ISSN: 2757-6817

Unika Sağlık Bilimleri Dergisi
Unika Journal of Health Sciences

Araştırma Makalesi/Research Article

Evaluation of Chemotherapy-Related Mania in Cancer Patients

Kanser Hastalarında Kemoterapi İlişkili Maninin Değerlendirilmesi

Fatih İNCİ[1], Habibe İNCİ[2]

Abstract: Objective: This study aims to evaluate chemotherapy-related mania in cancer patients. Methods: The mania status of 153 cancer patients who received chemotherapy was compared by applying the Young Mania Rating Scale before starting chemotherapy and after one session of the chemotherapy regimen. Results: When the mania total scores before and after treatment were compared according to the chemotherapeutic agents, it was seen that the post-treatment mania total scores increased in those using Fluorouracil-Folinic Acid-Oxaliplatin (Folfox) (p=0.014) and paclitaxel (p=0.036) chemotherapy regimens. In 8 (5.2%) patients who received the Folfox regimen, the mild mania score exceeded 20 points. Conclusions: Although the blood-brain barrier protects the central nervous system from the toxicity of many drugs, it is known that the stress of cancer diagnosis and some chemotherapeutics used in treatment cause disorders such as acute confusion, depression, and mania. In our study, as in case-based publications in the literature, a statistically significant increase in the total mania score was found in the Folfox regimen due to 5-fluorouracil's ability to cross the blood-brain barrier easily. According to published case reports in the literature, the possibility of mania symptoms appearing in the second, third, and sometimes subsequent sessions should be taken into consideration due to cumulative or delayed side effects of the drugs.
Keywords: Cancer patients, Mania, Chemotherapeutics, Risk.

Öz: Amaç: Bu çalışmanın amacı kanser hastalarında kemoterapiye bağlı maniyi değerlendirmektir. Gereç ve Yöntem: Kemoterapi alan 153 kanser hastasının mani durumu, kemoterapiye başlamadan önce ve bir seans kemoterapi rejimi sonrasında Young Mani Derecelendirme Ölçeği uygulanarak karşılaştırıldı. Bulgular: Kemoterapötik ajanlara göre tedavi öncesi ve tedavi sonrası mani toplam puanları karşılaştırıldığında, Fluorourasil-Folinik Asit-Oksaliplatin Folfox (p= 0,014) ve Paklitaksel (p=0,036) kemoterapi rejimi kullananlarda tedavi sonrası mani toplam puanlarının arttığı görüldü. Folfox rejimi alan 8 (%5,2) hastada mani skoru 20 puanın üzerine çıktı. Sonuçlar: Kan-beyin bariyeri merkezi sinir sistemini birçok ilacın toksisitesinden korusa da kanser tanısı stresi ve tedavide kullanılan bazı kemoterapötikler akut konfüzyon, depresyon ve mani gibi bozukluklara neden olabilir. Çalışmamızda, literatürdeki olgu bazlı yayınlarda olduğu gibi, 5-florourasil'in kan-beyin bariyerini kolaylıkla geçebilmesi nedeniyle Folfox rejiminde toplam mani skorunda istatistiksel olarak anlamlı bir artış tespit edildi. Literatürde yayınlanmış olgu sunumlarına göre ilaçların kümülatif veya gecikmiş yan etkileri nedeniyle ikinci, üçüncü ve bazen daha sonraki seanslarda mani belirtilerinin ortaya çıkma ihtimali dikkate alınmalıdır.
Anahtar Kelimeler: Kanser hastaları, Mani, Kemoterapötikler, Risk.

