Non-Hodgkin’s lymphoma treatment in early pregnancy: dilemmas between risks and benefits

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ABSTRACT

Background: Malignancy during pregnancy can cause medical complications and quandaries therefore it necessitates careful consideration of the risks and benefits of therapy for the mother’s and fetus’s safety, as well as the impact on the fetus’s health and development. In this case report, we highlight important aspects of a pregnant woman with second trimester who had non-Hodgkin’s lymphoma (NHL) receiving chemotherapy.

Case presentation: A 20-years old pregnant woman was referred to One-Stop Oncology Outpatient clinics (POSA) at Dr. Soetomo General Academic Hospital. The patient complained that during the first semester, the patient felt a lump in the right neck with the size of a marble (±1.5 cm), dense, supple, sticky, firm boundaries, and growing over time. The patient reported tired and nauseous almost every day, had lost 5 kg in one month, and also had night sweats. The patient slept in a sitting position to reduce complaints of shortness of breath and a feeling of chest tightening. Based on CT scan, cytology of fine needle aspiration biopsy (FNAB) and immunohistochemistry (IHC) examination the patient was diagnosed with NHL of right neck and mediastinum, stage II-B+ superior vena cava syndrome (SVCS) and microcytic hypochromic anemia. The patient was treated using the CHOP chemotherapy regimen, with doses based on body surface area: C (cyclophosphamide): 1.065 mg/iv, H (doxorubicin): 71 mg/iv, V (vincristine): 1.98 mg/iv and P (prednisone): 100 mg/day and discharged on the 13th day of the admission. However, four months after hospital admission, the patient had an obstetric ultrasound and the fetal had reduced heart rate. Pregnancy was terminated with a cesarean section resulting in a live baby with 2300 g body weight.

Conclusion: Chemotherapy on pregnant women should be considered after evaluating the benefits and negative effects for both mother and fetus. The consideration should be based on the evaluations from multidisciplinary aspects.

Keywords: Non-Hodgkin’s lymphoma (NHL), cancer, pregnancy, chemotherapy, fetus safety.

Introduction

Malignancy in pregnancy can cause medical complications and dilemmas because it necessitates careful consideration of the risks and benefits of therapy for the mother’s and the fetus’s safety. One in every 1000 pregnancies in North America is diagnosed with malignancy. Hematological malignancies (including Hodgkin’s lymphoma (LH) and non-Hodgkin’s lymphoma (LNH)) are the second-most prevalent malignancy in pregnant women (LH 6%, LNH 5%), with an incidence of 10-60 cases per 100,000 pregnant women. Cancer therapy in pregnant women must take into account both the advantages and disadvantages of the treatment, as well as the impact on the welfare and development of the fetus inside the uterus. Therefore, knowledge and understanding of modalities for making a safe prognosis for the mother and fetus, whether it needs to be treated, when to start therapy, what regimen is needed for treatment and how to dose and consider giving it, and how side effects that may arise are urgently needed by health workers in the management of pregnant women with malignancy, including LNH. In this case report, we present the case of a pregnant woman at her second trimester (5 months) with LNH and received chemotherapy.

Case Presentation

A female, 20 years old, Javanese, working as a housewife, and lives in Sidoarjo was referred to One-Stop Oncology Outpatient Clinic (POSA) at Dr. Soetomo General Academic Hospital by the Ramelan Naval Hospital in Surabaya due to chemotherapy unavailability. The patient complained of shortness of breath for the previous four months, which was worse one week before hospital admission. For the last one week, the patient slept in a sitting position to reduce the shortness of breath. When the pregnancy was one month, the patient felt a lump in her right neck the size of a marble (±1.5 cm), dense, supple, sticky, firm boundaries, and growing over time. The patient had biopsy examination at the previous hospital and was diagnosed as LNH and received chemotherapy. The patient also complained of a lump in the chest that felt like it was growing larger and more prominent, and it felt more gripping and caused pain, in particular in the right chest area, and spread to the right arm and neck, as well as the patient’s face, which felt increasingly swollen.

