Assessment and treatment of neutropenic sepsis within the emergency department.

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Abstract

Neutropenic sepsis is a life-threatening side effect of chemotherapy. Neutropenic sepsis has a mortality rate of 2-21% and may affect drug regimens of chemotherapy or other immunosuppressive drug therapy, leading to reduced drug efficacy and impact on cancer treatment outcomes, including disease-free intervals and survival rates. As there are more treatment options for those diagnosed with cancer, doctors, nurses, and allied healthcare professionals will be exposed to more acute oncological emergencies within the emergency department. These healthcare professionals need to recognise the signs and symptoms of neutropenic sepsis and be able to provide treatment within the hour to improve the patient’s outcome.

Keywords

Acute oncology, acute oncological emergencies, assessment, chemotherapy, emergency department, golden hour, neutropenic sepsis, nursing care, signs and symptoms, and systematic anti-cancer treatment.

Introduction

There are approximately 375,000 new diagnoses of cancer in the United Kingdom (UK) (Cancer Research 2022). Doctors, nurses, and allied health professionals will be exposed to acute oncological emergencies arising from complications from cancer and Systematic Anti-Cancer Treatment (SACT) (Walji et al. 2008). SACT has evolved, with the introduction of novel treatments alongside chemotherapy such as immunotherapies, monoclonal antibodies, and increased radiotherapy treatments, as first, second, third- and fourth-line treatments. Chemotherapy works by targeting fast-dividing cells at different stages of the cell cycle. However, chemotherapy cannot distinguish between cancerous and non-cancerous cells, which is why patients are experiencing side effects such as neutropenia, nausea and vomiting, stomatitis, and alopecia (Wyatt and Hulbert Williams 2015).

With this exposure to more available lines of treatments, there would be an increased impact on the bone marrow and cause further and more pronounced myelosuppression (Gabriel 2012). All blood cells derive from a single stem cell within the bone marrow. Chemotherapy damages these fast-dividing cells within the bone marrow, which reduces the number of cells within the blood, this is known as myelosuppression. Neutropenia can be described as an abnormal level of neutrophils within the blood and take up to 7 days to mature before being released into the bloodstream. Within the blood, neutrophils constitute up to 70% of the white blood cells and are a part of the body's defence against infection (Wyatt and Hulbert Williams, 2015). As chemotherapy affects the bone marrow, the neutrophil count can be at its lowest (Nadir) 7-10 days post-chemotherapy, however, will normally recover before the next treatment.

Sepsis is a dysregulated host response to an infection associated with life-threatening organ dysfunction (Singer 2016). It is estimated within the UK there are 918,000 adult sepsis admissions per year, and 66,096 deaths (Bion et al. 2022). Neutropenic sepsis (NS) has mortality between 2-21%, despite the use of colony-stimulating factors (NICE 2012, Forde and Scullin, 2017). National reports have been published since 2008, investigating various aspects of cancer and cancer care (Mansour et al. 2010). The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) 2008 report: ‘For better, for Worse’ highlighted unacceptably high death rates within 30 days of administration of cytotoxic chemotherapy (NCEPOD 2008). A recommendation from this report; the emergency department and clinicians should have the resources and capability to manage toxicities from SACT. The focal point of this recommendation is an agreed local policy and clinical pathway for the management of neutropenic sepsis. Succeeding the NCEPOD (2008) report, The National Chemotherapy Advisory Group (NCAG) report published in 2009 made recommendations for an acute oncology service (AOS) in every hospital with an Emergency Department (ED) (NCAG 2009). This report in addition also highlighted safety issues and the need to develop governance, education and training related to SACT and the side effects of these treatments. The Chemotherapy Services in England: Ensuring quality and safety report (2009) advises that “all patients should be given both verbal and written information about their treatment, likely side effects and whom they should contact if problems arise”.

There is no universal definition for NS (King et al. 2021). NS is defined as a temperature of greater than 38oC, with a neutrophil count of less than 0.5 X 109/l in a patient undergoing SACT (NICE 2012). However, there may be a lack of a delay in the local inflammatory response and absence of pyrexia (Dunkley and McLeod 2015, Clarke et al. 2013). Patients may have taken medications that can mask an elevated temperature and therefore a good patient history will establish this (Foulkes 2010). A low temperature on the other hand below 36°C, can be an indicator of severe sepsis (Angus and van der Poll 2013). Clarke et al. (2011) reviewed clinical guidance in UK cancer centres regarding neutropenic sepsis and noted a lack of consensus regarding trigger temperature values. An abnormal body temperature is described as a potential symptom of an infection-related cause, but its presence or absence is not included in the guidance as a diagnostic indicator of sepsis (Singer et al., 2016). These are examples of the controversies regarding the diagnosis, assessment, and management of NS.