[1]Sorumlu yazar: Doç. Dr., Karabük Üniversitesi, Tıp Fakültesi, ORCID: 0000-0002-7590-7630, fatihinci65@hotmail.com
Assoc. Prof., Karabuk University, Faculty of Medicine
[2]Doç. Dr., Karabük Üniversitesi, Tıp Fakültesi, ORCID: 0000-0003-2883-259X, drhbesler@hotmail.com
Assoc. Prof., Karabuk University, Faculty of Medicine

Makale Gönderim:02.11.2023 Makale Kabul:11.03.2024 Makale Yayın:25.04.2024

Introduction

A significant portion of cancer patients experience psychiatric disorders before, during, or after treatment is completed. Chemotherapy, radiotherapy, and surgery cause a decrease in the quality of life of patients and mental disorders such as major depression, personality disorders, anxiety disorders, delirium, and mania (Elboga et al., 2021). Previous studies show an association between psychiatric disorders and cancer (Shen et al., 2016). Emotional distress, such as bipolar disorder and anxiety, have been associated with lower survival rates in cancer patients (Hamer et al., 2009). Bipolar disorder is a chronic and common mood disorder that may have inherited characteristics, ranging from severe mania symptoms to severe depression symptoms (Craddock and Sklar, 2013; Hirschfeld et al., 2003). The lifetime prevalence of bipolar disorder in adults is 4.4% (Goodwin and Jamison, 2007; Merikangas et al., 2007). Most patients with this disorder have their first manic or depressive episode in adolescence or early adulthood, and the average reported age is 18.2 years (Jann, 2014). Manic episode is a psychiatric condition characterized by the presence of an euphoric and irritable mood. Clinical features of mania patients include high energy, elevated mood, increased goal-directed activity, risk-taking behaviors, decreased need for sleep, racing thoughts, distractibility, and increased talking. Although commonly attributed to bipolar and schizoaffective disorders, mania can also be triggered by other non-psychiatric causes such as substance use, medications, metabolic disorders, and organic brain pathology (Warren, Katakam and Espiridion, 2019).

Manic episodes often occur due to underlying primary bipolar disorder. However, manic episodes can also occur as a result of many other causes, including general medical conditions, substance abuse, and side effects of medications. Steroid-induced mania is among the most common causes of medication. One of the drugs that is assumed to accelerate manic episodes is the cytotoxic agent methotrexate. Various chemotherapy regimens have been associated with secondary mania and agitation in patients with no prior psychiatric history (Bellman et al., 2021). Inflammatory and neurochemical changes, vascular disorders, paraneoplastic, and autoimmune syndromes often occur in oncology patients as a result of the effects of chemotherapy (Pavlova and Weinrebe, 2020). However, chemotherapy agents can cause neurological and psychiatric complications (H. Garg et al., 2018). Some chemotherapeutics can cause acute confusion, depression, and mania (Bond et al., 2006). Agitation, hallucinations, and bipolar disorder have been reported in a patient with colon cancer treated with the combination of 5-FU, oxaliplatin, and bevacizumab, as well as in a female patient with breast cancer treated with the combination of 5-fluorouracil-epirubicin-cyclophosphamide. Including 5-FU in their

treatment regimens was a common feature of the patients (Fora et al., 2009). Mania has been studied in various diseases in the literature, but information about mania in cancer patients is limited. This study aimed to evaluate chemotherapy-related mania in cancer patients.

Methods

The mania status of 153 cancer patients who applied to the Medical Oncology outpatient clinic of Karabük University Training and Research Hospital between November 2021 and November 2022 was investigated. The sociodemographic data form and the Young Mania Rating Scale (YMRS) were applied and evaluated to patients diagnosed with cancer. The Young Mania Rating Scale was used to cancer patients before starting chemotherapy and in the routine outpatient clinic evaluation one week later to evaluate the side effects after chemotherapy, and these data were compared.

Sociodemographic Data Form: Age, gender, marital status, number of children, education level, place of residence, occupation, monthly income level, presence of social support of the cancer patient, cancer type, cancer stage, year of cancer, additional chronic disease history, psychiatric disease history were questioned.

Young Mania Rating Scale: It measures the severity and change of mania symptoms in the individual. It is a self-evaluation scale. It can be applied to psychiatric patients and other patient groups. It contains a total of 11 items. It is a Likert-type scale. The scoring type provides measurement by responding. The interview results with the patients are marked on the scale and filled in. It is not used to make a diagnosis but to evaluate the current mania state. The total score is obtained by adding the scores of each item. 20-25 points are considered mild mania, 26-37 points are regarded as moderate mania, and 38-60 points are considered severe mania. A Turkish validity study of the scale was conducted (Choi et al., 2001).