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in one month, and had night sweats. The patient reported that her voice was hoarse, a little difficult when swallowing, and the chest felt protruding with no bones to be felt. There had been no previous complaints, and there was no history of diabetes or hypertension. The patient's grandmother also had a history of a lump in the neck, which the patient did not know what type it was, and had undergone chemotherapy at Dr. Soetomo General Academic Hospital. The patient was a housewife and had pregnant for the first child at a gestational age of 19-20 weeks (the first trimester). There was no history of smoking, alcohol, pain medication, or herbal use. The patient had no drug or food allergies.

The patient was conscious with a weak condition, GCS E4V5M6, blood pressure 120/80 mmHg, pulse 105x/minute, respiratory rate 22x/minute, temperature 36.6°C, SpO₂ 99% with room oxygen, early warning score (EWS) 3, weigh 45 kg, height 162 cm, BMI 17.1 kg/m², body surface area (BSA) 1.42 m². An examination of the patient's head and neck revealed anemic conjunctiva, dyspnea, enlarged lymph nodes in the right neck region with a diameter of 3 cm x 3 cm, jugular venous pressure (JVP) increased 5+4 cmH₂O and edema on the patient's face. Thorax examination revealed symmetrical movement, no retraction, no icterus cordis visible, and palpation of the apex of the heart at ICS V midclavicular line left. A mass presented in the sternum measuring ± 10x10 cm with a firm consistency and fixed to the base. Examination of the abdomen showed G1P0000 19-20 weeks of gestation, the liver and spleen were not palpable. The examination of the extremities showed warm dry red acral, with edema in the superior extremities.

Laboratory examination revealed hemoglobin 9.0 g/dL; hematocrit 27.6%; white blood cells 5.440/µL; platelet 263.103/µL; neutrophils 87.1%; lymphocytes 5%; monocytes 7.5%; eosinophils 0.2%; basophil 0.2%; MCV 81.2 fL; MCH 26.5 pg; MCHC 32.6 g/dL; LED 68; APTT 27.2 sec; PPT 11.8 sec; BUN 4 mg/dL; serum creatinine 0.52 mg/dL; SGOT 36 U/L; SGPT 34 U/L; random blood glucose 74 mg/dL; total bilirubin 0.59 mg/dL; direct bilirubin 0.08 mg/dL; sodium (Na) 133 mmol/L, potassium (K) 3.7 mmol/L; chloride (Cl) 98 mmol/L; albumin 3.0 g/dL; calcium 7.6 mg/dL; phosphate 2.5 mg/dL; and magnesium 1.9 mg/dL.

The electrocardiography (ECG) revealed a 105x/minute tachycardic sinus rhythm with normal axis. A consultation with the Department of Obstetrics and Gynecology revealed that the patient was 19/20 weeks pregnant with G1P0000 and estimated fetal weight 300 grams. Consultation with the Department of Cardiology, revealed no signs of impending acute lung edema or cardiac tamponade (hypertension, distant heart sounds), but increased JVP could be related to vena cava superior syndrome (VCSS). The ECG revealed no evidence of low voltage. A chest X-ray (PA) indicated normal cardiothoracic ratio (CTR) 47%, mass in the mediastinum with 14 cm x 15 cm in size, indistinct boundaries, and multi-lobulated with impression malignant mediastinal tumor. Echocardiography revealed normal left ventricle (LV) systolic function revealed moderate pericardial effusion on the right lateral (1.1 cm), minimal pericardial effusion on the posterior (0.9 cm), and minimal pericardial effusion on the left lateral (0.6 cm) with no signs of right atrial-right ventricle (RA-RV) collapse.

