Evidence With Emphasis on Toxicity Profile of Metronomic Capecitabine in Non-Metastatic Triple-Negative Breast Cancer

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Abstract

Background: Metronomic chemotherapy, defined as the continuous administration of low-dose cytotoxic agents without extended drug-free intervals, has emerged as a promising therapeutic strategy aimed at minimizing toxicity while maintaining antitumor efficacy. Capecitabine, an oral fluoropyrimidine prodrug widely used in breast and gastrointestinal malignancies, has been increasingly investigated in metronomic regimens due to its favorable pharmacokinetic profile and tumor-selective activation. This approach is particularly relevant in patients with limited tolerance to conventional chemotherapy, including those with early-stage triple-negative breast cancer (TNBC), where treatment-related toxicity may compromise adherence and outcomes.

The toxicity profile of capecitabine has been well characterized in standard intermittent dosing schedules, with common adverse events including hand-foot syndrome, gastrointestinal disturbances, and hematologic suppression. However, the safety spectrum associated with metronomic administration differs in both incidence and severity, reflecting alterations in drug exposure and biological effects. Emerging evidence suggests that metronomic capecitabine is generally associated with reduced grade 3–4 toxicities, improved tolerability, and a lower need for dose interruptions, although certain chronic low-grade toxicities may persist and impact quality of life.

In the context of non-metastatic TNBC, where therapeutic options remain limited and recurrence risk is high, the incorporation of capecitabine—particularly in the adjuvant setting following residual disease—has gained clinical interest. While most studies have focused on conventional dosing, increasing attention is being directed toward metronomic strategies as a means to enhance tolerability, especially in patients unable to complete standard regimens. Nonetheless, data specifically addressing toxicity in this subgroup remain limited, necessitating extrapolation from broader oncologic populations.

This review aims to comprehensively evaluate the toxicity profile of metronomic capecitabine, with an emphasis on clinical evidence, underlying mechanisms, and practical management strategies. Special focus is placed on its application in non-metastatic TNBC, highlighting current evidence gaps and future research directions. Understanding these safety considerations is essential for optimizing treatment selection, improving patient adherence, and advancing the role of metronomic chemotherapy in modern oncology practice.

Keywords: *Toxicity Profile, Metronomic Capecitabine, Non-Metastatic Triple-Negative Breast Cancer*

Introduction

Metronomic chemotherapy has emerged as an alternative therapeutic paradigm in oncology, characterized by the continuous administration of low-dose cytotoxic agents with minimal or no drug-free intervals. Unlike conventional maximum tolerated dose (MTD) strategies, which prioritize tumor cytotoxicity at the expense of significant toxicity, metronomic regimens aim to achieve sustained antitumor activity through antiangiogenic, immunomodulatory, and tumor dormancy–inducing mechanisms. This approach has gained increasing attention in the management of solid malignancies, particularly in patient populations where treatment tolerability is a critical concern, such as the elderly, frail individuals, and those receiving prolonged adjuvant therapy. Capecitabine, an orally administered prodrug of 5-fluorouracil (5-FU), represents one of the most extensively studied agents in metronomic chemotherapy due to its tumor-selective activation and convenient administration profile [1].

In standard dosing schedules, capecitabine is typically administered intermittently at relatively high doses, leading to well-documented toxicities including hand-foot syndrome (HFS), diarrhea, mucositis, and hematologic suppression. While effective, these toxicities often necessitate dose reductions, treatment interruptions, or discontinuation, potentially compromising therapeutic outcomes. In contrast, metronomic capecitabine employs lower, continuous dosing strategies that aim to reduce peak plasma concentrations and cumulative toxicity, while maintaining therapeutic efficacy through alternative biological pathways. Emerging clinical evidence suggests that this dosing paradigm is associated with a more favorable toxicity profile, particularly with respect to severe (grade 3–4) adverse events, although chronic low-grade toxicities may still occur and affect patient quality of life [2].

Triple-negative breast cancer (TNBC), defined by the absence of estrogen receptor, progesterone receptor, and HER2 expression, represents a biologically aggressive subtype of breast cancer associated with a higher risk of early recurrence and poorer prognosis compared to other subtypes. In the non-metastatic setting, standard treatment consists of surgery combined with chemotherapy, often including anthracycline- and taxane-based regimens. Despite these interventions, a substantial proportion of patients—particularly those with residual disease following neoadjuvant therapy—remain at high risk of relapse. The addition of capecitabine in the adjuvant setting has demonstrated survival benefits in such patients, most notably in the CREATE-X trial, thereby establishing its role in high-risk early-stage TNBC [3].

However, the use of capecitabine in this setting is frequently limited by treatment-related toxicities, which may affect adherence and completion rates, particularly in prolonged adjuvant regimens. This has led to growing interest in metronomic capecitabine as a potentially more tolerable alternative, especially for patients unable to tolerate standard dosing schedules. While several studies have evaluated metronomic capecitabine across various solid tumors and metastatic breast cancer, data specifically addressing its toxicity profile in non-metastatic TNBC remain scarce. Consequently, clinicians often rely on extrapolation from heterogeneous patient populations, underscoring the need for a comprehensive synthesis of available evidence [4].