Cancer patients who were over 18 years old, had the cognitive functions to answer the questions, and could complete the survey were included in our study. Those with psychiatric illnesses and those with missing sociodemographic data were excluded from the study. This study was conducted by the Helsinki Principles, and ethical approval was obtained from the local ethics committee (Approval No: 2021/726).

Statistical analysis of the data was performed using IBM SPSS v.22.0. Pearson Correlation test was used for normal distribution values in non-categorical data, and the Paired sample test was used for parametric data. Statistical significance was determined as $p < 0.05$.

Results

One hundred fifty-three adult cancer patients were included in the study. The sociodemographic and clinical characteristics of the participants are shown in Table 1. 65.4% were women, and the average age was 59.06 ± 10.61 years. The majority of the participants were married (79.1%), primary school graduates (62.1%), unemployed (75.2%), living in the city center (70.6%), with a monthly income equal to their expenses (83.7%), and without a chronic disease (66.0%). All participants were patients who were not diagnosed with a psychiatric disease and had social support. The majority of participants were breast cancer patients (40.5%). 8 of the participants (5.2%) reached a score above 20 points, which is the mild mania score. When the mania subscale scores before and after chemotherapy were compared in the entire patient group, it was observed that the "decrease in sleep" scores increased ($p<0.001$) (Table 2).

Table 1: Sociodemographic and Clinical Characteristics of Cancer Patients

Variables	**Cancer patients (*n* =153)**
Age (year), (mean ± SD)	59.06 ± 10.61
Gender, *n* (%)	
Female	100 (65.4)
Male	53 (34.6)
Marriage status, *n* (%)	
Single	32 (20.9)
Married	121 (79.1)
Number of children (mean ± SD)	2.58±1.34
Education status, *n* (%)	
İlliterate	6 (3.9)
Literate	24 (15.7)
Primary school	95 (62.1)
High school	20 (13.1)
University	8 (5.2)
Occupation, *n* (%)	
Non-worker	115 (75.2)
Worker	17 (11.1)
Retired	21 (13.7)
Place of residence	
Town	45 (29.4)
City	108 (70.6)
Monthly financial gain	
Financial gain: low	3 (2.0)
Financial gain: equal	128 (83.7)
Financial gain: high	22 (14.4)
Social support	
Yes	153 (100)
No	0 (0)
Other chronic disease history, *n* (%)	
Yes	52 (34.0)
No	101 (66.0)
Cancer type	
Respiratory System cancers	29 (19.0)
Gastrointestinal System cancers	41 (26.8)
Genitourinary System cancers	21 (13.8)
Breast cancers	62 (40.5)
Mania points change	
Increased	59 (38.6)
Decreased	47 (30.7)

Equal	47 (30.7)
Chemotherapy regimen	
Adriamycin- Cyclophosphamide (AC)	31 (20.3)
Fluorouracil-Folinic Acid-Oxaliplatin (Folfox)	38 (24.8)
Gemcitabine- Cisplatin (GC)	16 (10.5)
Paclitaxel	33 (21.6)
Other	35 (22.9)

Table 2: Comparison of Mania Subscale Scores Before and After Chemotherapy in Patient Groups

All patients	**Before treatment**	**After treatment**	**p**
Elevated mood	0.83±0.96	1.05±1.22	**0.046**
Increased movement and energy	1.03±0.98	1.13±0.93	0.562
Increased sexual interest	0.69±0.89	0.70±0.90	0.822
Decreased sleep	0.94±0.90	1.35±0.95	**0.000**
Increased irritability	1.03±0.98	1.06±0.96	0.870
Increased speech rate and amount	1.01±0.98	1.00±0.84	0.873
Presence of mental disorder	0.66±0.88	0.64±0.83	0.967
Thought content increase	0.88±1.05	0.75±0.84	0.204
Increased destructive-aggressive behavior	0.70±0.84	0.61±0.86	0.369
Appearance	0.62±0.85	0.57±0.86	0.716
Insight	0.59±1.12	0.68±1.01	0.252
Total score	8.83±3.87	9.49±4.49	0.126