Thorax CT-scan with contrast revealed a mediastinal mass measuring 10.2 x 11.6 x 14.5 cm that extended into the right lung and caused inflammation; and extended to the lower left and right neck (Figure 1A-D), suspected as lymphoma, thymoma (malignant thymoma), impending VCSS, and Impending total atelectasis of the right lung. A cytology of fine needle aspiration biopsy (FNAB) examination confirmed the diagnosis of NHL. Immunohistochemistry (IHC) revealed diffuse positive CD20 on tumor cell membrane, negative CD3 on tumor cell membrane, negative CD20 on tumor cells, and positive Ki67 on 85% of tumor cell nuclei, resulting in the diagnosis of NHL b cell type, high grade, and positive CD20.

The patient was diagnosed as NHL of right neck, mediastinum, stage IIB with SVCS, microcytic hypochromic anemia (9.0) and G1P0000 19/20 weeks pregnancy. The patient was planned to undergo IHC examination, transfusion, consultation with the Department of

Figure 1. CT-scan of the patient revealed: (A) dense compaction, multiple small pieces (largest measuring 2 x 2.2 x 2.4 cm), accompanied by fibroinfiltrates occupying the right medial lobe attached to the right anterolateral wall (blue arrows); (B-D) soft tissue mass expands and measures 10.2 x 11, 6 x 14.5 cm in total, looks lobulated, fills the superior mediastinum; in cases and narrows the superior vena cava, left subclavian vein, and right pulmonary artery; presses against the trachea; incases and narrows the right main bronchus and slightly attached with an esophagus with unclear borders.
On the 4th day of treatment, the patient's chest pain, tightness, and swallowing pain all decreased, resulting in an improved appetite and the ability to sleep in a semi-sitting position. The general condition was good with comos mentis, blood pressure 110/70 mmHg, pulse 97x/minute, respiratory rate 20x/minute, SpO2 98% free water, and temperature 36.8°C. On blood examination, found hemoglobin 11.5g/dL; hematocrit 35%; white blood cells 9,680/µL; platelet 359.103/µL; sodium 135 mmol/L; potassium 3.8 mmol/L; chloride 104 mmol/L; albumin 3.2 g/dL; LDH 795 U/L; non-reactive HbsAg; non-reactive anti-HCV; non-reactive HIV, SI 29 µg/dL; TIBC 188 µg/dL; ferritin 324.89 µg/L. anti-HCV; non-reactive HIV , SI 29 µg/dL; non-reactive HbsAg; non-reactive 104 mmol/L; albumin 3.2 g/dL; LDH 795 U/L; SGPT 25 U/L. The patient was given the 2nd, 3rd, 4th, and 5th chemotherapy with the RCHOP chemotherapy regimen (R (Rituximab): 71 mg/iv, O (Vincristine): 1.98 mg/iv, P (Prednisone): 100 mg/day for 5 days. A complete blood count, renal and liver function tests, serum electrolytes, and post-chemotherapy evaluation albumin are all scheduled for the patient.

On the 5th day of treatment, the general condition was adequate, with comos mentis, blood pressure 120/70 mmHg, pulse 98 x/minute, respiratory rate 20 x/minute, SpO2 98% free water and temperature 36.9°C. The Department of Obstetric Gynecology in collaboration with the Departments of Internal Medicine, Anesthesia, and Forensics and Medicolegal, held a case conference with the Departments of Internal Medicine, Anesthesia, and Forensics, and the Departments of Obstetrics and Gynecology.

The patient received the 2nd, 3rd, 4th, and 5th chemotherapy with the RCHOP chemotherapy regimen (R (Rituximab): 450 mg/iv, with other regimens the same as the first chemotherapy). However, four months after the initial chemotherapy (36/35 weeks pregnancy), the patient had an obstetric ultrasound that revealed reduced fetal heart rate. The pregnancy was terminated by cesarean section resulting in a live baby with 2300 grams body weight. The patient's general condition was good on physical examination, with comos mentis awareness, blood pressure 110/70 mmHg, pulse 90x/minute, breaths 18x/minute, temperature 36.8°C, and SpO2 98% free water, hemoglobin 10.1 g/dL; hematocrit 29.5%; white blood cells 4,600/L; platelet 201.103/L; PPT 9.4 seconds; APTT 32.6 seconds.

