THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 14 Issue 4

REVIEW ARTICLE

Keeping in Mind the Fluoropyrimidine-Induced Neurotoxicity: A Critical Review of an Underrecognized Cause of Encephalopathy in Oncology Practice.

Otávio Manfrinati Petroni[1], Joslaine Merlini Coelho[1], Daniella Yumi Tsuji Honda[1], José Écio Batista Rosado Junior[1], Mauro Daniel Spina Donadio[1]

[1]Centro Paulista de Oncologia-Oncoclinicas - São Paulo, Brazil

OPEN ACCESS

PUBLISHED
30 April 2026

CITATION
Petroni, OM., Coelho, JM., et al., 2026. Keeping in Mind the Fluoropyrimidine-Induced Neurotoxicity: A Critical Review of an Underrecognized Cause of Encephalopathy in Oncology Practice. Medical Research Archives, [online] 14(4).

ISSN
2375-1924

ABSTRACT

Background: Chemotherapy-induced encephalopathy is an uncommon but clinically relevant complication of antineoplastic therapy, characterized by heterogeneous and often nonspecific neurological manifestations. Fluoropyrimidine-induced encephalopathy is particularly challenging due to its variable incidence, unclear pathophysiology, and absence of standardized diagnostic and management strategies.

Methods: We performed a narrative review of the literature, including case reports, retrospective studies, and selected clinical data addressing clinical features, pathophysiology, diagnosis, and management of chemotherapy-related encephalopathy, with emphasis on fluoropyrimidines.

Results: Clinical presentation ranges from mild cognitive impairment to seizures and coma, frequently overlapping with metabolic, infectious, toxic, and paraneoplastic conditions, requiring a diagnosis of exclusion. Neuroimaging and comprehensive laboratory evaluation are essential, although no specific diagnostic criteria exist. Hyperammonemia is commonly observed but not universal. Proposed mechanisms include urea cycle disruption and thiamine deficiency, with additional contributions from patient-related factors such as renal dysfunction, malnutrition, and pharmacogenetic variability, particularly involving DPYD. Management is largely empirical and centers on prompt discontinuation of the offending agent and supportive care. Evidence supporting adjunctive therapies, including ammonia-lowering strategies, corticosteroids, and uridine triacetate, remains limited. Rechallenge may be feasible in selected cases but carries a risk of recurrence.

Conclusions: Fluoropyrimidine-induced encephalopathy is a rare but potentially reversible condition that requires a high index of suspicion for timely diagnosis. The lack of high-quality evidence underscores the need for prospective studies and standardized approaches to improve recognition, risk stratification, and management.

Keywords: fluoropyrimidine; adverse events; neurotoxicity, encephalopathy

Introduction

Neurological complications related to medication use represent a clinically significant and often underrecognized source of morbidity, particularly in patients exposed to polypharmacy or agents with central nervous system activity.[1,2] Clinical manifestations are heterogeneous, ranging from mild cognitive impairment and disorientation to seizures, coma, and fulminant encephalopathy. These effects may arise from direct neurotoxicity, drug-induced metabolic derangements (eg, electrolyte imbalance, hepatic dysfunction), or pharmacologic interactions that amplify central nervous system depression or excitability.[1.2] Vulnerable populations—including older adults and patients with underlying neurological or hepatic disease—are disproportionately affected.[1-3] Importantly, delayed recognition is consistently associated with worse clinical outcomes, including prolonged hospitalization and increased mortality, underscoring the need for heightened clinical vigilance and systematic monitoring.[1-3]

Antineoplastic therapies are increasingly recognized as important contributors to central nervous system toxicity, with presentations spanning acute, subacute, and delayed syndromes.[4,5] These may manifest as altered mental status, seizures, behavioral changes, or focal neurological deficits, often in the absence of specific diagnostic markers.[4,5] The nonspecific nature of these presentations necessitates a diagnosis of exclusion, grounded in careful clinical assessment, targeted neuroimaging, and systematic evaluation of competing etiologies. Timely identification is critical, as continued exposure to the offending agent may result in irreversible neurological injury.[5]

The neurotoxicity profiles of established chemotherapeutic agents—including ifosfamide, vincristine, cisplatin, methotrexate, and paclitaxel—are well documented, although their pathophysiology remains incompletely understood.[6] Proposed mechanisms include direct neuronal injury, mitochondrial dysfunction, oxidative stress, and metabolic disturbances such as hyperammonemia.[7] Despite this, the clinical spectrum and predictors of toxicity remain poorly defined, limiting risk stratification in routine practice.