P, Paired Sample test

When the mania total scores before and after treatment were compared according to the chemotherapeutic agents, it was seen that the post-treatment mania total scores increased in those using the Fluorouracil-Folinic Acid-Oxaliplatin (Folfox) (p=0.014) and Paclitaxel (p=0.036) chemotherapy regimens (Table 3). When the mania total scores before and after treatment were compared in patients using Folfox, "increase in movement and energy" (p=0.002), "sleep" (p<0.001), "irritability" (p<0.001), "speech rate and amount" (p=0.002) and "insight" (p=0.040) scores increased (Table 4). When the mania total scores before and after treatment were compared in patients using paclitaxel, it was seen that the "increase in movement and energy" (p=0.002), "sleep" (p<0.001), and "irritability" (p=0.008) scores increased (Table 5).

Table 3: Comparison of Mania Total Scores Before and After Treatment According to Chemotherapeutic Agents

Chemotherapy regimen	**Before treatment**	**After treatment**	**p**
Adriamycin- Cyclophosphamide (AC)	10.68±3.15	10.10±3.52	0.089
Fluorouracil-Folinic Acid-Oxaliplatin (Folfox)	8.23±4.06	12.13±5.21	**0.014**
Gemcitabine- Cisplatin (GC)	8.31±3.07	8.06±2.81	0.534
Paclitaxel	7.48±4.39	8.84±5.28	**0.036**
Other	7.68±2.60	7.77±2.88	0.619
All patients	8.83±3.87	9.49±4.49	0.126

P, Paired Sample test

Table 4: Comparison of Mania Total Scores Before and After Treatment in Patients Using the Folfox Regimen

Folfox	Before treatment	After treatment	p
Elevated mood	1.00±1.03	1.05±1.18	0.637
Increased movement and energy	1.07±1.07	1.76±0.58	**0.002**
Increased sexual interest	0.65±0.87	0.63±0.85	0.869
Decreased sleep	0.68±0.84	1.60±0.67	**0.000**
Increased irritability	0.89±0.92	1.60±0.94	**0.001**
Increased speech rate and amount	0.76±0.85	1.36±0.88	**0.002**
Presence of mental disorder	0.97±0.91	0.81±1.06	0.501
Thought content increase	0.84±0.97	0.81±0.92	0.990
Increased destructive-aggressive behavior	0.60±0.78	0.84±1.07	0.237
Appearance	0.63±0.67	0.68±0.98	0.948
Insight	0.63±0.81	1.21±1.31	**0.040**
Total score	8.23±4.06	12.13±5.21	**0.014**

P, Paired Sample test

Discussion

It is known that the stress caused by cancer diagnosis and the drugs used in treatment cause significant negative neurological and psychiatric problems (Fora et al., 2009). Chemotherapy regimens have been associated with many psychiatric complications such as psychosis, mania, and anxiety (Harshit Garg et al., 2018). In our study, no significant increase in total mania scores was found in the patient population, including all chemotherapy regimen groups before and after treatment (p=0.126). However, when chemotherapy regimens were evaluated separately, a statistically significant increase in the total mania score of Folfox (p=0.014), a chemotherapy regimen containing 5-fluorouracil (5-FU) was found as in case-based publications in the literature 8 patients who received Folfox reached a mild mania score above 20 points. No patients whose post-treatment mania score exceeded 20 were detected in the Paclitaxel, Adriamycin-Cyclophosphamide (AC), Gemcitabine-Cisplatin (GC), and other chemotherapy regimen groups. In a case report, reversible encephalopathy was seen during the second session in a patient who received the Folfox regimen (Porcello Marrone et al., 2013). Side effects associated with 5-FU included cerebellar symptoms such as impaired gait, dysmetria, and nystagmus (Porcello Marrone et al., 2013). However, when case reports in the literature are evaluated, it has been observed that in almost all reports, mania symptoms typically occur during the second or third session and sometimes in later sessions (Niemann et al., 2004). Side effects of these medications may be cumulative or delayed. Since 5-FU can easily cross the blood-brain barrier, it has been reported to be associated with various neurological complications such as oculomotor disorder and peripheral neuropathy (Choi et al., 2001). It is thought that fluorocitrate, the final metabolite of 5-FU, causes citrate accumulation in neurons by inhibiting aconitase in the Krebs cycle, which may cause neurotoxicity (Park et