The aim of this review is to critically evaluate the toxicity profile of metronomic capecitabine, integrating data from clinical trials, real-world studies, and mechanistic insights. Particular emphasis is placed on its application in non-metastatic TNBC, with the objective of clarifying safety patterns, identifying predictors of toxicity, and informing clinical decision-making. By addressing existing research gaps and highlighting areas for future investigation, this review seeks to support the rational incorporation of metronomic strategies into contemporary oncologic practice [5].

Concept of Metronomic Chemotherapy

Metronomic chemotherapy refers to the frequent, regular administration of chemotherapeutic agents at relatively low doses without prolonged drug-free breaks. This concept contrasts sharply with the traditional maximum tolerated dose (MTD) paradigm, which relies on intermittent high-dose treatment cycles followed by recovery periods to allow normal tissue repair. The term “metronomic” reflects the rhythmic, continuous dosing strategy aimed at maintaining sustained drug exposure while minimizing acute toxic

effects. First conceptualized in the early 2000s, metronomic therapy has since evolved into a distinct therapeutic approach with growing clinical relevance, particularly in settings where long-term tolerability is essential [6].

One of the fundamental principles underlying metronomic chemotherapy is its antiangiogenic activity. Unlike MTD regimens that primarily target rapidly dividing tumor cells, metronomic dosing exerts a continuous inhibitory effect on tumor angiogenesis by targeting endothelial cells within the tumor vasculature. Endothelial cells are genetically more stable than tumor cells and less likely to develop resistance, making them an attractive therapeutic target. Preclinical studies have demonstrated that low-dose, continuous chemotherapy can suppress endothelial cell proliferation, reduce circulating endothelial progenitor cells, and inhibit vascular endothelial growth factor (VEGF)-mediated signaling pathways, thereby impairing tumor blood supply and growth [7].

In addition to antiangiogenic effects, metronomic chemotherapy has been shown to modulate the immune system in a manner that enhances antitumor activity. Low-dose chemotherapy can selectively deplete regulatory T cells (Tregs), which are known to suppress antitumor immune responses, while preserving or even enhancing the activity of effector T cells and natural killer (NK) cells. This immunomodulatory effect contributes to a more favorable tumor microenvironment and may synergize with emerging immunotherapeutic strategies. Such mechanisms are particularly relevant in triple-negative breast cancer (TNBC), a subtype increasingly recognized for its immunogenic potential [8].

Another key aspect of metronomic chemotherapy is its ability to induce tumor dormancy. Rather than achieving rapid tumor shrinkage, metronomic regimens may stabilize disease by maintaining a balance between tumor cell proliferation and cell death. This cytostatic effect can translate into prolonged disease control with fewer adverse effects, making it especially suitable for maintenance therapy or adjuvant settings where the goal is to prevent recurrence rather than reduce tumor burden. In early-stage cancers such as non-metastatic TNBC, this approach may offer a strategy to suppress micrometastatic disease while preserving patient quality of life [9].

Pharmacokinetically, metronomic dosing results in lower peak plasma concentrations and more stable drug exposure over time. This reduces the risk of dose-dependent toxicities commonly associated with high peak levels, such as severe gastrointestinal and hematologic adverse events. At the same time, continuous exposure may enhance drug activity against endothelial and immune targets that require sustained inhibition rather than intermittent high-intensity exposure. Capecitabine, due to its oral administration and tumor-selective activation via thymidine phosphorylase, is particularly well-suited for this dosing strategy [10].

Clinically, metronomic chemotherapy has been explored across a wide range of malignancies, including breast, colorectal, prostate, and ovarian cancers. Its role has been particularly emphasized in patients who are not candidates for aggressive therapy, such as the elderly or those with comorbidities. Importantly, accumulating evidence suggests that metronomic regimens are associated with a more favorable toxicity profile compared to conventional chemotherapy, with lower rates of grade 3–4 adverse events and improved treatment adherence. However, the spectrum of chronic low-grade toxicities and their long-term implications remain areas of active investigation [11].

Despite its advantages, several challenges remain in the clinical implementation of metronomic chemotherapy. These include the lack of standardized dosing regimens, variability in study designs, and limited high-quality randomized controlled trials in certain disease settings. Additionally, biomarkers to predict response and toxicity are not yet well established, which limits the ability to individualize treatment. In the context of non-metastatic TNBC, where evidence is still emerging, careful interpretation of available data is required to balance efficacy with safety considerations [12].

Pharmacology of Capecitabine in Metronomic Dosing

Capecitabine is an oral fluoropyrimidine carbamate designed to generate 5-fluorouracil (5-FU) preferentially within tumor tissue through a multistep enzymatic process. After oral administration, capecitabine is rapidly absorbed through the gastrointestinal tract and undergoes sequential hepatic and tumoral metabolism involving carboxylesterase, cytidine deaminase, and thymidine phosphorylase. The

final conversion step, mediated predominantly by thymidine phosphorylase, occurs at higher levels in tumor tissues compared to normal tissues, providing a degree of tumor selectivity. This pharmacologic property underpins the widespread use of capecitabine in breast and gastrointestinal malignancies and forms the basis for its adaptation into metronomic dosing strategies [13].

In conventional dosing regimens, capecitabine is typically administered at doses of 1000–1250 mg/m² twice daily for 14 days followed by a 7-day rest period, resulting in cyclical exposure to relatively high plasma concentrations of active metabolites. These peaks are associated with both antitumor efficacy and dose-limiting toxicities such as hand-foot syndrome and gastrointestinal adverse effects. In contrast, metronomic dosing employs substantially lower daily doses administered continuously, without planned interruptions. This approach leads to more stable plasma levels of 5-FU and its metabolites, reducing peak-related toxicity while maintaining sustained biological activity [14].