Oxaliplatin-associated neurotoxicity has been extensively characterized in the context of cumulative peripheral neuropathy; however, central nervous system complications, including encephalopathy, remain exceedingly rare and are largely confined to isolated case reports.[8,9] Similarly, hyperammonemic encephalopathy related to oxaliplatin has been only sporadically described, raising the possibility of underrecognition rather than true rarity.[7]

Fluoropyrimidine-induced neurotoxicity, although uncommon, is increasingly reported, with estimated incidence rates ranging from 2% to 4%.[10] Notably, higher rates have been observed in specific treatment regimens, with one study reporting encephalopathy in 5.57% of patients receiving continuous 5-fluorouracil infusion in combination with leucovorin, all of whom exhibited hyperammonemia and lactic acidosis.[11] Given the widespread use of fluoropyrimidines—affecting more than 2 million patients annually—even infrequent toxicities translate into a substantial absolute burden of disease.[12]

Despite its clinical relevance, fluoropyrimidine-induced encephalopathy remains poorly characterized, with evidence largely limited to case reports and small series. The absence of standardized diagnostic criteria and evidence-based management strategies represents a critical gap in the literature and poses a significant challenge to optimal oncologic care. This review

aims to critically appraise the current evidence, delineate the clinicopathological features, and highlight key diagnostic and therapeutic considerations, with the goal of improving recognition and management of this potentially reversible but often overlooked complication.

Clinical presentation and physiopathology

Although neurotoxicity is a well-recognized adverse effect of antineoplastic therapy, encephalopathy remains an uncommon and likely underrecognized manifestation, with incidence varying according to the therapeutic regimen.[5,13] Both clinical presentation and underlying mechanisms are highly heterogeneous, reflecting agent-specific toxic profiles that range from direct neurotoxicity to systemic metabolic derangements. Consequently, manifestations span a broad spectrum, from subtle cognitive impairment to seizures, focal neurological deficits, and profound alterations in consciousness.[5]

Certain agents with well-established central nervous system toxicity profiles—such as methotrexate—have been extensively characterized, resulting in heightened clinical awareness and earlier recognition of complications, including acute and transient focal neurological deficits.[5] In contrast, fluoropyrimidine-induced encephalopathy remains less frequently recognized, with reported incidence rates ranging from 0.1% to 5.7%, likely reflecting both true rarity and diagnostic underestimation.[11,14]

Clinically, fluoropyrimidine-related encephalopathy most often presents as toxic leukoencephalopathy, a white matter disorder characterized by ataxia, agitation, altered consciousness, seizures, and, in severe cases, coma. Symptom onset typically occurs during or within days of drug administration, although delayed presentations have been described.[14,15] While risk may be higher during initial exposure, toxicity can occur at any stage of treatment.[14] Hyperammonemia is a frequent laboratory finding, although not universal; notably, while associated with increased intensive care unit utilization, it has not been consistently linked to increased mortality, underscoring the complex and incompletely understood clinical trajectory of this condition.[16]

The pathophysiology of fluoropyrimidine-induced encephalopathy remains incompletely elucidated. One prevailing hypothesis implicates disruption of the urea cycle mediated by fluoroacetate, a metabolite of 5-fluorouracil (5-FU), leading to impaired ammonia clearance and subsequent neurotoxicity.[14,17,18] An alternative and not mutually exclusive mechanism involves increased thiamine metabolism induced by 5-FU, resulting in functional thiamine deficiency and clinical features resembling Wernicke–Korsakoff syndrome, including ataxia, nystagmus, and cognitive impairment.[19] The coexistence of these mechanisms likely contributes to the heterogeneity of clinical presentations.