al., 1995). 5-FU accumulation causes manic episodes to develop in the patient through damage to various brain structures and neurotransmitter pathways (Pacchiarotti et al., 2007). In addition, it has been reported that in cases where a manic attack is thought to have developed due to 5-FU, the manic episode disappears with the discontinuation of 5-FU and the administration of antipsychotic drugs (Ha et al., 2011). Similarly, mania symptoms were reported in a patient with colon cancer who received capecitabine, an oral fluorouracil analogue, in combination with oxaliplatin (H. Garg et al., 2018). Since the Folfox regimen is administered as a 46-hour infusion in the oncology inpatient service of our clinic, the patients' vital signs are constantly measured during the infusion and hospitalization files are prepared by the healthcare personnel.

Table 5: Comparison of Mania Total Scores Before and After Treatment in Patients Using Paclitaxel

Paclitaxel	**Before treatment**	**After treatment**	**p**
Elevated mood	0.84±1.00	0.87±1.26	0.973
Increased movement and energy	0.63±0.78	1.21±0.48	**0.002**
Increased sexual interest	0.87±0.96	0.75±0.96	0.431
Decreased sleep	0.48±0.66	1.24±0.86	**0.000**
Increased irritability	0.69±0.88	1.33±0.81	**0.008**
Increased speech rate and amount	0.87±1.02	0.93±0.65	0.787
Presence of mental disorder	0.36±0.60	0.39±0.78	0.769
Thought content increase	0.93±0.96	0.75±1.03	0.419
Increased destructive-aggressive behavior	0.75±0.86	0.54±0.86	0.257
Appearance	0.75±0.93	0.54±0.93	0.474
Insight	0.69±1.87	0.36±0.82	0.611
Total score	7.48±4.39	8.84±5.28	**0.036**

P, Related Sample test

Since most patients encounter a different, high-stress environment and a different treatment method for the first time in their lives, the number of people they interact with and the level of conversation increase, their sleep patterns are disrupted, and insomnia attacks begin. In addition, since hospital staff constantly visit patient rooms, it is thought that this situation contributes to the increase in patients' irritability levels. Although the increase was not as statistically significant in the Paclitaxel group as in the Folfox group, an increase close to numerical significance was found (p=0.036). It has been reported in the literature that mania symptoms developed in a patient with laryngeal cancer who received paclitaxel and carboplatin and that the symptoms disappeared one day after the treatment was discontinued (Ahmed et al., 2011). No significant change was found in AC, GC, and other treatment regimen groups. However, it has been reported in the literature that psychosis developed in a patient with a testicular tumor who was treated with cisplatin, etoposide, and bleomycin (BEP) combination (Puangthong and Pongpirul, 2015). In a series of patients who previously received cranial radiotherapy due to brain metastasis, including two breast cancers and one lung cancer, it was reported that acute encephalopathy developed after paclitaxel application and that the

symptoms regressed approximately 6 hours after paclitaxel was discontinued (Ziske et al., 2002). Although the blood-brain barrier penetration of paclitaxel is low, cranial passage of the drug increases when the blood-brain barrier is disrupted by surgery and radiotherapy (Fellner et al., 2002).

One of the most important limitations of our study is that the control test was performed after a single session of chemotherapy. A single dose of 8 mg dexematazone is used before chemotherapy. However, it has been reported in publications that mania may develop with steroid doses equivalent to dexematozone at a daily dose of 8-12 mg for 3-4 days (Cerullo, 2006). Additionally, the small number of patients and the lack of patient groups that include patients using other chemotherapy agents are among the limitations of our study.

