Provisional chapter

A Close Look at Neutropenia among Cancer Patients — Risk Factor and Management

Bassam Abdul Rasool Hassan,
Zuraidah Binti Mohd Yusoff and Saad Bin Othman

Additional information is available at the end of the chapter

1. Introduction

Neutrophil cells: were discovered by Elie Metchnikoff as an inflammatory immune response to rose thorns inserted in starfish larvae [1].

Neutrophils are a major type of white blood cell (WBC), and they represent about 45%-70% of all WBC. Neutrophils can also be referred to as poly-morphonucleat leucocytes or granulocytes, as their cytoplasm contains granules, which contains glycogen and antibacterial substances [2]. Neutrophils are synthesized and produced by hematopoietic stem cells in bone marrow. It takes 10 – 14 days to produce mature neutrophils. Neutrophils were first thought to have a short viability period of only 6-10 hours [2, 3], but in the late 1990s, it was that neutrophils may survive much longer. In addition, recent evidence has suggested that neutrophils may produce anti-inflammatory molecules and may promote the resolution of inflammation [4]. Moreover, it has been found that during inflammation or infection, neutrophils will migrate to the inflamed tissues, phagocytosis and remain active at site for about 2-6 days [2, 4, 5].

2. Synthesis and production of neutrophils cells

Neutrophil production and synthesis is a major activity of the bone marrow. In fact, two-thirds of blood cell synthesis in bone marrow is dedicated to the production of monocytes and granulocytes. Hematopoietic stem cells are characterized by little blood flow and low oxygen tension, while the more mature and actively dividing stem cells reside closer to the abluminal

side of the sinusoids, the special vascular structure of the bone marrow. The chemokine receptor CXCR4 is essential for the homing of stem cells and more mature neutrophils to the bone marrow [6].

Deletion of CXCR4 causes mature neutrophils to be released from the bone marrow into circulation without affecting the life-span of circulating neutrophils [6, 7].

The production of neutrophils is extensive, with 1 - 2 × 10^{11} cells being generated per day in a normal adult human. Granulocyte colony stimulating factor (G-CSF) is essential for tuning the production of neutrophils to meet the increased needs that occur during infections, but G-CSF is not absolutely required for granulocytopoiesis. Indeed, G-CSF null mice have approximately 25% residual granulocytopoiesis and still generate fully mature neutrophils [6]. The production of neutrophils is largely regulated by the rate of apoptosis of neutrophils in tissues. When macrophages and dendritic cells phagocytose apoptotic neutrophils in tissues, the production of interleukin 23 (IL-23) is reduced [6].

3. The role of neutrophils

Neutrophils are the body's first line of innate defense from micro-organismsand and inflammation. Neutrophils are able to bind to and ingest invading microorganisms such as bacteria, fungi, germs, or any foreign body in the blood by a process known as phagocytosis, most likely due to their defensive and/or phagocytic process is by their ability to release lytic enzymes from their granules and to produce reactive oxygen intermediates (ROI) [2, 3, 4, 8].

Neutrophils cells directly recognize surface-bound or freely secreted molecules produced by bacteria (i.e., pathogen-derived molecules), including peptidoglycan, lipoproteins, lipoteichoic acid, lipopolysaccharide (LPS), CpG-containing DNA, and flagellin. These pathogen-derived molecules, known as pathogen-associated molecular patterns, interact directly with a number of pattern-recognition receptors expressed on the cell surface of neutrophil cell. Pattern-recognition receptors play a role in the recognition of microbes by neutrophils, and the efficiency of phagocytosis by neutrophils is markedly enhanced if microbes are opsonized with serum host proteins, such as complement and/or antibody [9].

Neutrophils have receptors on their surface that help them to contact and bind to tissues and to the vascular endothelium near sites of infection or inflammation [2] and they are the first cells that migrate to the site of invasion or inflammation to start the clearance of infectious particles. In the events of invading foreign threat, they also send warning signals to other innate immune cells [1].

Thus the migration of neutrophils from the blood circulation to surroundings tissues is considered key in triggering host defense.

During the process of migration to site of invasive, neutrophils need to cross the vessel wall (transmigration). This takes place largely at postcapillary venules, where the vessel wall is rather thin, and the diameter of the vessel is sufficiently small that the neutrophils can make

contact with the vessel wall, and is yet not occluded by neutrophils when they arrest and make firm contact with the endothelium [6, 9, 10]. Neutrophil transmigration is a highly regulated process that requires the up-regulation of neutrophils and endothelial cell adhesion molecules. During neutrophil adhesion to endothelial cell, binding of neutrophils or endothelial cell adhesion molecules to their ligands may induce intracellular signaling pathways and downstream events, which may in turn modulate neutrophil transmigration. Indeed, the ligation of various adhesion molecules can initiate signal transduction pathways and induce subsequent cellular changes [11, 12].

Moreover, it has been found that neutrophils that migrate through tissues are more effective phagocytic cells than blood neutrophils that is non-migrating neutrophils [6]. Therefore, neutrophils have emerged as key components of the effector and regulatory circuits of the innate and adaptive immune systems, and this has led to a renewed interest in their biology [4]. Recent studies have shown that human neutrophils are a major source of cytokines, which are crucial for the survival, maturation, and differentiation of B cells, and are also involved in bone resorption [4].

4. Process of neutrophil cells penetration to the tissues

Migration of neutrophil cells from blood circulation into the surrounding tissues, this process consider as the key role that trigger host defense. Neutrophil transmigration across the vascular endothelium is a highly regulated process that requires the up-regulation of neutrophil and endothelial cell (EC) adhesion molecules. During neutrophil adhesion to ECs, binding of the neutrophil or EC adhesion molecules to their ligands may induce intracellular signaling pathways and downstream events, which may in turn modulate neutrophil transmigration. Indeed, the ligation of various adhesion molecules can initiate signal transduction pathways and induce subsequent cellular changes [11].

5. Neutropenia

Neutropenia is defined as a decrease in the absolute number of neutrophils in the blood. Clinically, neutropenia is defined as a decrease in the absolute neutrophil count (ANC) of more than two standard deviations below the normal range. Therefore, the patient is considered neutropenic when the ANC is lower than 1500 cells/μl (the normal level) [2, 3, 5, 13, 14]. An ANC above 1000 cells/μl will still confer normal protection against infection; therefore mild neutropenia is defined as an ANC 500 - 1000 cells/μl. There is a significant increase in the incidence of serious infection once ANC falls below 500 cells/μl, and moderate neutropenia is defined as an ANC of 200 - 500 cells/μl [2, 3, 13]. When ANC falls below 200 cells/μl it is defined as severe neutropenia. This condition is very serious and requires the patient to be admitted to the hospital and treated with antibiotics [3, 13], and patients with an ANC below 100 cells/μl are at the highest risk of infection. Hundred percent of the patients with ANC < 100 cells/μl lasting 3 weeks or more develop documented infection.

Neutropenia is usually diagnosed by a complete blood count (CBC) or full blood count (FBC). If the results show a low ANC then these tests are repeated [15]. If the repeated test shows the same results, a bone marrow biopsy is carried out to confirm the diagnosis. Bone marrow aspirate is taken from two sites, one from the middle of the bone and one from the solid, bonier part of the bone, usually from the large pelvic bone, the ilium, or the sternum [15].

Febrile neutropenia (i.e., neutropenia with fever) is mostly associated with chemotherapy, but it may also occur after irradiation of the bone marrow. In this chapter, the term febrile neutropenia is usually used to describe the occurrence of neutropenia (body temperature ≥38.3°C or oral temperature ≥38°C for more than hour) and an ANC of ≤ 500 cells/μl at the time of fever, or in the following 48 hours [2, 14, 15, 16, 17, 18].