Emerging evidence from retrospective studies and case series suggests that clinical vulnerability is modulated by patient-specific factors, including dehydration, renal dysfunction, infection, sarcopenia, and malnutrition, which may exacerbate both systemic exposure and metabolic susceptibility.[14,18] Additionally, higher drug doses and conditions that prolong drug half-life or increase metabolite accumulation—particularly enzymatic deficiencies—are associated with greater neurotoxicity.[14]

Among fluoropyrimidines, 5-FU remains the most widely used agent, functioning as a prodrug that undergoes intracellular conversion to active metabolites that inhibit thymidylate synthase and disrupt DNA synthesis, ultimately inducing apoptosis.[20] Capecitabine, the second most commonly used fluoropyrimidine, undergoes enzymatic conversion to 5-FU via cytidine

deaminase and related pathways, thereby sharing similar metabolic and toxicity profiles.[21]

Pharmacogenetic variability plays a critical role in modulating toxicity risk. Although polymorphisms in genes such as *CDA* and *TYMS* have been associated with increased fluoropyrimidine toxicity, their clinical impact is less consistently defined.[22,23] In contrast, variants in the *DPYD* gene—encoding dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme responsible for approximately 80% of 5-FU catabolism—are the most clinically relevant determinants of severe toxicity.[24] Reduced DPD activity has been reported in up to 39% to 61% of patients experiencing severe or life-threatening adverse events.[25] The *DPYD* locus is highly polymorphic, and while many variants are functionally neutral, specific allelic alterations may result in partial or complete loss of enzymatic activity.[26] Importantly, the phenotypic impact depends on the combined effect of both alleles, with compound heterozygosity further complicating risk prediction.[27]

Given the potentially severe and preventable nature of fluoropyrimidine toxicity, pre-treatment *DPYD* genotyping has been increasingly incorporated into clinical practice guidelines.[28,29] However, the distribution of clinically relevant variants varies significantly across populations. In highly admixed populations, such as in Brazil, variants including c.557A>G, c.1129-5923C>G/A (hapB3), c.1905+1G>A/C (DPYD*2A), and c.2846A>T collectively occur in approximately 2.4% of individuals.[30,31] In contrast, studies in European populations report partial DPD deficiency in 3% to 15% and complete deficiency in up to 0.5% of individuals. Notably, in a retrospective cohort of patients with fluoropyrimidine-induced encephalopathy, the prevalence of any degree of DPD deficiency reached 27%, supporting a mechanistic link between impaired drug metabolism and neurotoxicity.[16]

Diagnoses and differential diagnoses

Fluoropyrimidine-induced encephalopathy remains a poorly defined entity, lacking standardized diagnostic criteria and relying largely on clinical suspicion. While drug exposure is a necessary condition, the temporal relationship between administration and symptom onset is variable, ranging from during infusion to up to 21 days post-exposure, as reported in retrospective cohorts and case series.[14,16] The clinical presentation is typically nonspecific, necessitating a diagnosis of exclusion. Given that manifestations may include focal neurological deficits or global alterations in consciousness, neuroimaging—preferably magnetic resonance imaging (MRI)—is essential to exclude structural or alternative causes.[14-16,32]

The differential diagnosis is broad and requires systematic evaluation for competing toxic-metabolic and infectious etiologies (Table 1). Comprehensive laboratory assessment, including electrolyte panels, hepatic and renal function tests, and infectious workup, is critical. Although hyperammonemia is a frequently observed finding, it is neither sensitive nor specific and should not be considered diagnostic in isolation.[9,16,32] A detailed exposure history is equally important, encompassing concomitant medications, recreational or illicit substances, and potential environmental toxins, all of which may contribute to or mimic the clinical picture.[33]

