our knowledge, there are no published studies evaluating possible interactions of GP or PG with HD-Mel, their effect on toxicities, or their impact on clinical outcomes; therefore, it appears that this theoretical interaction is not well known. A drug interaction between the agents is not currently reflected in any product labeling, drug interaction databases, or clinical practice guidelines. In order to further investigate the significance of co-administration of these agents, a retrospective study of patients receiving GP or PG concomitantly with HD-Mel was undertaken to compare outcomes versus a cohort of patients not receiving these agents concurrently.

Materials and methods

Design

A retrospective review of consecutive patients with multiple myeloma undergoing outpatient auto-HCT and conditioning with single-agent HD-Mel at West Virginia University Medicine from January 2012 to July 2016 was conducted. This study was approved by the institutional review board at West Virginia University Medicine. The purpose of this study was to determine if patients receiving concomitant GP or PG had different toxicities and outcomes with HD-Mel compared to patients who were not receiving any additional medication known to interact with LAT1/LAT2.

Patient population

Patients aged ≥18 receiving an outpatient auto-HCT with a melphalan dose of ≥140 mg/m² were included. Exclusion criteria included concomitant use of levodopa, methyldopa, or baclofen, and deviation from the institutional standard anti-emetic regimen of steroids, ondansetron, and fosaprepitant. All patients who met the criteria between January 2012 and July 2016 were included.

For mucositis prophylaxis, patients at our institution are offered cryotherapy for 60 min surrounding melphalan infusion. Following outpatient auto-HCT, patient follow-up was conducted daily for labs, vitals, and nursing assessment with physician visits at least once per week.

Outcome measures

The primary endpoint was the rate of mucositis of any grade documented in patients receiving concomitant GP/PG compared to patients not receiving either medication. The secondary endpoints included hospital admission rate, total parenteral nutrition (TPN) utilization, patient-controlled analgesia initiation, intravenous opioid requirements prior to engraftment (in oral morphine equivalents), use of topical mucosal agents (e.g., lidocaine, ketamine), use of antidiarrheal agents (e.g., atropine/diphenoxylate, loperamide), use of rescue anti-emetics, number of days of nausea documented prior to neutrophil engraftment, number of days of vomiting documented prior to neutrophil engraftment, median daily pain scores, time to neutrophil engraftment, time to platelet-50 engraftment, 30-day treatment-related mortality (TRM), 100-day TRM, progression-free survival (PFS), and overall survival (OS).
**Study definitions**

Use of topical mucosal agents, use of anti diarrheal agents, and use of rescue anti-emetics were defined as and captured by tracking of breakthrough medication orders placed on clinic encounters, inpatient encounters if admitted, and prescriptions sent during the post-transplant period. Topical mucosal agents and anti diarrheal agents were not standardly prescribed in advance of transplant. Ondansetron and prochlorperazine prescriptions were standardly given to all patients prior to the start of conditioning, typically for quantity #30 with refills included. These prescriptions were only included in the analysis if additional supply was needed. Mucositis was graded according to the Common Terminology Criteria for Adverse Events criteria [12]. Neutrophil engraftment was defined as the first of 3 consecutive days to an absolute neutrophil count of > 500 cell/μL after post-transplantation nadir. Platelet-20 and platelet-50 engraftment were defined as the first of 7 consecutive days to platelet count above 20,000 or 50,000 cells/μL, respectively, without platelet transfusion. TRM for the 30- and 100-day benchmarks were assessed in all patients and were defined as death from any cause other than disease progression.

**Statistical analysis**

Descriptive statistics were used for baseline patient characteristics. For continuous variables, such as age, the Wilcoxon rank test was used to assess statistical significance by comparing the whole distribution between the treated and untreated groups without assuming a normal distribution (i.e., distribution free). For binomial categorical variables such as gender, the gender distribution (%) was compared between treated and untreated groups using Fisher’s exact test. For categorical variables with 3 or more levels such as performance status (PS 0 or 1 or 2), the distribution (%) across all three levels was compared between treated and untreated groups also using Fisher’s exact test. A sensitivity analysis was performed and assuming an alpha of 0.05 and a power of 80%, the data set had a minimal detectable effect of a 35% reduction in mucositis occurrence.