Conclusion

Although the blood-brain barrier protects the central nervous system from the toxicity of many drugs, it is known that the stress of cancer diagnosis and some chemotherapeutics used in treatment cause disorders such as acute confusion, depression, and mania. In our study, as in case-based publications in the literature, a statistically significant increase in the total mania score was found in the Folfox regimen due to 5-fluorouracil's ability to cross the blood-brain barrier easily. However, when case reports in the literature are examined, it is seen that mania symptoms typically appear during the second or third session and sometimes in later sessions in almost all publications, so the cumulative or delayed side effects of the drugs should be taken into consideration.

Funding: This research received no external funding.

Conflict of interest: The authors declare no conflicts of interest.

Author Contributions: Idea: Fİ, Hİ; Design: Fİ, Hİ; Check: Fİ, Hİ; Sources: Fİ, Hİ; Ingredients: Fİ, Hİ; Data collecting: Fİ, Hİ; Analysis: Fİ, Hİ; Literature Review: Fİ, Hİ; Posted by: Fİ; Critical Review: Fİ, Hİ.

Peer Review: Internal/External independent.

References

Ahmed, N., Usmani, S., Jabbour, N., & Hegde, U. (2011). Acute psychosis after paclitaxel infusion. Conn Med., 75(8), 465-466. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21980675/.

Bellman, V., Russell, N., Depala, K., Dellenbaugh, A., … Srinivas, S. (2021). Challenges in Treating Cancer Patients With Unstable Psychiatric Disorder. World J Oncol., 12(5), 137-148. http://dx.doi.org/10.14740/wjon1402.

Bond, S. M., Neelon, V. J., & Belyea, M. J. (2006). Delirium in hospitalized older patients with cancer. Oncol Nurs Forum, 33(6), 1075-1083. http://dx.doi.org/10.1188/06.ONF.1075-1083.

Cerullo, M. A. (2006). Corticosteroid-induced mania: Prepare for the unpredictable. Current Psychiatry, 5(6), 43.

Choi, S. M., Lee, S. H., Yang, Y. S., Kim, B. C., Kim, M. K., & Cho, K. H. (2001). 5-fluorouracil-induced leukoencephalopathy in patients with breast cancer. J Korean Med Sci., 16(3), 328-334. http://dx.doi.org/ 10.3346/jkms.2001.16.3.328.

Craddock, N., & Sklar P. (2013). Genetics of bipolar disorder. Lancet. 381(9878), 1654-1662. http://dx.doi.org/ 10.1016/S0140-6736(13)60855-7.

Elboga, G., Gizem Aksoy, P., Kus, T., Karayagmurlu, E., Aktas, G., Sahin, S., & Altindag, A. (2021). 5-fluorouracil-induced manic episode in patients with colon cancer: A case report and literature review. Annals of Medical Research, 26(6), 1123-1125.

Fellner, S., Bauer, B., Miller, DS., Schaffrik, M., … Fricker G. (2002). Transport of paclitaxel (Taxol) across the blood-brain barrier in vitro and in vivo. J Clin Invest., 110(9), 1309-1318. http://dx.doi.org/ 10.1172/JCI15451.

Fora, A., Alabsi, E., & Fakih, M. (2009). A case of 5-fluorouracil-induced acute psychosis. Clin Colorectal Cancer. 8(3), 166-168. http://dx.doi.org/ 10.3816/CCC.2009.n.027.

Garg, H., Prakash, S., Deb, KS., & Chadda, RK. (2018). Secondary mania following cancer chemotherapy with capecitabine. BMJ Case Rep. 2018 Mar 28;2018:bcr2017220995. http://dx.doi.org/ 10.1136/bcr-2017-220995.

Goodwin, F. K., & Jamison, K. R. (2007). Manic-depressive illness: bipolar disorders and recurrent depression. Oxford University Press.