**DISCUSSION**

Lymphadenopathy is characterized by abnormal lymph node size and consistency (more than 0.5 cm). Hard lymph nodes may indicate malignancy or infection. Clinical enlargement symptoms such as night sweats, fever, and weight loss can lead to a suspected malignancy diagnosis.6 NHL is a lymphocyte cancer that affects both B and T lymphocytes. Clinical symptoms of NHL include diffuse and local lymph node enlargement, fever, night sweats, and weight loss of more than 10% in the previous 6 months, and may be accompanied by extranodal symptoms.7,8 NHL, along with Hodgkin's lymphoma, is the sixth most common cancer in Indonesia.9

This patient had symptoms of growing lumps in the neck and chest, as well as a 5 kg weight loss in the previous month, fever, nausea, difficulty swallowing, and shortness of breath. The physical examination revealed an enlarged lymph node in the right neck measuring 3x3 cm and a firm sternal mass attached to the base measuring 10x10 cm. Based on these clinical symptoms, the patient was suspected of having cancer, specifically malignant lymphoma.

Standard diagnostic procedures must be followed by staging, determining the prognostic index, and determining the aggressiveness of lymphoma, which is then used to develop an appropriate therapeutic program in the management of NHL.11 The clinical symptoms of NHL are evaluated, followed by histopathological and IHC examinations to determine the type of cells that are malignant. Until now, surgical biopsy with anesthetic action has been deemed safe for patients, including those who are pregnant.5,12

In this case, the patient had a supporting examination of colli and sternal masses with the results of a chest CT scan with mediastinal mass contrast measuring about 10.2 x 11.6 x 14.5 cm suspicious of malignant lymphoma, histopathological results and IHC showed NHL diffuse large
B cell type high grade with positive CD20. As a result, the patient was classified as having NHL b cell type, high grade, and positive CD20.

The treatment of lymphoma during pregnancy requires a multidisciplinary approach involving obstetricians, radiologists, internists, and oncologists. Supportive therapy, therapy for complications, definitive systemic therapy (chemotherapy), surgical therapy, and radiotherapy are all part of NHL therapy in general. Surgical therapy is now almost exclusively used to obtain tissue/biopsy samples for histopathological examination. Surgical therapy can still be performed in special cases such as NH in non-lymphoid tissues such as the liver or stomach (MALT). In cases of NH during pregnancy, a thorough examination is required to determine whether the patient should be treated or simply observed, the best time to initiate therapeutic action, the preparations that must be made prior to therapy, the best and safest regimen and therapy program for the patient and the fetus, and potential side effects to the patient and the fetus.

Determining whether NHL in pregnant patients should be treated and when the most appropriate therapy time is highly dependent on the level of aggressiveness and the patient's gestational age. According to the Modified 2016 WHO classification of B cell lymphoid neoplasms, lymphoma can be divided into indolent lymphoma and aggressive lymphoma based on its aggressiveness. Indolent lymphoma is a type of lymphoma that develops slowly, and experts generally recommend a “watch and wait” strategy in the first trimester of pregnancy, with therapy considered if there are troubling clinical symptoms in the second or third trimester. Treatment for aggressive NHL during pregnancy (for example, diffuse large b cells or Burkitt's lymphoma) is dependent on the gestational age. If the gestational age is in the second or third trimester, therapy can be carried out without have to terminate the pregnancy first, taking into account the side effects of therapy on the mother and fetus.