**Results**

Eighty patients met the criteria for study inclusion. Baseline demographics are listed in Table 1. Thirty patients received concomitant GP/PG and 50 control patients did not receive any LAT1/LAT2 transported medications in addition to melphalan. There were no significant differences in baseline characteristics between the two groups.

Analysis of the primary endpoint demonstrated there was no significant difference in rates of mucositis. The rates of mucositis between the treated and untreated groups were 59% vs. 52% for grade 1, 24% vs. 19% for grade 2, 7% vs. 10% for grade 3, and 10% vs. 19% with no mucositis (p=0.833) in the GP/PG group vs. the control group, respectively. Mucositis of any grade occurred in 90% of patients in the GP/PG group and 81% of patients in the control group (p=0.5195).

Secondary endpoints showed no significant difference between the two groups. The percentage of patients

| Table 1 Patient demographics                  | GP or PG (n = 30) | GP or PG untreated (n = 50) | P-value |
|-----------------------------------------------|------------------|-----------------------------|---------|
| Age (y), median (range)                       | 60 (34–70)       | 60 (39–74)                  | 0.854   |
| Male gender, n (%)                            | 21 (70)          | 27 (54)                     | 0.238   |
| BMI (kg/m²), median (range)                   | 32 (20.8–46.6)   | 28.9 (20.6–43.9)            | 0.062   |
| Pre-transplant serum creatinine (mg/dL), median (range) | 0.97 (0.68–1.7)  | 0.93 (0.58–2.63)            | 0.758   |
| Melphalan dose 140 mg/m², n (%)               | 5 (17)           | 9 (18)                      | 0.999   |
| Melphalan dose 200 mg/m², n (%)               | 25 (83)          | 41 (82)                     | 0.999   |
| ECOG-PS 0–1 at transplant, n (%)              | 26 (87)          | 41 (82)                     | 0.757   |
| KPS, median (range)                           | 80 (60–100)      | 80 (50–100)                 | 0.269   |
| ≥ VGPR pre-transplant, n (%)                  | 14 (47)          | 17 (34)                     | 0.344   |
| HCT-CI < 3, n (%)                             | 26 (86.7)        | 36 (72)                     | 0.712   |
| Cell dose (CD34+ cells x 10⁶/kg), median (range) | 4.4 (2.1–9.8)    | 4.5 (1.5–9.8)               | 0.515   |
| Mayo Clinic myeloma risk category [13], n (%) |                  |                             |         |
| Standard                                      | 12 (40)          | 16 (32)                     | 0.714   |
| Intermediate                                  | 4 (13.3)         | 7 (14)                      |         |
| High                                          | 5 (16.7)         | 6 (12)                      |         |
| Unknown                                       | 9 (30)           | 21 (42)                     |         |

Abbreviations: BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; KPS, Karnofsky performance status; VGPR, very good partial response; HCT-CI, hematopoietic cell transplantation-comorbidity index.
developing ≥ grade 2 mucositis was 30% in the GP/PG-treated group compared with 40% in the control group \( (p = 0.473) \). The admission rate for nausea/vomiting/diarrhea was found to be 10% in the GP/PG-treated group compared with 18% in the control group \( (p = 0.439) \). Overall, parenteral nutrition utilization was low with no patients in the GP/PG-treated group and one patient (2%) in the untreated group requiring TPN \( (p = 0.999) \). Patient-controlled analgesia usage followed a similar trend with no patients in the GP/PG-treated group and one patient (2%) in the untreated group utilizing a PCA \( (p = 0.999) \). Average intravenous opioid requirements prior to engraftment were similar at 11.2 mg in the PG/PG-treated group and 13 mg in the control group \( (p = 0.849) \). Use of topical mucosal agents did not significantly differ between groups with 27% of patients in the GP/PG-treated group and 28% of patients in the untreated group requiring use \( (p = 0.999) \). Anti-diarrheal agent use between the two groups was not significantly different between groups with 63% in the GP/PG-treated group and 66% in the control group \( (p = 0.814) \). The percentage of patients requiring the use of rescue anti-emetics was similar between the two groups at 80% and 78%, respectively; the median number of rescue anti-emetic doses administered was two in the GP/PG-treated group compared with four in the control group \( (p = 0.999) \). The median number of days of nausea and vomiting documented prior to neutrophil engraftment were 3.5 and 0 vs. 4 and 0 days, respectively \( (p = 0.572 \) and \( p = 0.481) \). Median daily pain scores were similar in the GP/PG-treated group (2 out of 10) to the untreated group (1.25 out of 10, \( p = 0.733) \). Median time to neutrophil engraftment (12 vs 12 days, \( p = 0.511) \), median time to platelet-20 engraftment (15.5 vs 15, \( p = 0.156) \), and median time to platelet-50 engraftment (18 vs 19, \( p = 0.532) \) were not significantly different between treatment groups. Of note, no patients in the GP/PG-treated group and 6% \( (n = 3) \) of patients in the untreated group experienced TRM within 100 days \( (p = 0.288) \), with similar median PFS and OS at 694 vs. 720 days and 906 vs. 993 days, respectively \( (p = 0.540 \) and \( p = 0.58) \) (Figs. 1 and 2).