Paraneoplastic neurologic syndromes represent an additional and often challenging diagnostic consideration. These heterogeneous disorders may involve the central nervous system (eg, limbic encephalitis and paraneoplastic cerebellar degeneration), the neuromuscular junction (eg, Lambert–Eaton myasthenic syndrome and myasthenia gravis), or the peripheral nervous system (eg, autonomic and subacute sensory neuropathies).[34] Importantly, a substantial

proportion of these syndromes occur in the absence of an underlying malignancy, limiting their specificity as cancer-related complications: more than 70% of limbic encephalitis and subacute sensory neuropathy cases, approximately 50% of subacute cerebellar ataxia, and 40% of Lambert–Eaton myasthenic syndrome cases are non-paraneoplastic.[35] Accordingly, their diagnosis requires a multimodal approach integrating neuroimaging, serologic testing for onconeural antibodies, electroencephalography, nerve conduction studies, electromyography, and cerebrospinal fluid analysis to identify inflammatory or immune-mediated processes.[34]

Taken together, the absence of specific biomarkers or diagnostic criteria, combined with the broad and overlapping differential diagnosis, underscores the need for a structured and systematic approach to evaluation. Failure to adequately exclude alternative etiologies may lead to misdiagnosis, inappropriate management, and potentially avoidable morbidity.

Table 1. Main differential diagnosis of chemotherapy-induced neurotoxicity.

Differential diagnosis	Main clinical features	Diagnostic approach
Toxic-metabolic disorders (general) (9,32)	Altered level of consciousness, confusion, possible progression to coma; often associated with systemic disturbances	Comprehensive laboratory evaluation (electrolytes, renal/hepatic function, infectious markers)
Hyperammonemia associated with chemotherapy (e.g., 5-FU) (9,16)	Confusion, lethargy, acute encephalopathy; may coexist with lactic acidosis	Serum ammonia measurement; metabolic workup
Infectious encephalopathy / encephalitis (36)	Fever, altered mental status, seizures, focal deficits; higher risk in immunosuppressed patients	CSF analysis (cell count, protein, glucose, antibodies), blood cultures, neuroimaging (MRI/CT)
Exogenous intoxication (accidental or intentional) (33)	Nonspecific neurological symptoms (dizziness, dysarthria, altered consciousness); possible exposure history	Detailed clinical history; toxicological screening; neuroimaging in selected cases
Concomitant substance use (medications, illicit drugs, environmental exposures) (33)	Overlapping neurological manifestations; variable clinical presentation	Medication review; toxicology screening
Paraneoplastic neurologic syndromes (PNS) (34)	May involve CNS (e.g., limbic encephalitis), neuromuscular junction (e.g., Lambert–Eaton myasthenic syndrome, myasthenia gravis), or peripheral nervous system; typically subacute course	Neuroimaging, serologic testing (onconeural antibodies), EEG, nerve conduction studies, electromyography, CSF analysis

Non-paraneoplastic forms of PNS (35)	High proportion without underlying malignancy; clinical presentation similar to paraneoplastic forms	Exclusion of malignancy; comprehensive neurologic evaluation

PNS: paraneoplastic neurologic syndromes; MRI: magnetic resonance imaging; CT: computed tomography; CNS: central nervous system; EEG: electroencephalography; CSF: cerebrospinal fluid