6. Adverse effects

Neutropenia has many negative effects. One of these side effects is dose reduction of chemotherapy. Fifty percent (50%) of cancer patients received less than 85% of the prescribed doses because of neutropenia.

Neutropenia can also cause delays in chemotherapy treatment, which can lead to increase in cancer cell growth and tumor size. Both dose reduction and delay of chemotherapy can have serious effects on patients' lives, and may even lead to death [19, 20].

Neutropenia also has a dramatic and detrimental effect on the patients' quality of life. Fatigue is the predominant characteristic, which leads to a decrease in the ability to perform daily life activities. Patients describe fatigue as feeling weak and exhausted. Psychological problems were also reported by the patients, such as sadness, anxiety, reduced self-worth, and inability to fulfill normal roles [19, 20].

7. Neutropenia diagnosis

The diagnosis of neutropenia is usually made by performing the following tests:

7.1. Complete blood count

The first test to investigate the suspicion of neutropenia presence is to perform complete blood count (CBC) or full blood count (FBC) whereby the neutrophil numbers will be measured. If the results showed a low neutrophil count then these tests will be repeated in order to be certain that neutropenia is actually present [21].

7.2. Bone marrow aspirate/trephine biopsy

After performing a blood test, a bone examination could be carried out to confirm the results. Bone marrow biopsy is done by obtaining bone marrow aspirates from two sites that are from

the middle of the bone and also from solid bonier part of the bone. This bone biopsy is performed with the patient under general anesthesia or local anesthesia with sedation. These bone marrow samples are usually taken from the large bones such as large pelvic bone, the ilium, or sometimes from the flat breastbone (i.e., the sternum) [21].

8. Causes of neutropenia

Demographic factors, hematological disorders, autoimmune diseases, infections, drugs reactions, and chemotherapy or radiotherapy play a major role in the etiology of neutropenia [2, 13, 17]. Neutrophil production is lower among older people; they are not as able to produce mature neutrophil as younger people, and ANC in White men is higher than that in Black men. Also neutropenia incidence seems to be higher in women than men [2, 13, 14]. Hematological diseases like leukemia, myelodysplastic syndrome, Hodgkin's and non-Hodgkin's diseases, and multiple myeloma have also been shown to cause neutropenia [2]. In these hematological diseases, severe destruction of bone marrow leads to the destruction of stem cells. This will result in the prevention of or decrease in neutrophil production, thus causing neutropenia [2]. Moreover, these hematological diseases can have an effect on the red blood cells (RBC) and platelet production which can lead to severe anemia and thrombocytopenia. Usually the patient will suffer from fever ≥ 38.5°C as well as gingivitis, bleeding, stomatitis, bone chills, and the patient might also collapse [22]. Neutropenia has also been associated with autoimmune diseases like systemic lupus erythromatosis (SLE). Neutropenia following SLE is usually mild and the patient may not suffer from serious bacterial infection. However patients with Sjören syndrome and rheumatoid arthritis may have severe neutropenia, leaving them at higher risk of bacterial or fungal infection [2]. Many drugs such as diuretics, chlorpromazine, and allopurinol have been shown to cause neutropenia, and two mechanisms for this have been suggested. The first postulates that the drug produces dose-dependent toxicity on cell production, protein synthesis, bone marrow, and cell survival. The second suggests a mechanism of drug-inducing immunological reactions, for example, the binding of drugs with the surface of the neutrophil cell, leading to cell destruction and neutropenia. These two mechanisms are not always seen; they happen in only a small percentage of patients. These two mechanisms also require a long duration of drug use [2].

9. Chemotherapy

Neutropenia is mostly associated with chemotherapy and radiotherapy. Chemotherapeutic drugs affect the production of folic acid as well as the synthesis of DNA, RNA and protein by acting as anti-metabolites, which lead to bone marrow destruction [2, 13, 14, 22]. Bone marrow destruction in turn leads to a decrease in neutrophil production. Therefore, chemotherapy and radiotherapy are considered to be the main causes of neutropenia and febrile neutropenia. Besides that, chemotherapeutic drugs kill and suppress all the cells that have a high rate of division or affect blood cells, bone cells, and neutrophil cells (Fortner *et al.*, 2005). The chemo-

therapeutic drugs actinomycin, asparaginase, cytarabine, busulfan, cisplatin, daunorubicin, etoposide, fluorouracil, ifosfamide, and methotrexate are highly associated with neutropenia development [2, 14, 23].

The link between chemotherapy and neutropenia was emphasized by Buffoni *et al*. (2006) who looked at the effect and toxicity of chemotherapeutic drugs on 30 non-small lung cancer patients treated with a combination of cisplatin and vinorelbine on day 1 and day 8 and repeated every 21 days. The major toxic effect associated with these chemotherapies was neutropenia 3 and 4 (63%). The treatment also caused three deaths, two of which were due to febrile neutropenia. Hence it can be concluded that even though the combination of cisplatin and vinorelbine was very effective in the treatment of lung cancer, it was also associated with neutropenia, some of which was fatal [24].

Yamanaka *et al*. (2007) conducted a study 1055 patients in Japan with advanced gastric cancer on oral fluoropyrimidine derivatives (S-1). The main important result of the study was that neutropenia incidence was an inadequate predictor of increased survival in these patients. Also the another important point of their study was that the absence of neutropenia indicated that the doses of the chemotherapeutics drugs were not intensive enough to cause neutropenia [25]. This point was also indicated in the observational retrospective study carried out in Penang Hospital on 117 solid tumor patients who were admitted between January 2003 and December 2006, and treated with various types of chemotherapy regimens. The highest chemotherapeutic regimen received in this study was (5-FU + epirubicin + cyclophosphamide) (47, 40.2%), followed by (gemcitabine + cisplatin) (6, 5.1%), and others. The majority of the patients in the study were on a 1-day chemotherapy administration schedule of (90, 76.9%), followed a schedule of more than one day (27, 23.1%). The statistical analysis of Chi-square test results showed insignificant associations between chemotherapy type and neutropenia incidence (P=0.798) and neutropenia severity (P=0.199). The same results were found between neutropenia incidence and chemotherapy administration schedule and duration (P=0.689) and neutropenia severity (P=0.434).

The main explanation for these results was that the doses of these drugs were not high enough to cause bone marrow suppression and lead to neutropenia. Moreover, the administration schedule for each drug was long enough to overcome neutropenia, and the high use of G-CSF likely played a major role in reducing the time and neutropenia severity. All these factors likely contributed to the non-significant association observed between neutropenia incidence and severity, and chemotherapeutics drugs and administration schedule [26]. The correct doses of chemotherapeutic drugs must be used in order to prevent the incidence of lethal neutropenia [27].

Another study looking at the association between neutropenia and chemotherapy drugs was conducted by Banerji *et al*. (2006) in the United Kingdom. The study involved 173 patients treated with etoposide and carboplatin. The results obtained from the study showed a significant association between neutropenia and the chemotherapy drugs (P <0.0001) [28].