From a pharmacokinetic perspective, metronomic capecitabine minimizes fluctuations in drug concentration, thereby altering the balance between efficacy and toxicity. Lower peak concentrations are associated with reduced damage to rapidly proliferating normal tissues, including gastrointestinal mucosa and bone marrow, which are typically affected during standard chemotherapy. At the same time, continuous exposure ensures prolonged interaction with tumor-associated endothelial cells and immune components, which may be more sensitive to sustained low-dose therapy. This shift in pharmacokinetic dynamics is central to the improved tolerability observed in metronomic regimens [15].

The pharmacodynamic effects of metronomic capecitabine extend beyond direct cytotoxicity. Continuous low-dose exposure enhances antiangiogenic activity by suppressing endothelial cell proliferation and reducing circulating endothelial progenitor cells. Additionally, it may influence tumor metabolism and microenvironmental factors, including hypoxia and stromal interactions. Importantly, these effects occur at drug concentrations lower than those required for direct tumor cell kill, suggesting that the therapeutic benefit of metronomic dosing is mediated through mechanisms distinct from conventional chemotherapy [16].

Another critical factor influencing capecitabine pharmacology is interpatient variability, particularly related to the activity of dihydropyrimidine dehydrogenase (DPD), the key enzyme responsible for 5-FU catabolism. Deficiency in DPD, whether partial or complete, can lead to accumulation of active metabolites and increased risk of severe toxicity, even at low doses. This is highly relevant in metronomic regimens, as prolonged exposure may still result in cumulative toxicity in susceptible individuals. Screening for DPD deficiency, increasingly recommended in clinical practice, can help mitigate this risk and optimize dosing strategies [17].

Drug interactions also play a role in the pharmacologic profile of capecitabine. Concomitant use of medications that affect hepatic enzymes or gastrointestinal absorption may alter drug bioavailability and toxicity risk. Additionally, renal function significantly impacts capecitabine metabolism, as its metabolites are primarily excreted through the kidneys. Dose adjustments are therefore in patients with renal impairment, even when using metronomic schedules, to avoid unexpected accumulation and adverse effects [18].

In the context of non-metastatic triple-negative breast cancer, the pharmacologic advantages of metronomic capecitabine are particularly relevant. Patients in the adjuvant setting often require prolonged therapy to reduce recurrence risk, making tolerability a critical factor. Continuous low-dose administration may allow for sustained therapeutic exposure while minimizing interruptions due to toxicity, thereby improving adherence and potentially enhancing long-term outcomes. However, the optimal dosing schedule and duration in this specific population remain areas of ongoing research [19].

General Toxicity Profile of Capecitabine (Standard vs Metronomic)

Capecitabine is widely recognized for its predictable and relatively well-characterized toxicity profile, which largely reflects its conversion to 5-fluorouracil (5-FU). In standard dosing regimens, toxicity is primarily dose-dependent and related to peak plasma concentrations achieved during intermittent administration. The most commonly reported adverse events include hand-foot syndrome (HFS), diarrhea,

mucositis, nausea, fatigue, and hematologic suppression. These toxicities can range from mild to severe and often necessitate dose reductions, treatment delays, or discontinuation, particularly in prolonged treatment courses such as adjuvant therapy in breast cancer [20].

A defining characteristic of standard capecitabine therapy is the cyclical pattern of toxicity, with symptoms often intensifying toward the end of the dosing period (typically days 10–14 of a cycle) and partially resolving during the drug-free interval. This fluctuation is closely linked to pharmacokinetic peaks and cumulative exposure during each cycle. While this schedule allows for recovery of normal tissues, it also introduces variability in patient tolerance and may compromise adherence, especially in patients experiencing recurrent high-grade toxicities. In the context of non-metastatic triple-negative breast cancer, where treatment continuity is crucial, such interruptions can have important clinical implications [21].

In contrast, metronomic capecitabine fundamentally alters the toxicity profile by employing continuous low-dose administration without extended breaks. This approach reduces peak plasma concentrations, thereby decreasing the incidence of acute, high-grade toxicities commonly seen with standard dosing. Clinical studies have consistently demonstrated lower rates of grade 3–4 adverse events with metronomic regimens, particularly for gastrointestinal toxicity and hematologic suppression. As a result, patients are more likely to maintain treatment over extended periods, which is particularly relevant in maintenance or adjuvant settings [22].

However, while severe toxicities are less frequent, metronomic capecitabine is not devoid of adverse effects. Instead, the toxicity profile shifts toward more chronic, low-grade events that may persist over time. Hand-foot syndrome remains one of the most commonly reported toxicities even in metronomic schedules, although it is typically of lower grade and more manageable. Similarly, mild gastrointestinal symptoms such as low-grade diarrhea or nausea may occur continuously rather than episodically. These chronic toxicities, although less severe, can still impact patient quality of life and require proactive management [23].

Another important distinction lies in the cumulative nature of toxicity in metronomic therapy. Because treatment is administered continuously, even low-grade toxicities may accumulate over time, leading to delayed onset of clinically significant adverse events. This is particularly relevant for dermatologic toxicity such as HFS and for fatigue, which may progressively worsen with prolonged exposure. Therefore, ongoing monitoring and early intervention are essential to prevent escalation and maintain treatment adherence [24].