Factors are known to increase the risk of neutropenia these are those who are over 60 years of age, who are on SACT, on corticosteroids (as this can cause additional immunosuppression (Klastersky 2016). Those whose cancer is at an advanced stage, previous admissions of neutropenia, surgery, prolonged hospital admissions, malnutrition (which can be a side effect of the chemotherapy, due to mucositis), and those with a central venous access device and those with co- and multiple morbidities (Kochanek 2019, Morgan, 2018, White 2017, Klastersky 2016, Warnock 2016, Clark 2013). Patient’s receiving high-intensity chemotherapy regimens (haematological malignancies) and/or undergoing haematopoietic stem cell transplantations are at increased risk of neutropenia of 80% and more when the incidence varies between 10% and 50% in people with solid tumours and prolonged neutropenia (neutropenia lasting more than 7 days). Due to the increased risk and prolonged neutropenia, they are also at risk of fungal infections (King, Mcfadyen and Iles 2021, Kochanek 2019, White 2017, Clarke 2013, NICE 2012).

Patients with NS normally fall into one of three categories: those with microbiologically documented infection when both source and pathogen are known; pathogen not known and fever of unknown origin (where neither source nor a pathogen is found) (King, Mcfadyen and Iles 2021, The Immunocompromised Host Society 1990).

The best practice is the administration of the antibiotic within the golden hour. The patient presenting with suspected NS needs to receive empirical antibiotics within an hour of presentation, known as the ‘door to needle time’ (NCAG 2009). As noted, mortality from chemotherapy-induced sepsis ranges from 2 to 21%, and mortality from sepsis (all causes) is 30% rising to 50% for septic shock (Oakley et al. 2016). Authors acknowledged each hour of intravenous (IV) antibiotic delay further increases mortality by 8% and sepsis is a time-dependent medical emergency, which early administration of empirical IV antibiotics can reduce the mortality rate (Gaieski et al. 2010, Dellinger et al. 2008, Lin et al. 2008, Zukermann et al. 2008, Gross 2006, Kumar et al. 2006, Larche et al. 2003). Continuing with the controversy is the choice of antibiotic therapy and the duration of the course. Within the current practice, the antibiotic of choice for the treatment of NS has been a board-spectrum ẞ-lactam antibiotic such as Piperacillin/Tazobactam and Meropenem, in those who are penicillin-allergic treated with a quinolone or a combination therapy of Aztreonam and Vancomycin (NICE 2012, Boin, 2022, Lortholary 2008, Bal et al. 2007).

NICE guidelines recommend the Multinational Association for Supportive Care in Cancer (MASCC) risk index score, should be used in the assessment. This should be completed by the medical team as part of the assessment as best practice for the management and treatment of suspected NS (NICE 2012). This index tool is a weighted scoring system of seven clinical characteristics assessed at presentation. A score of more than 21, would indicate a lower risk and could potentially be converted to oral antibiotics after the administration of IV antibiotics. Those who score less than 21 are at substantial risk of developing serious medical complications and should continue to receive IV antibiotics (de Naurious et al. 2010, Innes et al. 2008, Klastersky et al. 2000). However, this is a tool to help aid clinical decisions and further antibiotics guidance should be in the discussion with the microbiologists and the acute oncology team.

[MASCC]

A patient may present themselves to the emergency department, medical assessment unit or designated area either being referred by calling the chemotherapy helpline or self-presenting. Those who call the helpline are triaged using the UKONS 24 Hour triage tool. This is a traffic light approach, this toolkit was developed in 2007 and uses the RAG Rating (UKONS, 2016). At this time of the arrival of the door to needle time starts, 60 minutes to administer the intravenous antibiotics.

Within the history taking, there are key questions to be asked and to ensure if they have any allergies as this would affect the choice of antibiotic.

Has the patient received systemic anticancer therapy within the last 6 weeks?

Does the patient have a temperature ≥38⁰C, or ≥37.5⁰C on two occasions recorded 1 hour apart?

Did the patient have a bone marrow transplant?

Is the patient immuno-suppressed (HIV or other)?

What chemotherapy is the patient on and when was the last treatment/tablet?

It is useful to enquire whether:

Blood products have been administered within the previous 6-24 hours as this may account for a febrile episode and if the rigours are associated with the use or flushing of a central venous line.