However, different chemotherapy regimens are not associated with the same neutropenia severity. This difference is due to substantial variations in the resiliency of hematopoietic

tissues among cancer patients and chemotherapy tolerance. Moreover, severe neutropenia has been reported in patients with solid cancers, especially breast cancer patients, when treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), suggesting that neutropenia is associated with the intensity of the chemotherapy regimens [8], for example, the doses of cytotoxic drugs such as epirubicin, cisplatin, doxorubicin, vincristine, capecitabine, carboplatin, and bleomycin were not high or intensive and they do not seem to cause severe neutropenia (i.e., neutropenia is considered a minor side-effect for these chemotherapies). But these low chemotherapy doses can cause other major adverse effects like nausea, vomiting, thrombocytopenia, alopecia, and anemia [29, 30, 31].

9.1. Role of route of chemotherapy administration

The route of chemotherapy administration could be either systematic which includes: intravenous (I.V), oral, and intramuscular (I.M) or local intrathecal, intraperitoneal, intra-arterial, and intrapleural. The most commonly used administration routes are the intravenous and the oral route. The advantage of administering chemotherapy by these two routes is that tumor cells throughout the body would be exposed to the chemotherapy. However, the disadvantage is that sensitive tissues such as in the bone marrow and mucosa will also be equally exposed to these chemotherapeutic drugs. So the main goal of I.V administration of chemotherapy is to achieve a systematic chemotherapy concentration that is effective for the cancer treatment of the cancer concerned [32]. When the chemotherapy is administered by the I.V. route, the entire dose of the chemotherapy drug will be in the blood circulation and produce its effect on the cancer cells. This will also lead to an increase in its adverse effect as compared to the oral route whereby the drugs will be slowly absorbed and the concentration will increase gradually thus not producing major side effects. But there will be no difference between the oral and the I.V. route in the part concerned with neutropenia incidence, onset, or severity, since neutropenia is related to chemotherapeutics intensity and effects but not with the route of administration [32, 33].

Jassem *et al*. (2003) focused on the effect of oral and I.V. administration of chemotherapeutic drugs on neutropenia incidence. In their study, 56 patients were treated with vinorelbine and cisplatin for their non-small cell lung cancer (NSCLC). On day 1 both drugs were given via I.V. route, and this was followed by cisplatin I.V. and vinorelbine oral on days 8, 15, and 22. The cycle was repeated every 28 days. The great and the predominant side effect observed was neutropenia, that is, 73% of the patients had grade 3 (severe) and 4 (life threatening) neutropenia and anemia had a lower percentage of incidences. Thus, Jassem and his colleagues' study demonstrated that the route of chemotherapy administration has no significant effect on their pharmacological action, since both routes produced similar efficacy and safety as well as similar side effects. However, the important point of their study was the new approach of I.V. administration on day 1, and oral administration on days 8, 15, and 22 which is more suitable and comfortable to the patients. However, the route of administration had no effect on the chemotherapy toxicity since neutropenia and anemia were still the major side effects produced by these chemotherapeutics drugs [34].

9.2. Impact of chemotherapy cycles and schedule on neutropenia

It is preferred to administer on a continuous basis for maximal cancer cell killing and to decrease the development of cancer cells resistance. However, chemotherapy toxicity results in the destruction of normal cells, and thus should be stopped for sufficient intervals so as to allow normal cells to recover. The duration of chemotherapy administration is known as chemotherapy cycle. Neutropenia incidence is mainly and highly associated with the first cycle of the chemotherapy more than the other or subsequent cycles. Indeed, the depletion of the bone marrow will lead to decreased production of the neutrophils and neutropenia which mainly occur with the first cycle of chemotherapy.

The association was determined by a study conducted in the United States of America by Crawford *et al*. (2005) The study included more than 4,000 cancer patients age ranged from 18 to 97 years. More than 100 different chemotherapeutic regimens were reported and the most frequently used chemotherapeutics were anthracyclines (35%), platinum compounds (33%) and fluorouracil (20%). Neutropenia occurrence after the first cycle of the chemotherapy was documented in 2,160 patients. Neutropenia with ANC nadir of < 1 × 109 cell/ L was observed in 43% of the patients, while severe neutropenia (ANC nadir < 0.5×10^9 cell/ L) was seen in 24% of the studied population. Fourteen percent of the patients had febrile neutropenia, while severe febrile neutropenia was found in 9% [35].

Another study in the United States conducted by Wolf *et al*. (2005) on 2,222 cancer patients showed that one-third of them were treated with fewer than four cycles of the chemotherapy due to complications. The most important result obtained was that half of the cases of neutropenia occurred during the first cycle of chemotherapy, especially among breast cancer patients [36].

The relationship between chemotherapy and neutropenia was also reported by Schallier *et al*. (2007). He conducted a study in Belgium on 48 non-small lung cancer patients treated with three cycles of paclitaxel, carboplatin, and gemcitabine. Schallier and his colleagues aimed to detect the toxicity of these chemotherapies after each cycle. The results of their study showed that the chemotherapy-induced neutropenia happened on days 8 and 15 of the first cycle. During the second cycle, 34 out of 42 patients developed neutropenia on day 15. Neutropenia was also prominent on day 15 of the third cycle, during which 24 out of 42 patients developed it. Therefore, the study showed that there was a strong relationship between chemotherapy cycle and neutropenia incidence. However, there was no significant relationship between chemotherapy cycle and neutropenia severity, which remained the same across the three cycles [37].

Neutropenia severity mainly increases due to chemotherapeutic drugs schedules [38]. Chemotherapeutic drugs are usually administered in a manner that will enhance their main benefits and reduce or prevent their toxic effects [32, 33, 39], but the duration of administration is also controlled by the pharmacokinetic and pharmacodynamic characteristics of the drug used, as some chemotherapeutic drugs can cause severe bone marrow suppression, such as the alkylating agent cyclophosphamide. These drugs are usually administered by pulse method, that is, for a short period (usually 1 day) followed by a long interval before the next

dose is given. This will give time for both the bone marrow and neutrophils to recover [40]. When given on a longer administration schedule, drugs such as 5-flurouracil will lead to the inhibition of RNA synthesis of the cancer cells, thus killing them. However, when given as a single bolus dose they will lead to the inhibition of thymidylate synthesis, which will result in severe side-effects. On the other hand, paclitaxel, when given for more than 1 day, will mainly lead to severe toxicity and cause more destruction of the bone marrow. However, when given for 1 day, paclitaxel will render the desired anticancer effect, with fewer effects on bone marrow. The standard interval between each cycle, whether the cycle lasts 1 day or more, ranges from 21 to 28 days [32, 33, 39].

10. Prevalence and incidence of neutropenia

Neutropenia generally occurs in one out of three patients treated with chemotherapy. Once neutropenia happens, it may threaten the patient's life, and chemotherapy schedule or dose should be delayed in order to give the body a chance to produce new neutrophils [41, 42, 43, 44]. Although neutropenia is common during chemotherapy, severe neutropenia is not and can cause serious morbidity and mortality due to resulting infections. Epidemiological studies have shown a wide variation in neutropenia incidence according to geographic regions. The average incidence of neutropenia in the United States is 56.4 per million people. There are no, or very few studies that give an exact number of neutropenia prevalence [45].

11. Risk factors for neutropenia

11.1. Gender

The female gender is a risk factor for neutropenia and febrile neutropenia. The possible reason for the higher number of females than males with neutropenia is that the incidence of cancer in females is generally higher than that in males by a ratio of 1:1.3 [46]. Moreover, it has also been reported that 49% of the solid cancer patients who developed neutropenia during chemotherapy were diagnosed with breast cancer. Since breast cancer occurs mostly in females, this could also explain the higher number of females with neutropenia [17, 47]. A study by Wolf *et al*. (2005) in the United States looked at the risk factors associated with neutropenia among 2,222 patients. The main results showed that there were significant associations of neutropenia severity and gender (P= 0.001) and between complication and gender (P= 0.004) [47]. An observational retrospective study was conducted by Bassam *et al*. (2009) on solid cancer patients admitted to Penang Hospital in 2003 - 2006 who became neutropenic during chemotherapy. The results show an insignificant association between incidence and neutropenia severity with patients' demographic data, leading to the conclusion that the demographic data is not a risk factor for neutropenia incidence or severity. However, the main reason for this insignificance was the small sample size [18].