Hematologic toxicity also differs between the two approaches. While standard capecitabine can cause notable neutropenia and anemia, metronomic dosing is generally associated with a lower incidence of significant bone marrow suppression. This is likely due to reduced peak drug levels and less direct cytotoxic impact on rapidly dividing hematopoietic cells. Nevertheless, mild cytopenias may still occur and should be monitored, especially in patients with prior chemotherapy exposure or compromised bone marrow reserve [25].

From a clinical standpoint, the improved tolerability of metronomic capecitabine has important implications for patient selection and treatment planning. It is particularly advantageous in populations where maintaining dose intensity is less critical than ensuring long-term exposure, such as in adjuvant therapy for high-risk non-metastatic triple-negative breast cancer. Additionally, it offers a viable option for patients who are unable to tolerate standard dosing due to age, comorbidities, or prior toxicity. However, careful patient education and monitoring remain essential, as the perception of “low-dose” therapy may underestimate the need for vigilance regarding adverse effects [26].

Overall, the transition from standard to metronomic capecitabine represents a shift not only in dosing strategy but also in the nature of treatment-related toxicity. While the reduction in severe adverse events is a clear advantage, the persistence of chronic low-grade toxicities requires a different approach to management. Understanding these differences is critical for optimizing therapeutic outcomes and tailoring treatment to individual patient needs, particularly in sensitive clinical settings such as non-metastatic TNBC [27].

Hematologic Toxicities of Metronomic Capecitabine

Hematologic toxicity is a well-recognized adverse effect of fluoropyrimidine-based chemotherapy, including capecitabine, and reflects the susceptibility of rapidly proliferating bone marrow progenitor cells to cytotoxic injury. In standard dosing regimens, capecitabine may induce neutropenia, anemia, and thrombocytopenia, with severity often correlating with dose intensity and peak plasma drug levels.

However, compared to intravenous 5-fluorouracil (5-FU), capecitabine is generally associated with a lower incidence of severe hematologic toxicity. The shift to metronomic dosing further modifies this toxicity profile, resulting in a distinct pattern characterized by reduced severity but potential chronicity [28].

Neutropenia is among the most clinically significant hematologic toxicities due to its association with infection risk and potential treatment interruptions. In conventional capecitabine regimens, grade 3–4 neutropenia can occur, particularly when combined with other cytotoxic agents. In contrast, metronomic capecitabine is associated with a markedly lower incidence of severe neutropenia, likely due to the absence of high peak drug concentrations and reduced cumulative marrow suppression. Most reported cases in metronomic settings are low-grade (grade 1–2) and rarely necessitate treatment discontinuation, making this approach particularly attractive for patients requiring prolonged therapy [29].

Anemia is another commonly observed hematologic effect, although it is generally mild in patients receiving metronomic capecitabine. The pathophysiology is multifactorial, involving both direct suppression of erythroid progenitors and indirect effects such as chronic inflammation and nutritional deficiencies. In the metronomic setting, anemia tends to develop gradually and is often manageable with supportive care measures rather than dose modification. However, in patients with pre-existing anemia or those heavily pretreated with chemotherapy, even low-grade declines in hemoglobin levels may have clinical significance and warrant closer monitoring [30].

Thrombocytopenia is less frequently observed with capecitabine compared to other cytotoxic agents, and this trend persists in metronomic regimens. When it does occur, it is typically mild and asymptomatic, with a low risk of bleeding complications. The relatively sparing effect on platelet counts may be attributed to the lower sensitivity of megakaryocytes to continuous low-dose fluoropyrimidine exposure. Nonetheless, caution is advised in patients with baseline thrombocytopenia or those receiving concomitant therapies that may exacerbate platelet suppression [31].

An important consideration in hematologic toxicity is cumulative bone marrow suppression over prolonged treatment durations. Although metronomic dosing reduces acute toxicity, continuous exposure may still lead to gradual depletion of hematopoietic reserves, particularly in vulnerable populations such as the elderly or those with prior extensive chemotherapy. This cumulative effect underscores the importance of periodic complete blood count monitoring, even in the absence of overt symptoms, to detect early changes and guide timely intervention [32].

Interindividual variability plays a significant role in determining hematologic toxicity risk. One of the most critical factors is the activity of dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for metabolizing fluoropyrimidines. Deficiency in DPD can lead to excessive accumulation of active metabolites, significantly increasing the risk of severe and potentially life-threatening toxicities, including profound myelosuppression. Even in metronomic regimens, patients with partial DPD deficiency may experience disproportionate hematologic toxicity, highlighting the importance of pre-treatment screening where available [33].

In the context of non-metastatic triple-negative breast cancer, hematologic toxicity assumes particular importance due to the need for sustained treatment in the adjuvant setting. Patients may have already received intensive neoadjuvant or adjuvant chemotherapy, resulting in compromised bone marrow reserve. The relatively favorable hematologic profile of metronomic capecitabine makes it a suitable option in this setting, allowing continued therapy with a lower risk of severe cytopenias. This is especially relevant for patients with residual disease who may benefit from extended treatment but are unable to tolerate standard dosing schedules [34].