On examination look for:

* General appearance, level of consciousness and cognition**.** Cognitive assessment should include recognition of new-onset confusion, disorientation, and/or agitation.
* Temperature, heart rate, respiratory rate and signs of respiratory distress, and blood pressure.
* Capillary refill time and oxygen saturation (abnormal results may indicate poor peripheral perfusion).
* Mottled or ashen skin; pallor or cyanosis of the skin, lips, or tongue; cold peripheries.
* Chills, shivers, rigours
* A non-blanching rash may suggest meningococcal disease.
* Any breach of skin integrity (for example cuts, burns, or skin infections) or other skin signs suggesting infection, such as erythema, swelling or discharge at a surgical site, or wound breakdown. Those who are neutropenic, may not have this due to the reduced immune and inflammatory response.
* Dry mucous membranes or other signs of dehydration**.**
* The possible underlying source of infection. Symptoms or signs indicating possible infection such as dysuria, diarrhoea, or productive cough. This includes people who are deteriorating unexpectedly or failing to improve as expected.
* Look at vascular access sites, especially central venous line insertion sites, stem cell aspiration sites, nail margins, skin tunnels, surgical incision sites
* NEWS 2 score

The patient should be managed following local guidance but should be following the sepsis ‘six’ bundle:

* Give oxygen therapy to people with reduced oxygen saturation or with an increase in oxygen requirement over baseline, to maintain oxygen saturation above 94% unless contraindicated.
* Take blood tests and microbiology samples including
	+ Blood gas including glucose and lactate measurement
	+ Blood culture — ideally done before antibiotic administration. This is done peripherally and from the CVAD.
	+ Full blood count
	+ C-reactive protein (CRP)
	+ Creatinine, urea, and electrolytes
	+ Liver function tests
	+ Clotting screen
* Urine analysis and culture, sputum microscopy and culture, chest X-ray, and additional investigations such as chest CT.
* Give an intravenous broad-spectrum antibiotic at the maximum recommended dose.
* Antibiotic treatment should not be delayed until neutropenia is confirmed.
* Give an intravenous fluid bolus to restore tissue perfusion.
* Check serial lactate measurement.
* Check urine output, monitor fluid balance hourly and monitor the person's clinical condition.
* Multinational Association of Supportive Care in Cancer (MASCC) prognostic index to identify people at minimal risk of complications.
* Do not give administer any oral chemotherapy

(NICE 2019, Kochanek 2019, Cecconi 2018, Lev 2018, Daniels 2017, Rhodes 2017, White 2017, Klastersky 2016, Singer 2016, Clarke 2013, Gauer, 2013)

At the time of the administration of the IV antibiotic, is when the clock stops. Many factors will influence the door to needle time. Delays in the administration of empirical IV antibiotics may also reflect the nebulous symptoms associated with NS and can be indistinct from the common side effects of SACT, such as diarrhoea and mucositis (Oakley et al. 2016; NICE 2012). It can be down to the work environment, waiting to be reviewed by the clinician and waiting for the prescription and due to the ongoing pressures within the NHS and those who present in a more critical condition would be made a priority. (Oakley 2010; Ko et al 2015). The patient should be alerted to the AOS Team for review. Infections in neutropenic patients typically take 2-7 days to respond to antimicrobial therapy. NS may affect drug regimens of chemotherapy or other immunosuppressive drug therapy, leading to reduced drug efficacy and impact on cancer treatment outcomes, including disease-free intervals and survival rates (Klastersky 2016, Warnock 2016, Morgan 201).

Conclusion

NS can be a life-threatening illness that can be a complication of SACT. Patients are educated about the side effects of the treatment and awareness of the chemotherapy helpline number they need to call. If NS is suspected, prompt and urgent treatment is required, due to the mortality rate, this is reduced with the administration of intravenous antibiotics within the hour. Nurses must recognise the signs and symptoms of NS and be able to act quickly. Ensuring a referral has taken place to the AOS team, to ensure the support of the patient is continued throughout the admission.

Implications for practice

Nurses should have a high level of suspicion for neutropenic sepsis in patients undergoing chemotherapy.

Intravenous antibiotics should not be delayed and administered within 1 hour of presentation.

Take blood cultures before the administration of antibiotics if possible.

Do not wait for blood results before the administration of antibiotic treatment.

Pyrexia may be absent and therefore not be a ruling factor when assessing for neutropenic sepsis

Conflict of interest statement

No conflict of interest

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Summary table of risk factors

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| Risk factors of neutropenia* Cancer at an advanced stage
* Co- and multiple morbidities
* Corticosteroids
* Haematopoietic stem cell transplant
* High intensity chemotherapy regimes
* Malnutrition
* Over the age of 60
* Previous neutropenia
* Prolonged hospital admissions
* Receiving SACT
* Surgery
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MASCC Scoring

|  |  |
| --- | --- |
| Prognostic Factor | Weight |
| Burden of illness |  |
| No or mild symptoms | 5 |
| Moderate symptoms | 3 |
| No hypotension (systolic blood pressure >90 mm Hg) | 5 |
| No chronic obstructive pulmonary disease | 4 |
| Solid tumour or no previous fungal infection | 4 |
| No dehydration requiring parenteral fluids | 3 |
| Outpatient status | 3 |
| Age < 60 years | 2 |

 MASXX Risk Index score $\geq $ 21 indicates that the patient is at a low-risk complications and mortality.