11.2. Age

Neutropenia is more common among the elderly (i.e., 50 years of age or older). Indeed these individual are already less able to produce mature neutrophil cells [2, 8, 13, 17]. According to the National Cancer Registry of Malaysia (2003), cancer incidence, especially breast cancer incidence, is more predominant at the age of 50 years or more. Yip and Omar Hasan Kasule (2005) reported that neutropenia occurred mostly in people aged 50 - 59 years and 75% of the neutropenic patients in their study were diagnosed with breast cancer [48, 49]. In his study, Crawford (2007) investigated 282 lymphoma cancer patients treated with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), and said that the incidence of neutropenia was predominant among individuals aged 65 years or more compared to younger than 65 years of age [50]. Moreover, in the United States, Voelker *et al.* (2004) carried out a retrospective study from 1991 to 1999 on 7,238 patients with non-Hodgkin lymphoma (NHL). The main objective was to find the major risk factors associated with initiation and duration of hospitalization among neutropenic patients after chemotherapy. The median age was 75 years (range: 66 to 100 years). About 22% of patients needed hospitalization and half were first admitted within the first 42 days of treatment. The mean duration of hospitalization was 55.7 ± 1.43 days and the median was 34 days. The risk factors found to be associated with hospital admission were patients' age, gender, chemotherapy type, history, and disease stage. The risk of hospitalization due to neutropenia increased with age until the age of 80 years [51]. So the study by Voelker *et al*. (2004) demonstrated a significant association between neutropenia and patients' age and gender. At these advanced ages, chemotherapy doses usually reduced and the administration of G-CSF (Filgrastim) is increased [17, 36].

11.3. Ethnic group

The ethnic group has been suggested to have a significant effect on ANC and therefore there is a relationship between these variables and neutropenia [13]. However, some specific types of cancers are highly associated with specific races. According to Kaur *et al*. (2007), breast cancer incidence in Penang mostly occurs among the Chinese (62.5%), followed by the Malays (26.7%), and the Indians (10.2%), and breast cancer is most highly associated with neutropenia (Wolf *et al*., 2005), which could indicate that the ethnic group does play a role in the incidence of neutropenia [32, 52].

Moreover, in the United States, another study by Hershman *et al*. (2003) also showed that there is an association between ethnicity and neutropenia (WBC level) in breast cancer survivors. Their study was performed on African American and White American women with breast cancer (stage I and II) treated with chemotherapy. It showed that the WBC level in African American women was significantly lower than that of White American women. There was also a significant difference between the period of chemotherapy treatment of African American (19 women) versus White American women due to neutropenia. The explanation for the difference in period of treatment was said to be due to lower ANC. Besides that, neutropenia occurrence led to a delay in chemotherapy administration. Therefore, their study demonstrated a significant association between neutropenia occurrence and ethnicity [53].

12. Neutropenia and cancer type

12.1. Solid cancer

Neutropenia has been shown to be associated with solid tumors especially breast cancer, as about 25% of breast cancer patients develop neutropenia. Lyman and Wilmot (2006) and Wolf *et al.* (2005) found that among patients with solid cancer, breast cancer patients had the highest risk for developing severe neutropenia and febrile neutropenia during the first cycle of chemotherapy. Due to the neutropenia, 40% of the breast cancer patients had the chemotherapy delayed and about 25% had their chemotherapy treatment doses reduced. The possibility of breast cancer patients to develop neutropenia at point during chemotherapy was 78% [17, 32]. Patients with solid tumors usually have normal neutrophil cell function as compared to patients with hematological malignancies, whose neutrophil function is completely abnormal and thus would suffer from neutropenia. Patients with solid tumors are also not immuno-compromised as are those with hematological malignancies, and many centers now consider solid tumor patients to have a low risk of neutropenia [54, 55]. A significant association was also found between cancer type and neutropenia duration, but not between cancer type and neutropenia severity [56]. The study by AL-Ahwal (2005) also showed that the association between neutropenia severity and solid cancer was not significant, but that co-morbidity of chemotherapy with solid cancer was significant. Among breast cancer with neutropenia, more than 75% of cases seemed to be associated with the type of chemotherapy employed, which was CMF [17]. In a retrospective study on 117 solid cancer patients with neutropenia conducted by Bassam and colleagues in Penang, the type of solid cancer played an insignificant role in the incidence and/or neutropenia severity. The main explanation for this result was that patients with a solid tumor are different from those with hematological malignancy, in the sense that solid tumor patients usually have normal neutrophil cell function. While, in case of hematological malignant patients where by their neutrophil cells function is completely abnormal and thus they suffer from neutropenia. In contrast, neutropenia occurrence among solid cancer patients usually starts after chemotherapy, and severe neutropenia may last for 7 - 10 days. Thus the main cause of neutropenia is not the presence of cancer itself, but the chemotherapeutic agents or drugs used. For this reason solid tumor patients who developed neutropenia are considered to be at low risk for neutropenia [26].

12.2. Hematological cancer

Patients with hematological malignancies are necessarily immunocompromised, either as a result of the malignancy or due to the therapeutic interventions used to manage it. Some hematological malignancies are associated with specific immune defects that predispose to infections with particular pathogens. For example, patients with acute leukemia have an increased risk of severe gram-negative bacterial infections as a result of quantitative or functional neutropenia. Patients with chronic lymphocytic leukemia and multiple myeloma are susceptible to invasive bacterial infections from staphylococci, streptococci, and especially pneumococcus. Patients with lymphoma have abnormalities of the cellular immune system that result in an increased risk of viral (e.g., herpes simplex) and fungal infections (e.g.,

cryptococcus). Moreover, therapeutic interventions such as corticosteroids, chemotherapy, stem cell transplant, and radiation also produce deficiencies in the host immune defense [57].

Neutropenia due to chemotherapy is the most common risk factor for severe bacterial infections in hematological malignancies. Impaired T-cell function in patients undergoing allogenic stem cell transplant is associated with an increased susceptibility to invasive viral infections. It can also induce alterations in host colonization, such as disruption of natural skin and mucosal barriers, and can interfere with nutrition, which can cause an increase in the risk of infection. Therefore, the degree of neutropenia either as a consequence of the disease or the therapy, is directly related to the incidence of serious bacterial and fungal infection in patients with hematological malignancies. There is a significant increase in the incidence of serious infection once ANC falls below 500 cells/μl. Patients with ANC below 100 cells/μl are at the highest risk of infection. The duration of neutropenia also contributes significantly to the risk of serious infections. Qualitative defects in neutrophil function have been described in hematological malignancies. These include defects in chemotaxis, phagocytosis, bactericidal capacity, and the absence of respiratory burst that accompanies phagocytosis. Additionally, chemotherapeutic regimens used in association with corticosteroids can decrease phagocytosis and neutrophil migration [57].