Initial management and treatment

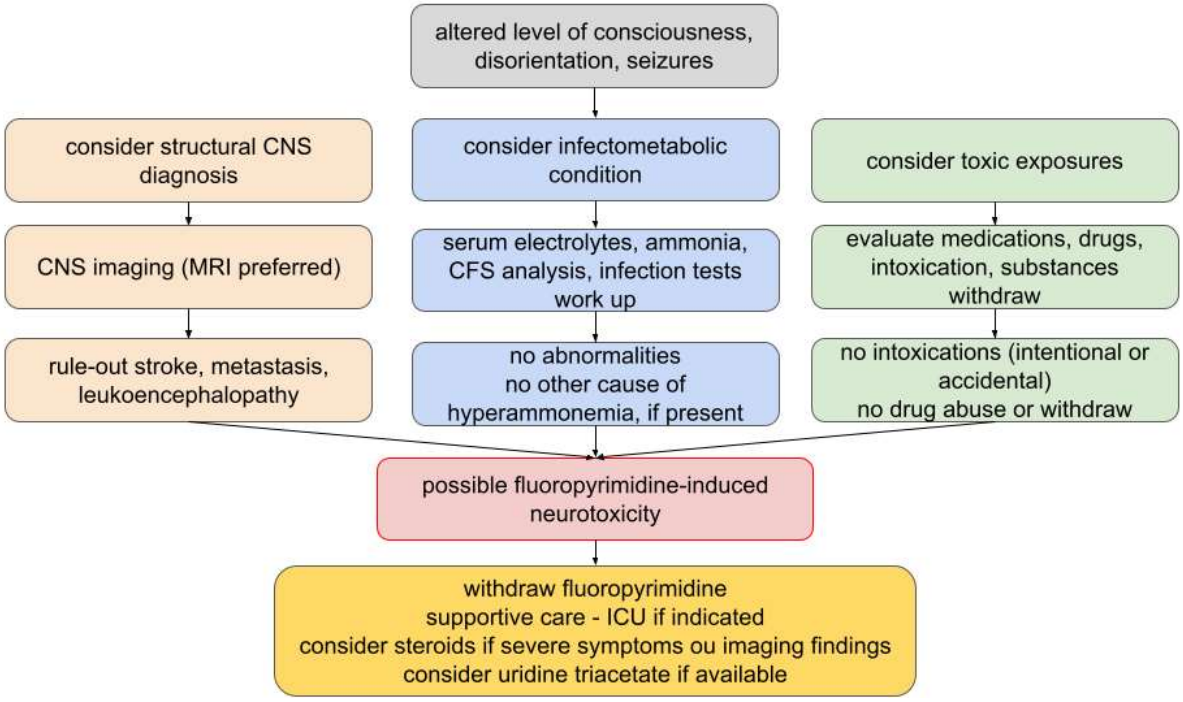
The management of antineoplastic therapy–induced encephalopathy is highly heterogeneous and largely dictated by the causative agent, reflecting the absence of unified therapeutic frameworks. While certain toxicities warrant targeted interventions—such as methylene blue in ifosfamide-induced encephalopathy—most cases rely predominantly on supportive care, underscoring the variability and, in many instances, empiricism of current practice.[37] In the presence of hyperammonemia, ammonia-lowering strategies may be implemented; however, the evidence supporting their clinical efficacy remains limited and inconsistent.[15,32]

For fluoropyrimidine-induced encephalopathy, the lack of mechanistic clarity has translated into an absence of standardized, evidence-based treatment strategies. Prompt discontinuation of the offending agent remains the cornerstone of management and is frequently associated with clinical improvement, particularly when instituted early.[16] Beyond this, therapeutic approaches are largely extrapolated from small case series and anecdotal experience. Corticosteroids have been proposed as a potential option in severe cases, particularly in the presence of significant neuroimaging abnormalities, although supporting data are sparse and uncontrolled.[38]

Uridine triacetate, an approved antidote for severe fluoropyrimidine toxicity related to impaired drug metabolism—particularly in the context of pathogenic *DPYD* variants—represents a biologically plausible intervention. However, its role in the management of neurotoxicity specifically remains ill-defined. Clinical use is further constrained by limited availability, high cost, and a narrow therapeutic window, as efficacy is contingent upon early administration.[39,40] Moreover, robust data supporting its benefit in encephalopathy are lacking, precluding routine recommendation.

Overall, current management strategies are characterized by a reliance on supportive care and expert opinion rather than high-quality evidence. This therapeutic uncertainty highlights a critical unmet need for prospective studies and standardized treatment algorithms to guide clinical decision-making. An initial diagnostic and management approach for suspected cases is outlined in Figure 1.

Fig. 1 Fluxogram for diagnosis and initial management of suspected fluoropyrimidyne-induced encephalopathy.