When the primary and secondary outcomes were stratified by the dose of GP or PG, there were no statistically significant differences between the high-dose group and the low-dose group (Table 2). Low-dose GP/PG was defined as ≤ 900 mg per day and ≤ 150 mg per day, respectively. A high dose was defined as the converse. Seventeen patients were defined as low-dose and 13 patients were defined as high dose.

**Discussion**

This is the first study to our knowledge reviewing the clinical implications of the interaction between GP/PG and HD-Mel. There were no significant differences in primary or secondary outcomes between the two groups, and it appears to be safe to continue GP/PG therapy throughout auto-HCT with HD-Mel. While not significant, we observed a numerical decrease in higher-grade (grade ≥ 2) mucositis, nausea, and vomiting in the GP/PG group. This effect may possibly be related to a decrease in mucosal melphalan concentrations due to the interaction with LAT1/LAT2. Another proposed mechanism may be documented anti-emetic properties of GP and PG, with proven efficacy in the treatment of post-operative nausea and vomiting (PONV) and chemotherapy-induced nausea and vomiting (CINV) [14, 15]. When the primary and secondary outcomes were stratified by the dose of GP or PG, there appeared to be a numerical reduction in the direction of higher doses correlating with lower incidence of mucositis, nausea, vomiting, and pain. These differences did not reach statistical significance, however, and a larger GP/
Table 2  Outcomes stratified by gabapentin/ pregabalin dose

| Result                                      | Low-dose GP/PG1 median or % (range); P-value (n = 17) | High-dose GP/PG median or % (range); P-value (n = 13) | Untreated median or % (range) (n = 50) |
|---------------------------------------------|------------------------------------------------------|------------------------------------------------------|---------------------------------------|
| Highest severity of mucositis               | 1 (0–3); p = 0.285                                   | 1 (0–3); p = 0.066                                   | 1 (1–3)                               |
| Days of nausea                              | 4 (2–11); p = 0.184                                  | 3 (1–8); p = 0.555                                   | 4 (0–16)                              |
| Days of vomiting                            | 0 (0–4); p = 0.719                                   | 0 (0–3); p = 0.502                                   | 0 (0–7)                               |
| Oral morphine equivalents (mg)              | 0 (0–66); p = 0.424                                  | 0 (0–228); p = 0.726                                 | 0 (0–177)                             |
| Use of topical agent                        | 35.3%; p = 0.558                                    | 15.4%; p = 0.486%                                    |                                       |
| Rescue anti-emetic use                      | 82.4%; p = 1.0                                       | 77%; p = 1.0                                          | 78%                                   |
| Number of IV anti-emetic rescue doses       | 2 (0–41); p = 0.826                                  | 2 (0–22); p = 0.204                                  | 4 (0–67)                              |
| Repeat fosaprepitant administration        | 17.6%; p = 1.0                                       | 0%; p = 0.184                                         | 18%                                   |
| Olanzapine administration                   | 11.8%; p = 0.595                                     | 0%; p = 1.0                                           | 6%                                    |
| Daily pain scores (0–10)                    | 0 (0–8); p = 0.992                                  | 4 (0–9); p = 0.465                                   | 1 (0–9)                               |
| Antidiarrheal administration                | 70.6%; p = 0.775                                     | 53.8%; p = 0.522                                       |                                       |
| Time to neutrophil engraftment (days)       | 12 (11–18); p = 0.944                               | 12 (11–14); p = 0.441                                | 12 (10–20)                            |
| Time to Plt-20 engraftment (days)           | 16 (12–25); p = 0.131                                | 15 (12–26); p = 0.271                                 | 13.5 (11–31)                          |
| Time to Plt-50 engraftment (days)           | 19 (14–28); p = 0.478                                | 18 (12–35); p = 0.826                                 | 18 (13–35)                            |
| Progression-free survival (days)            | 706 (188–1769); p = 0.920                           | 537 (76–1748); p = 0.596                             | 720 (14–1898)                         |
| Overall survival (days)                     | 941 (451–1769); p = 0.575                           | 871 (83–1748); p = 0.412                             | 992.5 (14–1898)                       |
| 30-day TRM                                  | 0%; p = 1.0                                          | 0%; p = 1.0                                           | 2%                                    |
| 100-day TRM                                 | 0%; p = 0.565                                        | 0%; p = 1.0                                           | 6%                                    |