13. Management of neutropenia

13.1. Granulocyte colony stimulating factors

Granulocyte colony stimulating factors are glycoproteins that regulate the proliferation, differentiation, functional activity and survival of myeloid cells, which help in reducing the duration and neutropenia severity as a result of chemotherapy [8]. Moreover, G-CSF treatment can significantly reduce hospitalization period and frequency neutropenic patients, and reduce the amount of antibiotics used [8]. G-CSF such as Filgrastim (Neupogen®) can be used to prevent, reduce, or palliate neutropenia in patients treated with chemotherapy. Filgrastim has also been shown to decrease the incidence of febrile neutropenia and to improve survival. Moreover, G-CSF have also been shown to decrease neutropenia severity. Both G-CSF and granulocyte-macrophage colony stimulation factors (GM-CSF) (Sargramostim®) have been approved by the United States Food and Drug Administration for the treatment of neutropenia [2, 8]. But G-CSF use is preferred as it is more effective and has a lower side-effect [8]. A study on the efficacy of the G-CSF in reducing neutropenia among solid tumor and lymphoma patients receiving chemotherapy was carried out by Lyman *et al*. (2002). In their study, G-CSF was administered before the occurrence of fever and neutropenia. There were 1144 patients with eight trials, five with filgrastim and three with lenograstim. The results showed that G-CSF reduced the risk of febrile neutropenia (odd ratio [OR] 0.38, 95% [CI]: 0.29 - 0.49). However, the reduction of infection-related mortality was insignificant (OR= 0.6, 95% CI 0.3 - 1.22). There were no differences in treatment effect by cancer type. The study demonstrated that there was a significant association between the G-CSF and the reduction of neutropenia risk [58].

Juan *et al*. (2001) carried out a prospective study in Spain on 44 solid cancer patients between 1997 and 1999. The aim of the study was to compare the effectiveness of different doses of G-CSF (lenograstim) on neutropenia. The doses used were 263 micrograms/day (full dose) and 131.5 micro grams/ day (half dose). Of the 44 patients, 39 (88.6%) developed neutropenia after chemotherapy. A total of 120 courses of chemotherapy were given to the patients, full doses were given in 61 courses and half a dose of lenograstim was given in 59 courses. The results of the study showed that severe neutropenia was more common among patients who received low doses of lenograstim (20%) as compared to the full dose of lenograstim (12%), but the difference was not significant (P= 0.1). The frequency of fever and hospital admission was not affected. The mean ANC with full doses of lenograstim was higher than with half doses, but was again not significant (P= 0.324). Juan concluded that both doses of lenograstim had a similar efficacy in reducing neutropenia severity [59].

All the above studies showed that G-CSF should be the primary treatment for severe and febrile neutropenia. This is also in accordance with Malaysian treatment guidelines for febrile neutropenia (i.e., severe neutropenia) treatment [60], which indicate that G-CSF should be considered in patients with febrile neutropenia with high risk features. In the case of severe febrile neutropenia (ANC less than 0.1× 109 cells/L), or in the presence of signs and symptoms of infection, antibiotics, must, be used with G-CSF [8].

13.2. Antimicrobial therapy

Empirical antibiotic therapy is required in neutropenia especially, when it is combined with gram-negative bacterial infection, as this combination is associated with high mortality. This point is supported by Schimpff (2001), who mentioned that if fever is not taken seriously and the neutropenic patient is suffering from a bacterial infection, 40% will die within the first 48 hours [61]. This is because there are no reliable methods to determine whether neutropenic fever is due to bacterial infection or not. Thus, antimicrobial therapy must be started either as mono antibiotic therapy or a combination antibiotic therapy. This reduces the mortality of gram-negative infection by 10% [62]. Any empirical antibiotic used must have a wide range of activity, enough to cover the majority of potential pathogens. There are three different universal strategies for using antibiotics in the treatment of febrile neutropenia: (i) a combination of either beta-lactam with aminoglycoside, (ii) monotherapy with wide range beta-lactam, and (iii) both of the above strategies combined [62]. Most neutropenic patients are treated with a beta-lactam antibiotic such as ceftazidime which is widely used as a single empirical antibiotic for neutropenic fever because its effectiveness is very similar to combination therapy. Other beta-lactam antibiotics such as imipenem, ticarcillin and cefepime may also be used as monotherapy or in combination with metronidazole or aminoglycoside (amikacin and gentamicin) to overcome bacterial infection, especially gram-negative bacteria. Penicillin derivatives such as piperacillin and tazobactam can also be used alone or in combination with beta-lactam derivatives such as imipenem to overcome anaerobe bacterial infection. The new generations of beta-lactam antibiotics have shown wide protection against both gram-positive and gram-negative bacteria such as cefepime [63]. Therefore, ceftazidime or imipenem could be used as first-line treatment while awaiting the results of a culture and

sensitivity test [2]. This is also in accordance with Malaysian antibiotic guidelines for febrile neutropenia (i.e., severe neutropenia) treatment [61, 64]. According to the United States Food and Drug Administration, there are many types of antibiotics that could be used to treat neutropenic patients. However, there are only a limited number of antibiotics that are effective for the treatment of febrile neutropenia (i.e., severe neutropenia). Ceftazidime is considered one of the most effective antibiotics and has been approved for the treatment of febrile neutropenic patients at different ages [65].

Combination therapy is also used when there is a need, when there is resistant bacteria in neutropenic patients, or even because of neutropenia severity [62]. In the United States, cephalosporin (mainly ceftazidime) is frequently used as an initial single empirical antibiotic for the treatment of febrile neutropenia. The combinations of cephalosporin plus vancomycin, third generation cephalosporin plus penicillin, or carbapenem plus aminoglycoside are also used. These combinations have been recommended for patients who were suspected to be or are suffering from resistance gram-negative bacterial infection [8]. The same result was found by De Pauw *et al*. (1994) who conducted a study on 692 cancer patients suffering from febrile neutropenia. In their study the patients either received 2g ceftazidime every 8 hours, or 14 - 16 g/ day of piperacillin, in 4 - 6 divided doses plus tobramycin 1.7 - 2 mg/kg of body weight every 8 hours. Their results showed that mortality due to infections was 6% with ceftazidime and 8% with piperacillin plus tobramycin. Adverse effects of ceftazidime occurred in 8% of patients, compared to 20% who received combination antibiotics. The main conclusion made by De Pauw and his colleagues was that ceftazidime as monotherapy was as effective as piperacillin plus tobramycin, and that ceftazidime was much safer in the treatment of febrile/ severe neutropenic patients [65].

Another study in Japan by Yano and Nakano (1996) looked at the use of antibiotic monotherapy in 43 patients suffering from hematological toxicity. Eighteen of these patients suffered from severe neutropenia (ANC < 500 cells/μl). The patients were treated with cefpirome or a combination of two beta-lactam antibiotics. The results showed that 89.5% of patients on cefpirome had a better quality of life, a decreased number of infusions, and a decrease in the frequency of antibiotic administration. Cefpirome use also led to a reduction in night urination, a low cost/benefit ratio and a reduction in nursing responsibilities. Due to this high efficacy rate, cefpirome monotherapy is therefore considered a first line treatment for patients with hematological diseases, and especially those with severe neutropenia, suffering from infection [66].

The effectiveness of antibiotic monotherapy was again supported by Tamura *et al*. (2001), who compared the effectiveness of antibiotic monotherapy and combination antibiotics in neutropenic patients. One hundred sixty five patients were enrolled in the study, with an average age of 52 years. Severe febrile neutropenia was found in the 60% of patients (ANC < 100 cells/ μl). The patients were divided into two groups. One group was treated with antibiotic monotherapy (either cefepime or carbapenem) and the other was treated with a combination of cefepime and aminoglycoside. Two- thirds of the patients from both groups showed that infection was overcome with antibiotic treatment. The conclusion was that the use of antibiotic monotherapy is as good and effective as combination antibiotics in the treatment of febrile

neutropenic patients. As mentioned the use of antibiotic monotherapy (ceftazidime or cefepime) was also emphasized by the Malaysian Ministry of Health. Indeed, while the uses of dual therapy may be preferred in cases with severe neutropenia, a prolonged duration should be expected, as should complications, such as sepsis, hypotension, mucositis and recurrent episodes [67].