From a management perspective, hematologic toxicities associated with metronomic capecitabine are generally manageable with routine monitoring and supportive care. Dose interruptions or reductions are rarely required but may be considered in cases of persistent or worsening cytopenias. Growth factor support is typically not necessary, given the low incidence of severe neutropenia, but may be used selectively in high-risk patients. Overall, the hematologic safety profile of metronomic capecitabine contributes significantly to its feasibility as a long-term therapeutic strategy in oncology [35].

Non-Hematologic Toxicities of Metronomic Capecitabine

Non-hematologic toxicities constitute the most prominent and clinically impactful adverse events associated with capecitabine therapy. These toxicities are largely related to the systemic and local effects of its active metabolite, 5-fluorouracil (5-FU), on rapidly dividing epithelial tissues and microvascular structures. While metronomic dosing significantly reduces the incidence of severe (grade 3–4) toxicities, it does not eliminate them. Instead, it reshapes the toxicity profile toward more chronic, low-grade manifestations that may persist over prolonged treatment durations. Understanding these toxicities is essential for optimizing patient adherence and maintaining quality of life, particularly in the adjuvant setting of non-metastatic triple-negative breast cancer [36].

Hand-Foot Syndrome (Palmar-Plantar Erythrodysesthesia)

Hand-foot syndrome (HFS) is the most characteristic and frequently reported toxicity of capecitabine, often serving as a dose-limiting adverse effect in standard regimens. Clinically, HFS presents with erythema, swelling, pain, and desquamation of the palms and soles, which can progress to blistering and ulceration in severe cases. The pathogenesis is thought to involve drug accumulation in eccrine sweat glands and localized vascular damage, leading to inflammation and epithelial injury. In standard dosing schedules, the incidence of HFS can be substantial, with a significant proportion of patients experiencing grade 2–3 symptoms requiring dose modification [37].

In metronomic capecitabine, HFS remains the most common non-hematologic toxicity; however, its severity is generally reduced. Most cases are grade 1–2, allowing continued treatment with supportive care measures such as emollients, urea-based creams, and dose adjustments when necessary. Despite its lower severity, the chronic nature of HFS in metronomic therapy can still significantly affect daily activities and patient compliance. Early recognition and proactive management are therefore critical to prevent progression and maintain treatment continuity [38].

Gastrointestinal Toxicity

Gastrointestinal (GI) toxicity, including diarrhea, nausea, vomiting, and mucositis, is another major adverse effect associated with capecitabine. These toxicities result from damage to rapidly proliferating gastrointestinal epithelial cells, leading to impaired mucosal integrity and altered absorption. In conventional dosing, diarrhea can be severe and dose-limiting, occasionally leading to dehydration, electrolyte imbalance, and hospitalization. Mucositis, although less frequent than with intravenous 5-FU, can also contribute to treatment intolerance [39].

Metronomic dosing significantly attenuates the severity of GI toxicity by avoiding high peak drug concentrations. Most patients experience mild, manageable symptoms that do not require treatment interruption. However, continuous exposure may lead to persistent low-grade diarrhea or dyspepsia, which can cumulatively impact nutritional status and quality of life. In the context of non-metastatic TNBC, where prolonged therapy may be indicated, even mild GI symptoms should be actively managed to prevent treatment discontinuation [40].

Fatigue

Fatigue is a common but often underrecognized toxicity of capecitabine therapy. It is multifactorial in origin, involving direct drug effects, metabolic changes, anemia, and psychological factors. In standard regimens, fatigue may fluctuate with treatment cycles, often peaking during active dosing periods.

Although typically less severe than other toxicities, it can significantly affect functional status and overall well-being [41].

In metronomic therapy, fatigue tends to present as a chronic, low-grade symptom rather than an acute episodic event. The continuous nature of treatment may contribute to cumulative fatigue over time, particularly in patients receiving therapy for extended durations. This is especially relevant in early-stage TNBC patients undergoing adjuvant treatment, where maintaining daily functioning and quality of life is a priority. Addressing contributing factors such as anemia, sleep disturbances, and nutritional deficiencies is essential in managing this symptom [42].

Cardiotoxicity

Cardiotoxicity is a less common but clinically significant adverse effect associated with fluoropyrimidines, including capecitabine. Manifestations can range from mild chest discomfort to more severe conditions such as coronary vasospasm, arrhythmias, myocardial infarction, and, rarely, sudden cardiac death. The underlying mechanisms are not fully understood but are thought to involve endothelial dysfunction, vasospasm, and direct myocardial toxicity [43].

While most data on cardiotoxicity derive from standard dosing regimens, available evidence suggests that metronomic capecitabine may carry a lower risk due to reduced peak plasma concentrations. However, cases have still been reported, indicating that risk is not completely eliminated. Patients with pre-existing cardiovascular disease or risk factors should be carefully evaluated before initiating therapy, and any cardiac symptoms during treatment should prompt immediate investigation. In such cases, discontinuation of capecitabine and cardiology consultation may be warranted [44].

Other Non-Hematologic Toxicities

Additional non-hematologic toxicities associated with capecitabine include dermatologic reactions (beyond HFS), such as rash and hyperpigmentation, as well as mild hepatic dysfunction characterized by transient elevations in liver enzymes. These effects are generally mild and reversible but should be monitored during prolonged therapy. Ocular toxicity, including conjunctivitis and excessive tearing, has also been reported, although it is relatively uncommon [45].