Abbreviations: Plt-20, time to reach a transfusion independent platelet level of 20,000; Plt-50, time to reach a transfusion independent platelet level of 50,000; TRM, treatment-related mortality.

1Low-dose GP/PG was defined as ≤ 900 mg per day and ≤ 150 mg per day, respectively.

PG-treated group cohort number may help to clarify the association between dose and outcome measures.

It has been shown that melphalan pharmacokinetics can vary by as much as sixfold between patients based on various characteristics. A study by Kuhne et al. sought to determine if LAT1 and LAT2 polymorphisms could account for this interpatient variability in exposure [16]. Although this study found no difference in kinetics based on LAT1 or LAT2 gene heterogeneity, there was almost no genetic variability in the protein-coding regions, meaning most polymorphisms studied were in the intronic or non-coding gene regions. The variability present in non-coding regions and the melphalan pharmacokinetic differences associated with LAT1 and LAT2 polymorphisms cannot be reliably explained by SNPs occurring in regions with proximity to the LAT1 and LAT2 gene expression promoter sequences because although numerous variants were found, there was no evidence for LAT1 and LAT2 genetic variants affecting the expression of these genes. Both LAT1 and LAT2 have a very low nucleotide diversity in the transporter protein-coding region compared to other human genes, meaning they are functionally important genes [16]. More recently, polymorphisms observed in SLC7A5 and SLC7A8, responsible for encoding LAT1 and LAT2, have been associated with increased TPN dependence after HD-Mel administration, which suggests alterations in LAT1 and LAT2 transport confer significant differences in the degree of mucosal injury experienced by patients receiving HD-Mel [7]. Despite the pharmacokinetic interaction between GP/PG with melphalan, as well as the influence polymorphisms in LAT1 and LAT2 genes have on melphalan toxicity, the co-administration of GP/PG with melphalan during auto-HCT appears to be safe. Data from this analysis suggests co-administration may confer a protective effect in terms of nausea, vomiting, and grade ≥2 mucositis; however, further studies are needed to better understand this effect. The numerically lower PFS and OS seen in the high-dose GP/PG groups could be explained by the presence of relatively worse neuropathy in a more heavily pre-treated group. This could also be related to a decrease in anti-myeloma activity due to the interaction, and further studies should be done to evaluate this parameter.

Limitations of this study included the retrospective design which may have limited the ability to accurately report gastrointestinal adverse events, single-center data, and the relatively small number of patients that were able to be included for analysis. SLC7A5 and SLC7A8 polymorphism testing was not completed for the patient cohort, although polymorphisms could have potentially impacted melphalan exposure. Patients who had not received fosaprepitant prior to HD-Mel were excluded; therefore, the total number of patients included in the analysis was limited to those from 2011 onwards when the administration of fosaprepitant was...
made the standard of care. A prospective observational arm of this study is currently planned in order to more rigorously collect data to assess the incidence of mucositis, nausea, vomiting, diarrhea, and endpoints related to pain.

In conclusion, this study represents the first data exploring the clinical implications of a pharmacokinetic drug-drug interaction with the potential to impact morbidity and mortality in auto-HCT recipients. It appears safe to continue GP/PG therapy throughout HD-Mel therapy with no negative outcomes described at this time. Larger studies, including pharmacokinetic analysis, are necessary to better characterize the clinical implications of concomitant therapy.