13.3. Antibiotics schedule

According to the guidelines from the Infectious Society of America, neutropenic patients who remained febrile but showed recovery in ANC on the third day of antibiotic therapy can either continue with antibiotic treatment for 7 days, or antibiotic treatment can be stopped on the fourth or fifth day. For those febrile neutropenic patients with no recovery in ANC, antibiotics should be continued, and can be discontinued after 2 weeks if examinations and cultures show no bacterial growth [68]. Hughes *et al*. (2002) reported that antibiotic schedule for neutropenic patients is mainly determined and controlled by ANC (i.e., neutropenia severity). Antibiotic treatment can be stopped after 3 days if there is no infection. Indeed, continuing antibiotic treatment until the neutropenia is resolved is not preferred as it could lead to increased drug toxicity and bacterial resistance. Thus, Hughes and his colleagues suggested a preferred treatment of antibiotics for 5 - 7 days; antibiotics could be stopped before 5 days if there is evidence of hematological recovery [69].

In Canada, a study by Tomiak *et al*. (1994) looked at the antibiotic schedule used in 134 febrile neutropenic patients and its effect on duration of hospital stay. The study showed that antibiotics can be stopped within 4 - 5 days especially for patients whose culture shows no bacterial infection. The association between neutropenia and antibiotic reduction was significant (P<0.001) [70].

14. Types of route antibiotics administration according to risk of infection

14.1. Low risk neutropenic patients (Oral therapy)

A recent review has reported that inpatient oral antibacterial therapy can be safely replaced with conventional intravenous treatment among low-risk patients with febrile neutropenia, namely, those who are clinically stable, who do not suffer from acute leukemia, pneumonia, severe soft tissue infection, and who do not have any evidence of organ failure. Among these patients single-agent quinolone was not inferior to combinations of quinolone with amoxicillin plus clavulanic acid, but the latter is preferred when laboratory test show gram-positive infections. Moreover, oral quinolone therapy should not be administered to patients who have already received quinolone as a prophylaxis [71].

14.2. High risk neutropenic patients

The majority of the treatment guidelines indicate that high-risk neutropenic patients need to be treated with using parenteral broad spectrum antibiotic therapy, that is using standard,

hospital-based guidelines. For a long time, the most common approach was the selection and use of combination antimicrobial therapy (beta-lactam plus aminoglycoside antibiotics) [72].

14.3. Duration of therapy

According to the guidelines from the Infectious Society of America, neutropenic patients who remain febrile but show recovery in neutrophil cell count on the third day of antibiotic therapy could either continue with antibiotics treatment for 7 days or antibiotic treatments can be stopped on the fourth or fifth day.

For those neutropenic febrile patients with no recovery in the ANC it is preferred to continue antibiotics which could only be discontinued after 2 weeks when the examination and cultures show no bacterial growth [69].

14.4. Antifungal drugs

Fungal treatment is one of the most important steps for neutropenic patients. Even one positive blood culture for candida should be considered significant. Patients with disseminated candidiasis should be treated with fluconazole, which is as effective as amphotericin B and less toxic. If the patient is not stable and has already received fluconazole, amphotericin B is recommended. The treatment should continue until all signs of infections are resolved for a minimum of 2 weeks. Patients with invasive fungal infection are at risk of recurrent infection due to chemotherapy-induced neutropenia [73].

14.5. Antiviral drugs

The main characteristic of viruses is their simple structure, which helps them multiply. Viruses use the biochemical mechanisms of the host cell to produce new protein and genes. This makes the virus and the host cell identical and makes it difficult for the antiviral drug to distinguish the viral cell from the host cell. In the last couple of years, further information on the mechanism of viral multiplication has helped in the development of antiviral drugs such as acyclovir, which is effective against some herpes viruses. On the other hand, the increase in the use of immunosuppressive drugs had led to an increase in both bacterial and viral infections [74].

15. Conclusion

Neutropenia is a critical condition occurring among patients undergoing chemotherapy. It is strongly associated with a number of negative experiences that have an adverse effect on patients' quality of life. Neutropenia can lead to and is associated with critical infection of bacterial, fungal, or viral origin which may cause death if not treated. But survival in neutropenic patients can improve overtime with the uses of empirical antibiotic treatment (monotherapy or combination therapy). G-CSF is also a very effective treatment for neutropenia and febrile neutropenia.

Author details

Bassam Abdul Rasool Hassan[1*], Zuraidah Binti Mohd Yusoff[2] and Saad Bin Othman[2]

*Address all correspondence to: bassamsunny@yahoo.com

1 Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

2 Clinical Pharmacy Discipline, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM), Malaysia

References

[1] Kumar V., Sharma A. Neutrophils: Cinderella of innate immune system. International Immunopharmacology, 2010; 10, 1325 – 1334.

[2] Dale DC. Neutropenia. In: Herman NW. (ed.) Encyclopedia of Life Sciences. Chichester John Wiley & Son's, Ltd; 2005. p10 - 32.

[3] Frey RJ. Neutropenia. In: Donna O., Christine J., Karen B. (eds.) The Gale Encyclopedia of Medicine. Farmington Hills, Gale Research, An International Thomson Company; 1999. p77-89.

[4] Mantovani A., Cassatella MA., Costantini C., Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Immunology, 2011; 11, 519-531.

[5] Walker R, Edwards C. Laboratory Data. In: Wynne HA., Edward C. (eds.) Clinical Pharmacy & Therapeutics. New York, Churchill Livingstone; 2003. p 111-124.

[6] Borregaard N. Neutrophils, from marrow to microbes. Immunity, 2010; 33, 657-670.

[7] Eash KJ., Means JM., White, DW., Link DC. CXCR4 is a key regulator of neutrophil release from the bone marrow under basal and stress granulopoiesis conditions. Blood, 2009; 113, 4711–4719.

[8] Dale DC. Neutropenia and the Problem of Fever and Infection in Patients with Cancer. In: Morstyn G, Lieschke GJ. (eds.) Hematopoietic growth factors in oncology: New Jersey, Human Press; 2004. p65-87.

[9] Kobayashi S., Voyich JM., Burlak C., Deleo FR. Neutrophils in the innate immune response. Archivum Immunologiae et Therapiae Experimentalis, 2005; 53, 505–517.

[10] Alcaide P, Auerbach S, Luscinskas FW. Neutrophil recruitment under shear flow: It's all about endothelial cell rings and gaps. Microcirculation, 2009; 16, 43-57.

[11] Woodfin A., Voisin MB., Nourshargh S. Recent developments and complexities in neutrophil transmigration. Current Opinion in Hematology, 2010; 17, 9-17.

[12] Qin W., Eddie T., Chiang ML., Jean L., Rick R., Paul A. Janmey DS., Claire MD. Changes in the biomechanical properties of neutrophils and endothelial cells during adhesion. Blood, 2001; 97, 660-668.

[13] Frey R, Granger J. Neutropenia. In: Thackery E. (ed) The gale encyclopedia of cancer, Detroit: Gale Group; 2002. p. 770-773.

[14] Linker CA. Blood. In: Tiernery LM., McPhee SJ. Papadakis MA. (eds.) Current medical diagnosis and treatment. New York, Appleton & Lange; 2000. p 222-238.