In metronomic regimens, these toxicities tend to be less pronounced but may persist over time due to continuous drug exposure. The chronic nature of these effects highlights the importance of regular clinical assessment and patient education. Early identification and supportive management can prevent escalation and improve overall treatment tolerability, particularly in patients undergoing long-term therapy for non-metastatic TNBC [46].

Mechanisms of Reduced Toxicity in Metronomic Therapy

The improved tolerability of metronomic capecitabine compared with conventional dosing is not merely a consequence of lower drug doses, but rather reflects a complex interplay of pharmacokinetic, pharmacodynamic, and biological mechanisms. Central to this concept is the avoidance of high peak plasma concentrations of 5-fluorouracil (5-FU), which are typically responsible for acute cytotoxic damage to rapidly dividing normal tissues. By maintaining continuous low-level drug exposure, metronomic regimens reduce the intensity of off-target toxicity while preserving sustained therapeutic activity, thereby shifting the balance toward improved safety without necessarily compromising efficacy [47].

One of the primary mechanisms underlying reduced toxicity is the stabilization of drug plasma levels. In standard capecitabine schedules, intermittent high dosing leads to significant fluctuations in systemic drug concentrations, with peaks associated with gastrointestinal mucosal injury, bone marrow suppression, and dermatologic toxicity. In contrast, metronomic dosing produces a more uniform pharmacokinetic profile, minimizing these peaks and reducing acute cellular damage. This steady-state exposure is particularly beneficial for tissues with high proliferative rates, such as the gastrointestinal epithelium and hematopoietic system, which are highly sensitive to cytotoxic insults [48].

Another important factor is the differential sensitivity of tumor versus normal tissues to continuous low-

dose chemotherapy. Tumor-associated endothelial cells, which play a critical role in angiogenesis, are especially susceptible to sustained low-dose exposure. These cells exhibit limited capacity for repair and regeneration compared to normal tissues, making them preferential targets of metronomic therapy. As a result, antitumor effects can be achieved through antiangiogenic mechanisms without the need for high cytotoxic doses that would otherwise damage normal tissues. This selective targeting contributes to the reduced systemic toxicity observed with metronomic regimens [49].

Metronomic chemotherapy also exerts immunomodulatory effects that may indirectly influence toxicity. Low-dose continuous treatment has been shown to reduce populations of regulatory T cells (Tregs), which suppress antitumor immune responses, while preserving or enhancing effector immune cell function. This modulation of the immune system may allow for improved tumor control with less reliance on direct cytotoxicity. Importantly, because immune cells are less exposed to high-dose cytotoxic stress, the risk of profound immunosuppression—and associated complications such as severe infections—is reduced compared to conventional chemotherapy [50].

In addition, metronomic dosing may limit the activation of inflammatory pathways that contribute to treatment-related toxicity. High-dose chemotherapy is known to induce the release of pro-inflammatory cytokines and reactive oxygen species, leading to tissue injury and systemic side effects such as fatigue, mucositis, and organ dysfunction. By reducing the intensity of cellular damage, metronomic regimens may attenuate these inflammatory responses, resulting in a more favorable side effect profile. This mechanism is particularly relevant in the context of chronic toxicities, where ongoing low-grade inflammation can significantly impact patient quality of life [51].

The role of drug metabolism and enzymatic activity is also critical in modulating toxicity. Capecitabine is preferentially activated in tumor tissues due to higher expression of thymidine phosphorylase, while normal tissues are relatively spared. In metronomic regimens, the continuous low-dose exposure may further enhance this tumor selectivity by maintaining consistent activation within the tumor microenvironment while avoiding saturation of metabolic pathways in normal tissues. However, variability in enzymes such as dihydropyrimidine dehydrogenase (DPD) can still influence toxicity risk, emphasizing the importance of individualized assessment [52].

Another contributing factor is the reduced need for treatment interruptions and dose modifications in metronomic therapy. In standard regimens, acute high-grade toxicities often necessitate breaks in treatment, which can disrupt therapeutic continuity and lead to fluctuating exposure levels. Metronomic dosing, by minimizing severe adverse events, allows for more consistent drug delivery over time. This continuity not only supports sustained antitumor activity but also avoids the cyclical stress and recovery patterns that may exacerbate toxicity in normal tissues [53].

In the context of non-metastatic triple-negative breast cancer, these mechanisms are particularly relevant. Patients in the adjuvant setting often require prolonged therapy to eradicate micrometastatic disease, making long-term tolerability a critical consideration. The reduced toxicity associated with metronomic capecitabine enables extended treatment durations with fewer interruptions, potentially improving adherence and clinical outcomes. Moreover, the immunomodulatory and antiangiogenic effects may provide additional therapeutic benefits in TNBC, a subtype characterized by aggressive biology and limited targeted treatment options [54].

Overall, the reduced toxicity observed with metronomic capecitabine is the result of multiple interrelated mechanisms that collectively favor a more tolerable and sustainable treatment approach. Understanding these mechanisms not only provides a scientific rationale for metronomic therapy but also supports its integration into clinical practice, particularly in settings where balancing efficacy and safety is paramount [55].