CNS: central nervous system; MRI: magnetic resonance imaging; ICU: intensive care unit

Data on rechallenge following fluoropyrimidine-induced encephalopathy remain limited and inconsistent. Small cohort studies have reported recurrence rates of up to 57% upon re-exposure to the offending agent, whereas other series describe successful re-administration without subsequent neurological complications, highlighting substantial variability in clinical outcomes.[16,38] This heterogeneity likely reflects differences in patient susceptibility, underlying metabolic capacity, and treatment-related factors.

Notably, recurrence appears to be more frequent in patients re-exposed to equivalent or higher doses, suggesting a dose-dependent component to neurotoxicity.[16] However, the absence of prospective data and standardized rechallenge protocols precludes reliable risk stratification. Consequently, decisions regarding treatment reintroduction must be individualized, balancing oncologic benefit against the risk of recurrent neurotoxicity.

When rechallenge is considered, a cautious approach is warranted, typically involving dose reduction, close clinical monitoring, and, where feasible, correction of modifiable risk factors. Even under these conditions, the safety of re-exposure remains uncertain, underscoring the need for more robust evidence to inform clinical practice.

Discussion

Fluoropyrimidine-induced encephalopathy exemplifies these challenges. Although uncommon, its true incidence is likely underestimated, particularly in the context of widespread fluoropyrimidine use. The variability in reported rates, clinical manifestations, and outcomes reflects not only biological heterogeneity but also inconsistencies in recognition and reporting. Importantly, the overlap with more common conditions—such as metabolic derangements, infections, drug interactions, and paraneoplastic syndromes—necessitates a structured and systematic diagnostic approach. Failure to adequately exclude these competing diagnoses may

result in both over- and underdiagnosis, with direct implications for patient safety and oncologic decision-making.

From a mechanistic standpoint, the current understanding remains incomplete and likely multifactorial. Proposed pathways—including hyperammonemia related to urea cycle disruption and thiamine depletion—offer plausible explanations but do not fully account for the diversity of clinical presentations. The contribution of patient-specific vulnerability factors, such as renal dysfunction, malnutrition, and sarcopenia, further complicates this landscape. In this context, pharmacogenetic variability, particularly involving *DPYD*, emerges as one of the most clinically actionable determinants of toxicity risk. However, even this association does not fully explain the occurrence of encephalopathy, suggesting that additional, yet unidentified, modifiers are involved.

Therapeutically, the field remains constrained by a lack of prospective data and standardized management strategies. Drug discontinuation and supportive care continue to represent the cornerstone of treatment, reflecting a reactive rather than proactive approach. While interventions such as ammonia-lowering therapies, corticosteroids, and uridine triacetate have been proposed, their use is supported primarily by low-level evidence, and their efficacy in this specific context remains uncertain. Similarly, decisions regarding treatment rechallenge are based on limited and conflicting data, requiring individualized risk–benefit assessment in the absence of validated predictive models.

These limitations underscore several critical priorities for future research. First, there is a need for prospective, systematically collected data to better define the incidence, clinical spectrum, and outcomes of fluoropyrimidine-induced encephalopathy. Second, the development of standardized diagnostic criteria and clinical algorithms would improve recognition and reduce diagnostic variability. Finally, integration of clinical, metabolic, and pharmacogenetic data may enable more accurate risk stratification and, ultimately, personalized treatment approaches.

In conclusion, fluoropyrimidine-induced encephalopathy remains a rare but clinically meaningful complication with significant implications for patient safety and treatment continuity. Its diagnosis requires a high index of suspicion and systematic exclusion of alternative etiologies, while management remains largely supportive. Bridging the current evidence gap will require coordinated efforts to standardize definitions, improve reporting, and generate high-quality data to inform both prevention and treatment strategies.

Acknowledgments

Funding:

None.

Conflicts of Interest:

The authors have no conflicts of interest to declare.