In this case, the diagnosis of malignancy was made after the patient entered the second trimester of pregnancy, and the type of NHL suffered was the aggressive Diffuse Large B Cell type with SVCS complications, so it was decided to immediately begin definitive therapy in the form of chemotherapy without waiting for the fetus’s birth.

As with all patients with cancer who will undergo chemotherapy or other supportive therapies, NHL patients who are pregnant must also be prepared and screened. Several complications, such as worsening HIV symptoms and reactivation of hepatitis B and C, can occur in patients following anti-lymphoma therapy, necessitating the use of screening tests for these viruses. Routine blood tests, LDH, creatinine, uric acid, urea, electrolytes, S-proteins, AST, bilirubin, and alkaline phosphatase must also be performed to obtain basic information on the pre-chemotherapy patient’s condition. Routine blood tests, LDH, creatinine, uric acid, urea, electrolytes, S-proteins, AST, bilirubin, and alkaline phosphatase must also be performed to obtain basic information on the pre-chemotherapy patient’s condition. Preferably, screening data is collected less than one week before the start of therapy. Prior to chemotherapy with anthracycline groups, relevant examinations such as cardiac examination and echocardiography must also be performed.

Until beginning chemotherapy, it is also necessary to determine the staging and prognosis of NHL because this will significantly influence the therapeutic modality and the number of cycles. Until now, the Ann Arbor classification has been used to determine NHL staging, while the prognosis of NHL can be assessed using the International Prognostic Index (IPI), which is supplemented by an Eastern Cooperative Oncology Group (ECOG) performance status assessment.

In this case, the patient underwent basic screening prior to chemotherapy and had a hemoglobin 11.5g/dL; hematocrit 35%; white blood cells 9.680/μL; platelet 359.103/μL; sodium 135 mmol/L, potassium 3.8mmol/L; chloride 104 mmol/L; albumin 3.2 g/dL; LDH 795 U/L; non-reactive HbsAg; non-reactive anti-HCV; non-reactive HIV, SI 29 μg/dL; TIBC 188 μg/dL; ferritin 324.89 μg/L. While the echocardiographic examination revealed normal LV systolic function, there was moderate pericardial effusion on the right lateral (1.1 cm), minimal pericardial effusion on the posterior (0.9 cm), and minimal pericardial effusion on the left lateral (0.6 cm) with no signs of right atrial-right ventricle collapse. The ECG shows a normal heart rhythm. The data presented above demonstrate that the patient meets the criteria for chemotherapy. The patient in this case has an IPI score of 1, indicating that she has a good prognosis, with overall survival after therapy of 79%.

Following the confirmation of the diagnosis of NHL in pregnancy and the staging and prognostic index, the next step is to determine the patient's therapeutic regimen. Supportive therapy and management of NHL complications are also required for complete NHL management in pregnancy. Chemotherapy side effects such as nausea, vomiting, or infection due to neutropenia can be treated with anti-nausea and antibiotics as needed. Emergency management for NHL complications such as SVCS must be implemented from the start to avoid morbidity and mortality. Cito chemotherapy and radiotherapy can be used in pregnant patients with NHL if the tumor is not in an area exposed to direct ionizing rays and the patient has previously received abdominal shielding. Corticosteroids are the primary treatment for emergency SVCS, particularly during pregnancy. Steroids can help reduce airway edema caused by tumor mass suppression.

Pregnant patients should also be counseled on fertility and breastfeeding options. Before starting chemotherapy, patients must be educated about the possibility of infertility, and patients are not advised to breastfeed after giving birth while still in a chemotherapy cycle. In this case, the patient was informed about the risks of post-chemotherapy fertility problems and was not advised to breastfeed her baby while undergoing a series of chemotherapy cycles. Most experts believe that systemic therapy in the form of chemotherapy with a standard LNH regimen can be used in the second and third trimesters of pregnancy, just as it is for patients who...
are not pregnant. The CHOP regimen was employed (cyclophosphamide, doxorubicin, vincristine, prednisone). Patients with positive CD20 IHC should receive targeted therapy with a rituximab regimen.4,5,17,18 Although chemotherapy in 2nd and 3rd trimester pregnant women with LNH follows the same protocol as chemotherapy in LNH patients without pregnancy, knowledge about the potential side effects of cytotoxic drugs on patients and the fetus, as well as drug pharmacokinetic knowledge in pregnant women, must be mastered before starting chemotherapy to avoid long-term side effects, especially in terms of fetal development and growth. Therefore, doses, cycles and timing of chemotherapy need to pay attention to these aspects.19