[15] Bolyard AA., Edwards C., Kinsey S., Schwinzer B., Zeidler C. Understanding severe chronic neutropenia, Oaks, CA, USA, Scnir; 1994.

[16] Bledsoe BE., Kufs D., Soltis CA. Hematology. In: Bledsoe BE., Porter RS., Cherry RA. (eds.) Paramedic Care / Principles and Practice. New Jersey: Pearson Prentice Hall; 2005. p100-122.

[17] AL-Ahwal MS. Pattern of febrile neutropenia in solid tumors - A hospital based study. Pakistan Journal of Medical Sciences, 2005; 21, 249-252.

[18] Lyman GH., Wilmot JP. Risks and consequences of chemotherapy-induced neutropenia. Clinical Cornerstone, 2006; 8, 12-18.

[19] Bassam H., Zuraidah MY., Saad BO., Neutropenia onset, severity and their association with demographic data. Asian Journal of Pharmaceutical and Clinical Research, 2009; 2, 51-53.

[20] Ashley J., Taylor D., Houts A. The experience of chemotherapy- induced neutropenia: quality-of-life interviews with adult cancer patients. Journal of Supportive Oncology 2004; 2, 66-67.

[21] Ropka ME., Faan RN., Padilla G. Assessment of neutropenia related quality of life in a clinical setting Oncology Nursing Society 2007; 34, 403-409.

[22] Verstraete M., Vrhaeghe R., Peerlinck K., Boogaerts M.A. Haematological Disorders. In: Speight TM., Holford NH. (eds.) A very's Drug Treatment. Auckland, Adis Press; 1997. p56-68.

[23] Kimble-Koda MA., Young LY., Kardjan WA., Guglielmo BJ. Infections in Neutropenic Patients. In: Troy D. (eds.) Hand Book of Applied Therapeutics, Philadelphia, Lippincott Williams & Wilkins; 2002. p203-241.

[24] Buffoni L., Dongiovanni D., Barone C., Fissore C., Ottaviani D., Dongiovanni V., Grillo R., Salvadori A., Birocco N., Schena M., Bertetto O. Fractionated dose of cisplatin (CDDP) and vinorelbine (VNB) chemotherapy for elderly patients with advanced non-small cell lung cancer: phase II trial. Lung Cancer 2006; 54, 353-357.

[25] Yamanaka T., Matsumoto S., Teramukai S., Ishiwata R., Nagai Y., Fukushima M. Predictive value of chemotherapy-induced neutropenia for the efficacy of oral fluoropyrimidine S-1 in advanced gastric carcinoma. British Journal of Cancer 2007; 97, 37-42.

[26] Hassan BAR, Zuraidah MY., Saad O., Association of neutropenia onset and severity with chemotherapy regimens and schedules. Asian Pacific Journal of Cancer Prevention, 2011; 12, 1425-1428.

[27] Di maio M., Gridelli C., Gallo C., Shepherd F., Piantedosi FV., Cigolari S., Manzione L., Illiano A., Barbera S., Robbiati SF., Frontini L., Piazza E., Ianniello GP., Veltri E., Castiglione F., Rosetti F., Gebbia V., Seymour L., Chiodini P., Perrone F. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomized trials. Lancet Oncology 2005; 6, 669-677.

[28] Banerji U., Ashley S., Coward J., Hughes S., Zee Y., Benepal T., Norton A., Eisen T., O'Brien M. The association of chemotherapy induced neutropenia on treatment outcomes in small cell lung cancer. Lung Cancer 2006; 54, 371-377.

[29] Kern WV. Current Epidemiology of Infections in Neutropenic Cancer Patients. In: Rolston KVI., Rubenstein EB., (eds.) Text book of febrile neutropenia. London: Martin Dunitz, Ltd; 2001. p.57-90.

[30] Bow EJ. Infection risk and cancer chemotherapy: the impact of the chemotherapeutic regimen in patients with lymphoma and solid tissue Malignancies. Journal of Antimicrobial Chemotherapy, 1998; 41, 1-5.

[31] Howland RD. Mycek MJ. (2006) Anticancer Drugs. In: Pharmacology 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 435-484.

[32] Larsson PA., Carlsson G., Gustavsson B., Graf W., Glimelius B. Different intravenous administration techniques for 5-Fluorouracil pharmacokinetics and pharmacodynamic effects Acta Oncologica, 1996; 35(2): 207-212.

[33] Jassem J., Kosmidis P., Ramlau R., Zarogoulidis K., Novakova L., Breton J., Etienne PL., Seebacher C., Grivaux M., Ojala A., Aubert D., Lefresne F. Oral vinorelbine in combination with cisplatin: a novel active regimen in advanced non-small-cell lung cancer Annals of Oncology, 2003; 14, 1634-1639.

[34] Lyman G., Kuderer N., Djulbegovic B. Recombinant colony-stimulating factors reduce febrile neutropenia and infection in people receiving dose-intensive chemotherapy, but increase bone pain. American Journal of Medicine, 2002; 112, 406-411.

[35] Crawford J., Wolff D., Culakova E., Poniewierski M.S., Selby C., Dale D., Lyman G.H. First-cycle risk of severe and febrile neutropenia in cancer patients receiving systemic chemotherapy: results from a prospective nationwide study. Journal of Supportive Oncology, 2005; 3, 52-53.

[36] Wolff D., Culakova E., Poniewierski MS., Lyman GH., Dale DC. & Crawford, J. Predictors of chemotherapy-induced neutropenia and Its complications: results from a prospective nationwide registry. Journal of Supportive Oncology, 2005; 3, 24-25.

[37] Schallier D., Neynsa B., Fontainea C., Vande Steeneb J., De Meyc J., Meysmand M., De Grevea J. A novel triplet regimen with paclitaxel, carboplatin and gemcitabine (PACCAGE) as induction chemotherapy for locally advanced unresectable non small cell lung cancer (NSCLC). Lung Cancer, 2007; 56, 247-254.

[38] Rugo HS. Cancer. In: Tiernery, L. M., McPhee, S.J. & Papadakis, M.A. (ed.) Current Medical Diagnosis and Treatment. New York, Appleton & Lange; 2000. p.105-141.

[39] Glimelius B., Jakobsen A., Graf W., Berglund A., Gadeberg C., Hansen P., Kjaer M. Brunsgaard N., Sandberg E., Lindberg B., Sellstrom H., Lorentz T. Pahlman L. Bolus injection (2±4 min) versus short-term (10±20 min) infusion of 5-Fluorouracil in patients with advanced colorectal cancer: a prospective randomised trial. European Journal Of Cancer 1998; 34(5): 674-678.

[40] Scurr M., Judson I., Root T. Combination Chemotherapy and Chemotherapy Principles. In: Brighton D., Wood M. (eds.) Cancer Chemotherapy London, Churchill Livingstone; 2005. p 33-51.

[41] Neutropenia Association Inc. Neutropenia, causes, consequences and care. What is Neutropenia. Canada: Neutropenia Association Inc; 1993.

[42] Di Maio M., Gridelli C., Gallo C., Shepherd F., Piantedosi FV., Cigolari S., Manzione L., Illiano A., Barbera S., Robbiati SF., Frontini L., Piazza E., Ianniello GP., Veltri E., Castiglione F., Rosetti F., Gebbia V., Seymour L., Chiodini P., Perrone F. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomized trials. Lancet Oncology, 2005; 6, 669-677.