Ethical Statement:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. Br J Clin Pharmacol. 2011;72(3):381-393. doi:10.1111/j.1365-2125.2011.03991.x

2. Fugate JE, Rabinstein AA. Central nervous system complications of chemotherapy. Neurol Clin. 2011;29(1):209-221. doi:10.1016/j.ncl.2010.10.005

3. Marcum ZA, Hanlon JT. Recognizing the risks of chronic medication use in older adults: polypharmacy and adverse drug events. Clin Geriatr Med. 2012;28(2):173-186. doi:10.1016/j.cger.2012.01.004

4. Lim YJ, Kim HJ, Lee YJ, et al. Clinical features of encephalopathy in children with cancer requiring cranial magnetic resonance imaging. Pediatr Neurol. 2011;44(6):433-438. doi:10.1016/j.pediatrneurol.2011.01.007

5. Kim HG, Rashid MA, Poleschuk M, et al. Cognitive dysfunction in chemobrain. Biomed Pharmacother. 2025;192:118581. doi:10.1016/j.biopha.2025.118581

6. Pirzada NA, Ali II, Dafer RM. Fluorouracil-induced neurotoxicity. Ann Pharmacother. 2000;34(1):35-38. doi:10.1345/aph.18425

7. Magge RS, DeAngelis LM. The double-edged sword: neurotoxicity of chemotherapy. Blood Rev. 2015;29(2):93-100. doi:10.1016/j.blre.2014.09.012

8. Brandes AA, Schiff D, Wen PY, eds. Cancer Neurology in Clinical Practice. Ann Oncol. 2003;14(5):809. doi:10.1093/annonc/mdg205

9. Yeh KH, Cheng AL. High-dose 5-fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. Br J Cancer. 1997;75(3):464-465. doi:10.1038/bjc.1997.79

10. Branca JJV, Carrino D, Gulisano M, et al. Oxaliplatin-induced neuropathy: genetic and epigenetic profile to better understand how to ameliorate this side effect. Front Mol Biosci. 2021;8:643824. doi:10.3389/fmolb.2021.643824

11. Ogata T, Satake H, Ogata M, et al. Oxaliplatin-induced hyperammonemic encephalopathy in a patient with metastatic pancreatic cancer: a case report. Case Rep Oncol. 2017;10(3):885-889. doi:10.1159/000481398

12. Scrip's Cancer Chemotherapy Report. Scrip World Pharm News. London, UK: PJB Publications Ltd; 2002.

13. Was H, Borkowska A, Bagues A, et al. Mechanisms of chemotherapy-induced neurotoxicity. Front Pharmacol. 2022;13:750507. doi:10.3389/fphar.2022.750507

14. Mitani S, Kadowaki S, Komori A, et al. Acute hyperammonemic encephalopathy after fluoropyrimidine-based chemotherapy: a case series and review of the literature. Medicine (Baltimore). 2017;96(22):e6874. doi:10.1097/MD.0000000000006874

15. Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. N Engl J Med. 2001;345(6):425-432. doi:10.1056/NEJM200108093450606

16. Boilève A, Thomas L, Lillo-Le Louët A, et al. 5-Fluorouracil-induced hyperammonaemic encephalopathy: a French national survey. Eur J Cancer. 2020;129:32-40. doi:10.1016/j.ejca.2020.01.019

17. Koenig H, Patel A. Biochemical basis for fluorouracil neurotoxicity: the role of Krebs cycle inhibition by fluoroacetate. Arch Neurol. 1970;23(2):155-160. doi:10.1001/archneur.1970.00480260061008

18. Liaw CC, Wang HM, Wang CH, et al. Risk of transient hyperammonemic encephalopathy in cancer patients receiving continuous infusion of 5-fluorouracil. Anticancer Drugs. 1999;10(3):275-281. doi:10.1097/00001813-199903000-00004

19. Heier MS, Dornish JM. Effect of fluoropyrimidines on cellular uptake of thiamine. Anticancer Res. 1989;9(4):1073-1077

20. Miura K, Kinouchi M, Ishida K, et al. 5-FU metabolism in cancer and orally administrable 5-FU drugs. Cancers (Basel). 2010;2(3):1717-1730. doi:10.3390/cancers2031717