**Author contributions** All authors have made substantial contributions to the conception/design of the project, data analysis and interpretation, and manuscript draft and review.

**Data availability** All data and materials comply with standards.

**Code availability** Not applicable.

**Declarations**

**Ethics approval** This study was approved by the institutional review board at West Virginia University Medicine.

**Consent to participate** Not applicable – research was retrospective in nature.

**Consent for publication** All authors grant final approval of the manuscript draft for publication.

**Competing interests** The authors declare no competing interests.

**References**

1. del Amo EM, Urtti A, Yliperttula M (2008) Pharmacokinetic role of L-type amino acid transporters LAT1 and LAT2. Eur J Pharm Sci 35(3):161–174
2. Dickenson D, Webb SD, Antonyuk S, Giannoudis A, Owen A, Rädisch S, Hasnain SS et al (2013) Transport of gabapentin by LAT1 (SLC7A5). Biochem Pharmacol 85(11):1672–1683
3. Shi L, Luo W, Huang W, Huang S, Huang G (2013) Downregulation of L-type amino acid transporter 1 expression inhibits the growth, migration and invasion of gastric cancer cells. Oncol Lett 6(1):106–112
4. Patel M, Dalvi P, Gokulgandhi M, Kesh S, Kohli T, Pal D, Mitra AK (2013) Functional characterization and molecular expression of large neutral amino acid transporter (LAT1) in human prostate cancer cells. Int J Pharm 443(1 2):245–253
5. Shah N, Callander N, Ganguly S, Gul Z, Hamadani M, Costa L et al (2015) Hematopoietic stem cell transplantation for multiple myeloma: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 21(7):1155–1166
6. Nath CE, Shaw PJ, Montgomery K. Earl JW (2007) Population pharmacokinetics of melphalan in paediatric blood or marrow transplant recipients. Br J Clin Pharmacol 64(2):151–164
7. Cho YK, Sborov DW, Lamprecht M, Li J, Wang J, Hade EM et al (2017) Associations of high-dose melphalan pharmacokinetics and outcomes in the setting of a randomized cryotherapy trial. Clin Pharmacol Ther 102(3):511–519
8. Giglia J, White M, Hart A, Toro J, Freytes C, Holt C et al (2014) A single nucleotide polymorphism in SLC7A5 is associated with gastrointestinal toxicity after high-dose melphalan and autologous stem cell transplantation for multiple myeloma. Biol Blood Marrow Transplant 20(7):1014–1020
9. Beijers AJ, Vreugdenhil G, Oerlemans S, Eurelings M, Minnema MC, Eeltink CM et al (2016) Chemotherapy-induced neuropathy in multiple myeloma: influence on quality of life and development of a questionnaire to compose common toxicity criteria grading for use in daily clinical practice. Support Care Cancer 24(6):2411–2420
10. Guttuso TJ Jr (2014) Gabapentin’s anti-nausea and anti-emetic effects: a review. Exp Brain Res 232(8):2535–2539
11. Puris E, Gynther M, Auriola S, Huttunen KM (2020) L-Type amino acid transporter 1 as a target for drug delivery. Pharm Res 37(5):88
12. National Cancer Institute (2010) Common terminology criteria for adverse events (CTCAE), v4.03. National Cancer Institute, Bethesda
13. Mikhail JR, Dingli D, Roy V et al (2013) Management of newly diagnosed symptomatic multiple myeloma: updated mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc 88(4):360–376
14. Cruz FM, de Iraciema Gomes Cubero D, Taranto P, Lerner T, Lera AT, da Costa Miranda M et al (2012) Gabapentin for the prevention of chemotherapy-induced nausea and vomiting: a pilot study. Support Care Cancer 20(3):601–606
15. Tiippanova EM, Hamunen K, Kontinen VK, Kalso E (2007) Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg 104(6):1545–1556
16. Kuhne A, Kaiser R, Schirmer M, Heider U, Muhlke S, Niere W et al (2007) Genetic polymorphisms in the amino acid transporters LAT1 and LAT2 in relation to the pharmacokinetics and side effects of melphalan. Pharmacogenet Genomics 17(7):505–517

**Publisher’s note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.