The anthracycline class of cytotoxic agents has a toxicity mechanism that damages DNA structure by inhibiting the formation of active cell walls, so the use of this class of cytotoxic drugs can have serious consequences for both cancer cells and fetuses, including growth disorders and heart problems in both mother and fetus.20 However, because anthracycline has a molecular weight greater than 50 Dalton and its transport is dependent on the placental P-glycoprotein transporting system, its concentration in fetal tissues is very low.21

Teratogenic alkylating agents, such as cyclophosphamide, are used in standard NHL chemotherapy regimens. Patients may experience myelosuppression, ovarian damage, and menstrual irregularities, while the fetus may experience malformations and organogenesis disorders if given during the first trimester of pregnancy. Although used in the second and third trimesters does not result in malformations, the fetus may experience growth and development disorders, microcephaly, and neonatal pancytopenia after birth. As a result, even though it is considered a standard regimen that can be given to NHL patients in their second and third trimesters, patient education about fetal side effects must still be provided.16,21

Although some experts claim that it is completely safe and has no effect on the fetus, the use of vincristine can result in atrial septal defects, renal hypoplasia, and pancytopenia, so it must be administered with clear informed consent.4,16,21 The use of rituximab in NHL pregnancies is considered quite safe if given in the second and third trimesters, so it should be done immediately if there is an indication.3,22

In the first cycle, this patient received CHOP chemotherapy. Following a positive CD20 IHC result in the second cycle, the chemotherapy regimen was supplemented with rituximab 450 mg/iv. This regimen is compatible with the regimen for LNH patients who are not pregnant. Chemotherapy will be administered in up to six cycles.

Although chemotherapy is the primary treatment for hematological malignancies in pregnant women, radiotherapy is still used in some cases, such as when there are localized masses or masses that cause local compression complications such as SVCS. In the case of SVCS, radiotherapy measures aim to reduce/eliminate the tumor mass, thereby reducing/eliminating the urgency caused by SVCS. Radiotherapy is not required in cases of NHL pregnancy because NHL is highly chemosensitive and the effects of ionizing radiation are harmful to the fetus.3,15 There was a complication in this case in the form of SVCS. Because the patient was pregnant, the only treatment for SVCS was the administration of the steroid dexamethasone 3x10 mg without radiotherapy. Following the therapy, the patient’s condition improved and his SVCS was reduced. The IPI score in this patient was 1, indicating that it was in the low/intermediate IPI risk group, with a 73% 5-year survival rate suggesting the patient has a good prognosis.

CONCLUSION

We reported a young woman aged 20 years who was pregnant in the second trimester (19-20 weeks) and had NHL B cell type high grade with positive CD20. After consulting with multi-disciplinary departments, it was decided that chemotherapy could be carried out without terminating the pregnancy before the chemotherapy. The patient responded well to chemotherapy using the RCHOP regimen, with only minor side effects; however, the pregnancy has to be terminated at 36/37 weeks.

PATIENT CONSENT

The patient signed informed consent before the study and agreed that the case would be published in an academic journal without revealing the patient’s identity.

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DISCLOSURE OF CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTION

SM contributed to the study conceptual, data acquisition, clinical data assessment, follow-up of the patient and during manuscript preparation. SUYB contributed to the study conceptual, data validation and during manuscript revision.

REFERENCES


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