21. Thorn CF, Marsh S, Carrillo MW, et al. PharmGKB summary: fluoropyrimidine pathways. Pharmacogenet Genomics. 2011;21(4):237-242. doi:10.1097/FPC.0b013e32833c6107

22. Loganayagam A, Arenas-Hernandez M, Corrigan A, et al. Pharmacogenetic variants predicting fluoropyrimidine toxicity. Br J Cancer. 2013;108(12):2505-2515. doi:10.1038/bjc.2013.262

23. Frances A, Cordelier P. Emerging role of cytidine deaminase in human disease. Mol Ther. 2020;28(2):357-366. doi:10.1016/j.ymthe.2019.11.026

24. Diasio RB, Harris BE. Clinical pharmacology of 5-fluorouracil. Clin Pharmacokinet. 1989;16(4):215-237. doi:10.2165/00003088-198916040-00002

25. Meulendijks D, Henricks LM, Jacobs BAW, et al. Pretreatment uracil as predictor of fluoropyrimidine toxicity. Br J Cancer. 2017;116(11):1415-1424. doi:10.1038/bjc.2017.94

26. Amstutz U, Froehlich TK, Largiadèr CR. DPD as predictor of 5-FU toxicity. Pharmacogenomics. 2011;12(9):1321-1336. doi:10.2217/pgs.11.72

27. Lunenburg CATC, van der Wouden CH, Nijenhuis M, et al. DPYD guideline. Eur J Hum Genet. 2020;28(4):508-517. doi:10.1038/s41431-019-0540-0

28. Caudle KE, Thorn CF, Klein TE, et al. CPIC guideline for DPYD. Clin Pharmacol Ther. 2013;94(6):640-645. doi:10.1038/clpt.2013.172

29. European Medicines Agency. Fluorouracil-related substances recommendations. EMA/125891/2020. Published March 13, 2020.

30. ABraOM – Arquivo Brasileiro Online de Mutações. Repositório público de variantes genômicas de brasileiros idosos (SABE-WGS-1171, SABE-609-WES). Universidade de São Paulo; 2019-. Accessed June 26, 2025. https://abraom.ib.usp.br

31. Donadio MDS, Carraro DM, Torrezan GT, et al. DPD polymorphisms. Ecancermedicalscience. 2022;16:1344. doi:10.3332/ecancer.2022.1344

32. Boilève A, Osman D, Marthey L, et al. Drug-induced coma after chemotherapy. J Neurol Sci. 2018;392:137-138. doi:10.1016/j.jns.2018.07.015

33. Li Q, Yu W, Qu Y, et al. Acute toxic encephalopathy following bromadiolone intoxication. BMC Neurol. 2021;21(1):8. doi:10.1186/s12883-020-02034-2

34. Pelosof LC, Gerber DE. Paraneoplastic syndromes. Mayo Clin Proc. 2010;85(9):838-854. doi:10.4065/mcp.2010.0099

35. Honnorat J, Antoine JC. Paraneoplastic neurological syndromes. Orphanet J Rare Dis. 2007;2:22.

36. Tunkel AR, Glaser CA, Bloch KC, et al. Management of encephalitis. Clin Infect Dis. 2008;47(3):303-327. doi:10.1086/589747

37. Verstappen CC, Heimans JJ, Hoekman K, et al. Neurotoxic complications of chemotherapy. Drugs. 2003;63(15):1549-1563. doi:10.2165/00003495-200363150-00003

38. Jose N, Joel A, Selvakumar RJ, et al. 5-FU-induced leukoencephalopathy. J Egypt Natl Canc Inst. 2022;34(1):22. doi:10.1186/s43046-022-00117-4

39. Ison G, Beaver JA, McGuinn WD Jr, et al. FDA approval: uridine triacetate. Clin Cancer Res. 2016;22(18):4545-4549. doi:10.1158/1078-0432.CCR-16-0638

40. Lampropoulou DI, Laschos K, Amylidi AL, et al. Fluoropyrimidine toxicity and DPD deficiency. J Oncol Pharm Pract. 2020;26(3):747-753. doi:10.1177/1078155219865597