Ha, J. H., Hwang, D. Y., Yu, J., Park, D. H., & Ryu, S. H. (2011). Onset of Manic Episode during Chemotherapy with 5-Fluorouracil. Psychiatry Investig., 8(1), 71-73. http://dx.doi.org/ 10.4306/pi.2011.8.1.71.

Hamer, M., Chida, Y., & Molloy, G. J. (2009). Psychological distress and cancer mortality. J Psychosom Res., 66(3), 255-258. http://dx.doi.org/ 10.1016/j.jpsychores.2008.11.002.

Hirschfeld, R. M., Calabrese, J. R., Weissman, M. M., Reed, M., … Wagner, KD. (2003). Screening for bipolar disorder in the community. J Clin Psychiatry, 64(1), 53-59. http://dx.doi.org/ 10.4088/jcp.v64n0111.

Jann, M. W. (2014). Diagnosis and treatment of bipolar disorders in adults: a review of the evidence on pharmacologic treatments. Am Health Drug Benefits, 7(9), 489-499.Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4296286/.

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry, 64(5), 543-552. http://dx.doi.org/ 10.1001/archpsyc.64.5.543.

Niemann, B., Rochlitz, C., Herrmann, R., & Pless, M. (2004). Toxic encephalopathy induced by capecitabine. Oncology, 66(4), 331-335. http://dx.doi.org/ 10.1159/000078335.

Pacchiarotti, I., Mazzarini, L., Pellegrini, P., Venturelli, V., … Girardi, P. (2007). A case of manic episode during treatment with 5-fluorouracil, epirubicin and cyclophosphamide for breast cancer. Gen Hosp Psychiatry, 29(5), 461-463. http://dx.doi.org/ 10.1016/j.genhosppsych.2007.04.007.

Park, Yoo-Mi, Kwon, Hye-Young, Kım, Hoo-Won, & Kım, Dong-Kwon. (1995). A case of diffuse leukoencephalopathy caused by 5-Fluorouracil. Journal of the Korean Neurological Association, 1007-1010.

Pavlova, O., & Weinrebe, W. (2020). Chemotherapy-induced fulminant, severe hyperactive delirium in a patient with a new diagnosed multiple myeloma. Archives of Clinical and Medical Case Reports, 4(3), 312-328. Retrieved from https://www.fortunejournals.com/articles/chemotherapyinduced-fulminant-severe-hyperactive-delirium-in-a-patient-with-a-new-diagnosed-multiple-myeloma.html.

Porcello Marrone, L. C., Marrone, B. F., Pascoal, T. A., Schilling, L.P., … da Costa, J. C. (2013). Posterior Reversible Encephalopathy Syndrome Associated with FOLFOX Chemotherapy. Case Rep Oncol Med., 2013, 306983. http://dx.doi.org/ 10.1155/2013/306983.

Puangthong, U., & Pongpirul, K. (2015). Chemotherapy-induced acute psychosis in a patient with malignant germ cell tumour. BMJ Case Rep., 2015, bcr2014208982. http://dx.doi.org/ 10.1136/bcr-2014-208982.

Shen, C. C., Hu, L. Y., Hu, Y. W., Chang, W. H., … Su, T. P. (2016). The Risk of Cancer in Patients With Obsessive-Compulsive Disorder: A Nationwide Population-Based Retrospective Cohort Study. Medicine (Baltimore). 95(9), e2989. http://dx.doi.org/ 10.1097/MD.0000000000002989.

Warren, K. N., Katakam, J., & Espiridion, E. D. (2019). Acute-onset Mania in a Patient with Non-small Cell Lung Cancer. Cureus., 11(8), e5436. http://dx.doi.org/ 10.7759/cureus.5436.

Ziske, C. G., Schöttker, B., Gorschlüter, M., Mey, U., … Schmidt-Wolf, I. G. (2002). Acute transient encephalopathy after paclitaxel infusion: report of three cases. Ann Oncol., 13(4), 629-631. http://dx.doi.org/ 10.1093/annonc/mdf025.