Table (1): Comparison of toxicities of the studied patients in our study

	N=30	%
Abdominal pain	8	26.7%
Nausea	10	33.3%
Vomiting	2	6.7%
Leucopenia	8	26.7%
Hand, foot syndrome		
Absent	18	60%
Mild	6	20%
Moderate	2	6.7%
Severe	4	13.3%

Eight patients had abdominal pain (26.7%) and leucopenia (26.7%). Two patient developed vomiting and 33.3% had nausea. Six patients had mild hand and foot syndrome and four patients had severe hand and foot syndrome

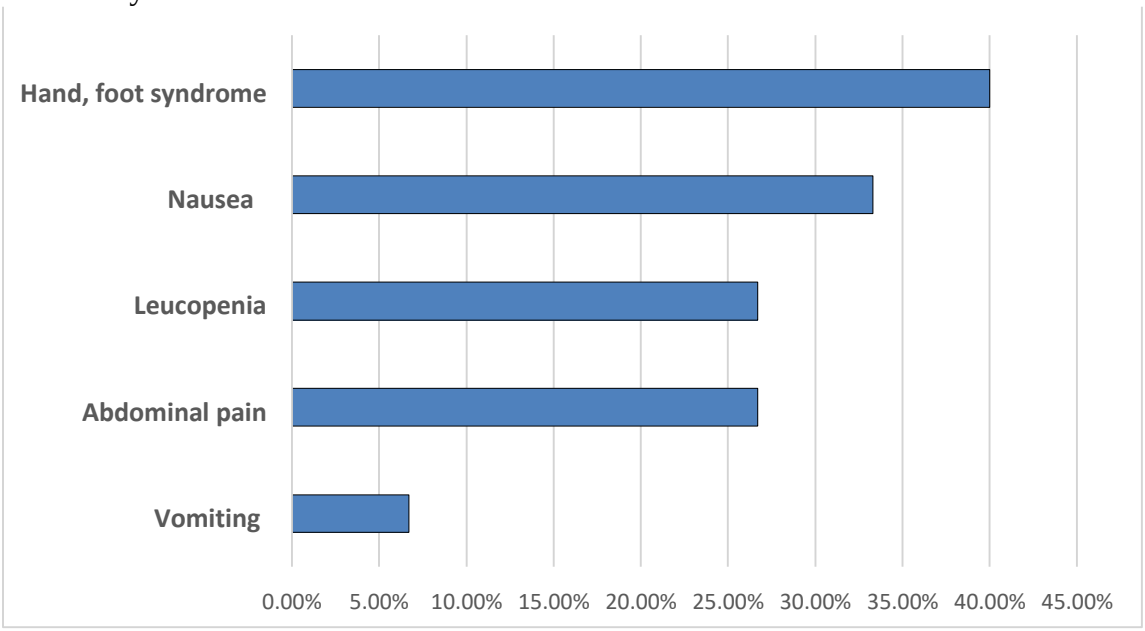

Figure (1): Simple bar chart showing adverse effects of the studied patients.

Evidence in Breast Cancer

Capecitabine has become an integral component of breast cancer management, particularly in patients with triple-negative and HER2-negative disease. Its role spans metastatic, neoadjuvant, and adjuvant settings, with multiple studies demonstrating both efficacy and a manageable safety profile. In conventional dosing schedules, capecitabine has shown meaningful clinical benefit, but toxicity—especially hand-foot syndrome (HFS) and gastrointestinal adverse events—often limits its long-term use. These limitations have prompted investigation into alternative dosing strategies, including metronomic administration, aimed at improving tolerability without compromising efficacy [55].

In metastatic breast cancer, several studies have evaluated metronomic capecitabine either as monotherapy or in combination with other agents. These studies consistently report lower rates of grade 3–4 toxicities compared to standard regimens, with improved treatment adherence and prolonged disease control. Importantly, while the incidence of severe adverse events is reduced, chronic low-grade toxicities such as HFS and fatigue remain common. These findings support the feasibility of metronomic capecitabine as a

long-term treatment option, particularly in patients who are not candidates for aggressive chemotherapy [53].

In early-stage breast cancer, the role of capecitabine has been most clearly defined in the adjuvant setting, particularly for patients with residual disease following neoadjuvant chemotherapy. The landmark CREATE-X trial demonstrated a significant survival benefit with the addition of adjuvant capecitabine in HER2-negative breast cancer, with the greatest benefit observed in the triple-negative subgroup. However, toxicity remained a notable concern, with a substantial proportion of patients requiring dose reductions or treatment discontinuation due to adverse events, particularly HFS and gastrointestinal toxicity [52].

These findings have led to increasing interest in metronomic capecitabine as a potentially more tolerable alternative in the adjuvant setting. Although direct evidence in early-stage disease is limited, extrapolation from metastatic and mixed-population studies suggests that metronomic dosing may reduce the incidence of severe toxicities while allowing prolonged drug exposure. This is particularly relevant in patients with non-metastatic triple-negative breast cancer, where extended therapy may be beneficial but is often limited by tolerability issues [54].

Real-world studies further support the use of metronomic capecitabine in breast cancer, particularly in older or frail patients. These studies highlight the practical advantages of continuous low-dose therapy, including reduced hospital visits, improved compliance, and a lower need for supportive interventions. Importantly, the safety profile observed in real-world settings is consistent with clinical trial data, reinforcing the generalizability of metronomic approaches. However, variability in dosing schedules and patient selection remains a challenge in interpreting these findings [55].