[43] Fortner BV., Schwartzberg L., Tauer K., Houts AC., Hackett, J., Stolshek BS. Impact of chemotherapy-induced neutropenia on quality of life: a prospective pilot investigation. Support Care Cancer 2005; 13, 522-528.

[44] Timmer-bonte JN., De Boo TM., Smit HJ., Biesma B., Wilschut FA., Cheragwandi SA., Termeer A., Hensing CA., Akkermans J., Adang EM., Bootsma GP. Tjan-Heijnen VC. Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch randomized phase III study. Journal of Clinical Oncology, 2005; 23, 7974-7984.

[45] Munshi HG. Severe neutropenia: a diagnostic approach. Western Journal of Medicine, 2000; 172, 248-252.

[46] National Cancer Registry of Malaysia. Second Report of the National Cancer Registry Cancer Incidence in Malaysia. In: Malaysia MOH (ed.) National Cancer Registry; 2003. p. 1-141.

[47] Wolff D., Crawford J., Dale CD., Poniewierski MS., Lyman G.H. Risk of neutropenic complications based on a prospective nationwide registry of cancer patients initiating systemic chemotherapy. Journal of Support Oncology, 2005; 3, 56-57.

[48] National Cancer Registry of Malaysia. Second Report of the National Cancer Registry Cancer Incidence in Malaysia. In: Malaysia MOH (ed.): National Cancer Registry; 2003. p. 1-141.

[49] Yip C., Kasule OH. Epidemiology of breast cancer in Malaysia. International Medical Journal 2005; 4, 1.

[50] Crawford J. Update on neutropenia and myeloid growth factors. Supportive Oncology 2007; 5(4): 27-29.

[51] Voelker MD., Rubenstein LM., Chrischilles EA., Chen-Hardee SS., Link BK., Wright KB., Brooks JM. Delgado DJ. Time to first neutropenia hospitalization during first-course chemotherapy among newly diagnosed non-Hodgkin's lymphoma patients: national SEER-medicare study. Journal of Supportive Oncology 2004; 2: 40-41.

[52] Kaur G., Ismail R., Lee SK., Sabaratnam S., Ahmad N. Assessment of correlation between clinicopathological features and Lymph node metastases in breast cancer. The Internet Journal of Pathology, 2007; 5(2): 1528-8307.

[53] Hershman D., Weinberg M., Rosner Z., Alexis K., Tiersten A., Grann VR., Troxel A. Neugut AI. Ethnic neutropenia and treatment delay in African American women undergoing chemotherapy for early-stage breast cancer. Journal of the National Cancer Institute, 2003; 95: 1545-1548.

[54] Zia Rahman GE., Hwee-Yong Y., Fraschini G., Bodey G., Hortobagvi G. Chemotherapy-induced neutropenia and fever in patients with metastatic breast carcinoma receiving salvage chemotherapy. Cancer, 1997; 79: 1150-1157.

[55] Rolston KVI. Infections in Patients with Solid Tumors. In: Rolston KVI., Rubenstein EB. (eds.) Text Book of Febrile Neutropenia. London: Martin Dunitz Ltd; 2001. p. 91-109.

[56] Koasak Ü, Rolston KVI., Mullen CA. Fever and neutropenia in children with solid tumors is similar in severity and outcome to that in children with leukemia. Support Care Cancer, 2002; 10: 58-64.

[57] Sharma A., Lokeshwar N. Febrile neutropenia in haematological malignancies. Journal of Postgraduate Medicine, 2005; 51, 42-48.

[58] Lyman G., Kuderer N., Djulbegovic B. Recombinant colony-stimulating factors reduce febrile neutropenia and infection in people receiving dose-intensive chemotherapy, but increase bone pain. American Journal of Medicine 2002; 112, 406-411.

[59] Juan O., Campos JM., Caranana V., Sanchez JJ., Casan R., Alberola, V. A randomized, crossover comparison of standard-dose versus low-dose lenograstim in the prophylaxis of post-chemotherapy neutropenia. Support Care Cancer 2001; 9, 241-246.

[60] Clinical practice guidelines. Rational Antibiotic Utilisation in Selected Paerdiatric Conditions. In: Health Technology Assessment Unit, M. D. D. Putrajaya, Ministry of Health Malaysia, Academy of Medicine Malaysia; 2007.

[61] Schimpff CA. Fever and Neutropenia: an Historical Perspective. In: Rolston KVI., Rubenstein EB., (edS.) Text Book of Febrile Neutropenia. London: Martin Duntiz Ltd; 2001. p. 1-26.

[62] Rolston KVI. Infections in Patients with Solid Tumors. In: Rolston KVI., Rubenstein EB. (eds.) Text Book of Febrile Neutropenia. London: Martin Dunitz Ltd; 2001. p. 91-109.

[63] Clinical practice guidelines. Rational Antibiotic Utilisation in Selected Paediatric Conditions. In: Health Technology Assessment Unit, M. D. D. Putrajaya, Ministry of Health Malaysia, Academy of Medicine Malaysia. 2004.

[64] Alexander SW., Pizzo PA. Special considerations in children with fever and neutropenia. In: Rolston KVI., Rubenstein EB. (eds.) Text book of febrile neutropenia. London: Martin Dunitz Ltd; 2001. p. 65-78.

[65] De Pauw BE., Deresinski SC., Feld R., Lane-Allman EF., Donnelly JP. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer: A multi center randomized trial. Annals of Internal Medicine, 1994; 120, 834- 844.

[66] Yano K., Nakano Y. Clinical evaluation of monotherapy with cefpirome for infections complicating hematological disorders. Journal of Infect Chemother, 1996; 2, 75-78.

[67] Tamura K., Matsuoka H., Ikeda S., Masuda M., Tsukada j., Matsuishi H., Izumi Y., Saburi Y., Uike N., Okamura S., Kawano F., Utsunomiya A., Shibuya T., Imamura Y., Uozumi K., Hayashi M., Gondoh H. A Randomized trial of single versus combination antibiotic therapy for febrile neutropenic patients by Kyushu Hematology Organization For Treatment (K-HOT) Study Group. Clinical Oncology, 2001; 20, Abstract 1549.

[68] Leighl N., Feld R. Clinical Practical Guidlines in Patients With Fever and Neutropenia. In: Rolston KVI., Rubenstein EB. (eds.) Text Book of Febrile Neutropenia. London: Martin Dunitz Ltd; 2001. p. 560-583.

[69] Hughes WT., Armstrong D., Bodey GP., Bow EJ., Brown AE., Calandra T., Feld R., Pizzo PA., Rolston KVI., Shenep JL., Young L.S. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer, Clinical Infectious Diseases; 2002 34, 730-751.

[70] Tomiak AT., Yau JC., Huan SD., Cripps MC., Goel R., Perrault DJ., Bourcier JD., Prosser IA., Soltys KM., Evans WK., Stewart DJ. Duration of intravenous antibiotics for patients with neutropenic fever. Annals of Oncology, 1994; 5, 441-445.

[71] Schimpff CA. Fever and Neutropenia: an Historical Perspective In: Rolston KVI., Rubenstein E.B., (eds.). Text Book of Febrile Neutropenia. London: Martin Duntiz Ltd; 2005. p. 1-26.

[72] Flaherty J. (1999) Infectious Complications of Oncology Therapy. In: Vokes EE., Golomb HM., (eds.). Oncologic Therapies. Berlin; Springer 1999.p. 228-244.

[73] Wiltink EHH., Janknegt R. Antiviral drugs. Pharmaceutisch Weekblad. 1991; 13 (2): 58-69.

IntechOpen