Non-Metastatic Triple-Negative Breast Cancer

In non-metastatic triple-negative breast cancer (TNBC), the interest in capecitabine is driven by the persistently high risk of relapse after standard anthracycline- and taxane-based treatment, particularly in patients with residual invasive disease after neoadjuvant therapy. This makes the adjuvant setting highly relevant for any strategy that can extend treatment exposure without adding prohibitive toxicity. From a clinical standpoint, the toxicity profile becomes as important as efficacy, because prolonged oral therapy is only useful if patients can realistically complete it. This is precisely where metronomic capecitabine becomes attractive: it offers continuous fluoropyrimidine exposure with the expectation of fewer high-grade adverse events than conventional intermittent schedules [56].

The strongest efficacy benchmark for adjuvant capecitabine in high-risk early TNBC remains CREATE-X, which used standard intermittent dosing rather than a metronomic schedule. In that phase III trial, capecitabine improved outcomes in patients with residual disease after preoperative chemotherapy, with particularly meaningful benefit in the triple-negative subgroup. However, toxicity was substantial, and hand-foot syndrome was the dominant adverse event, occurring in nearly three-quarters of treated patients according to the trial report. For the present review, CREATE-X is important not because it proves metronomic benefit, but because it establishes both the clinical value of capecitabine in early TNBC and the practical toxicity problem that lower-dose continuous strategies attempt to solve [56].

By contrast, the GEICAM/CIBOMA phase III trial evaluated extended adjuvant capecitabine after standard neo/adjuvant chemotherapy in early TNBC and did not meet its primary endpoint for the overall study population. That negative result is important because it shows that simply adding more capecitabine is not automatically beneficial across all early TNBC populations. It also reinforces the need to distinguish between patient selection, dose intensity, schedule, and biologic risk. For a toxicity-focused review, CIBOMA is particularly useful as a reminder that any adjuvant fluoropyrimidine strategy must be judged not only by efficacy but also by whether the adverse-event burden is justified in a curative-intent setting [57].

The most directly relevant randomized evidence for metronomic capecitabine in early TNBC is the SYSUCC-001 trial, which used low-dose continuous capecitabine at 650 mg/m² twice daily for 1 year after standard treatment. In the reply and discussion around that study, the investigators explicitly noted that this regimen was chosen on the basis of prior data suggesting similar efficacy with improved

tolerability compared with intermittent schedules. Reported toxicity was generally manageable, with hand-foot syndrome as the most common capecitabine-related adverse event, occurring in 45.2% of patients overall and grade 3 in 7.7%. The lower-dose continuous schedule was associated with fewer severe gastrointestinal and hematologic toxic effects than would typically be expected with full-dose intermittent capecitabine, which makes SYSUCC-001 the central study when discussing metronomic toxicity in non-metastatic TNBC [58,59].

Supportive smaller studies point in the same direction. In a prospective phase II study of extended adjuvant metronomic capecitabine in TNBC, Alagizy and colleagues used 500 mg twice daily continuously for 6 months after adjuvant chemotherapy and reported good tolerability, with only grade 1 palmar-plantar erythrodysesthesia in 31.7%, grade 1 diarrhea in 12.2%, and grade 1 vomiting in 4.9%, without major high-grade toxicity signals. Although the sample size was small and the study was not practice-changing on its own, it is valuable because it shows the same qualitative pattern seen in larger maintenance-style datasets: severe toxicity becomes less common, while chronic low-grade dermatologic and gastrointestinal toxicity remains the main issue. That pattern is highly relevant in non-metastatic TNBC, where long-term adherence may be undermined more by persistent nuisance toxicity than by abrupt life-threatening events [60].

Taken together, the evidence suggests that in non-metastatic TNBC, metronomic capecitabine should be viewed less as a direct substitute for CREATE-X-style standard capecitabine and more as a tolerability-oriented extended-adjuvant strategy for selected patients. The most consistent toxicity signal across studies is hand-foot syndrome, but at lower continuous doses it appears more often as a manageable chronic toxicity than as a frequent cause of major treatment discontinuation. This distinction matters clinically, especially for patients with residual disease, prior intensive chemotherapy exposure, borderline performance status, or concern about completing standard-dose therapy. Meta-analytic and real-world data also support the broader role of adjuvant capecitabine in early TNBC, but they still leave an evidence gap regarding the exact place of metronomic dosing in modern non-metastatic TNBC pathways, especially in the era of platinum-containing neoadjuvant therapy and immunotherapy [61,62].

Conclusion

Metronomic capecitabine represents a clinically meaningful shift from conventional chemotherapy paradigms, offering a more tolerable and sustainable treatment approach through continuous low-dose administration. Across available evidence, its toxicity profile is characterized by a clear reduction in severe (grade 3–4) adverse events, particularly hematologic and gastrointestinal toxicities, while maintaining a manageable spectrum of chronic low-grade effects such as hand-foot syndrome and fatigue. This balance between efficacy and tolerability is especially relevant in settings requiring prolonged therapy, where treatment adherence and quality of life are critical determinants of overall benefit.

In non-metastatic triple-negative breast cancer, where recurrence risk remains high and therapeutic options are limited, metronomic capecitabine emerges as a promising strategy to extend treatment exposure with acceptable toxicity. Although high-level evidence remains limited compared to standard dosing regimens, existing data suggest that this approach may improve tolerability without substantially compromising clinical outcomes in selected patients. Future research should focus on optimizing dosing schedules, identifying predictive biomarkers for toxicity, and integrating metronomic strategies within evolving treatment frameworks, including immunotherapy-based approaches, to fully define its role in modern oncology practice.

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