CHAPTER 2

Literature Review

This literature review consists of leukemia in children, uncertainty in illness theory, uncertainty in illness among children with leukemia, and factors related to uncertainty in illness among children with cancer receiving chemotherapy.

Leukemia in Children

Leukemia is the most common childhood cancer (Leukemia & Lymphoma Society, 2013; WHO, 2014). Leukemia in children under 15 years of age accounts for about 70% of childhood cancers in the United States (National Cancer Institute, 2014) and for about 50% of childhood cancers in Thailand (Wiangnon et al., 2011).The average incidence of American children aged under 15 years was 53.5per million (National Cancer Institute, 2014). The latest figure showed annual incidence for leukemia in Thai children in this age group as 38.1 per million (Wiangnon et al., 2011).

Leukemia most likely arises from abnormal proliferation of immature white blood cells or blast cells in the bone marrow, which crowd out other normal cells (Feinberg, 2007; MacDonald, 2010; Tubergen, Bleyer, & Ritchey, 2011). As the blast cells take over the bone marrow, eventually red blood cell and platelet production are affected.

The presenting signs and symptoms of a child with leukemia reflect the impact of bone marrow infiltration with leukemic cells and the extent of extramedullary disease spread (Margolin, Rabin, Steuber, & poplack, 2011). In all types of leukemia proliferating cells compete with normal cells for space and the necessary nutrients (Carroll & Raetz, 2012). Bone marrow production of other cells is suppressed, thus the most significant signs and symptoms are extremely low red blood cell counts (anemia), white blood cells (neutropenia) and platelet (thrombocytopenia) (Doyle,

2010). The typical symptoms and clinical findings are manifestations of the underlying anemia, thrombocytopenia, and neutropenia, which in turn reflect the failure of normal hematopoiesis. Pallor, fatigue, bone pain, petechiae, purpura, bleeding, and fever are commonly present (Margolin et al., 2011; American Cancer Society, 2013). Lymphadenopathy, hepatomegaly, and splenomegaly are frequent manifestations of extramedullary leukemic spread (Margolin et al., 2011).The other site of leukemia infiltration is the central nervous system causing increased intracranial pressure (Bryant, 2009).

Types of Leukemia

Leukemia in children was categorized into four types based on clinical presentation and morphologic appearance of the malignant blast cells; acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and chronic lymphoblastic leukemia (CLL) (Hutter, 2010). Overall in incidence of leukemia in children, ALL accounts for about 80% of childhood leukemia cases; AML accounts for about 15%, and chronic leukemia is relatively rare (James & Ashwill, 2007).

Acute lymphoblastic leukemia (ALL) is lymphoid malignancies resulting from abnormalities in genes that control cellular proliferation and differentiation of lymphoid precursors. It is the commonest cancer in children and accounts for one-fourth of all childhood cancers (Jemal et al., 2009; Bartram, Schrauder, Kohler, & Schrappe, 2012). Chemotherapy outcome of ALL has evidently improved the 5-year survival rate of childhood ALL above 85% (Pui et al., 2009; Mitchell, Richards, Harrison, & Eden, 2010). From 2002 to 2008, the survival rate was 91.2 % for children younger than 15 years (Leukemia & Lymphoma Society, 2013)

Acute myeloid leukemia (AML) is myeloid malignancies resulting from abnormalities in genes that control cellular proliferation and differentiation of myeloid precursors (Rubnitz & Inaba, 2012). AML in children is an erratic and heterogeneous disease of seven cases per million children younger than 15 years. AML is still a life-threatening malignancy in children in which very high blast counts at diagnosis goes with an increased risk of death and nonresponse to treatment (Creutzig et al., 2012).

However, the five-year relative survival rate showed 64.2 for children with AML (Leukemia & Lymphoma Society, 2013).

Chronic leukemias are myeloproliferative disorders characterized by a predominance of relatively mature cells. White blood cells are more mature and can carry out some of their normal functions. There are some blast cells present. Thus, chronic leukemia gets worse gradually (Altman & Fu, 2011). Besides this, chronic leukemias are rare in childhood, making evidence-based recommendations difficult (Andolina, Neudorf, & Corey, 2012). The most common type, chronic myelocytic leukemia (CML), accounts for less than 5% of all childhood leukemias (Altman & Fu, 2011). Likewise, chronic lymphocytic leukemia (CLL) is extremely rare in children (O'Brien, 2008).

Chemotherapy in Children with Leukemia

The intensity of systemic treatment for childhood leukemia is chemotherapy to eliminate the leukaemia cells (Makin, 2013). Stable developments in continuous complete remission and survival rates have issued primarily from the development of effective combinations of chemotherapy regimens (Hutter, 2010). Chemotherapy regimens of childhood cancer are composed of multiple anticancer drugs that are administered at their maximum tolerated doses (MTD). The MTD is based on the severity of toxicity, as the optimal dose, rather than using a therapeutic endpoint to establish the optimal dose (Adamson, Bagatell, Balis, & Blaney, 2011). The use of combination chemotherapy is to overcome drug resistance to individual agents and increase the percentage of children achieving complete remission and to prolong the duration of their remissions (Adamson et al., 2011).

Chemotherapeutic agents are anticancer drugs, which are injected into a vein, into a muscle, into the cerebrospinal fluid, or taken as pills. Chemotherapy uses mixtures of several cytotoxic agents and gives them in cycles, with each period of treatment followed by a rest period to give the body time to recover. Generally, treatment for ALL uses lower doses of cytotoxic drugs over 2 to 3 years and AML uses higher doses of cytotoxic drugs over a shorter period of time(Adamson, Bagatell, Balis, & Blaney, 2011; American Cancer Society, 2013).

Types of chemotherapy agents for childhood leukemia.

Cytotoxic agents are categorized by their mechanism of action, and are usually used in combination chemotherapy regimens that contain drugs with demonstrated single-agent activity against the blast cell being treated. Cytotoxic drugs in common use for children with leukemia include vincristine, methotrexate, 6-mercaptopurine, cytarabine, cyclophosphamide, etoposide, doxorubicin, L-asparaginase, and corticosteroids,

1. Vincristine is classified as tubulin poisonsorvinca alkaloidsand derived from the periwinkle plant (English, 2009). It binds to monomeric tubulin and prevents polymerization to microtubules and mitotic spindles thus blocking cells in mitosis (Makin, 2013). Vincristine is very widely used against childhood cancer and is part of the treatment regimens for ALL. The drug should be injected intravenous 2 mg/m^2 weekly for children (Abrams, Pennington, & Lammon, 2009). Vincristine produces an autonomic neuropathy and bone marrow suppression (Makin, 2013).

2. Methotrexate, as the antimetabolites, is a folic acid analogue and binds to and inhibits the enzyme dihydrofolate reductase, leading to depletion of intracellular tetrahydrofolate and inhibition of DNA synthesis (Makin, 2013). These actions deprive the cell of substances needed for formation of DNA or cause formation of abdominal DNA (Abrams et al., 2009). Methotrexate is part of the treatment of ALL both in low doses of the oral maintenance treatment and high doses of intravenousmethotrexate. Methotrexate is also used intrathecally as both treatment and prophylaxis for CNS disease in acute leukemia, both ALL and AML (Makin, 2013). Administrating drugs for leukemic children is both induction,PO, IV 3 $mg/m^2/d$, and maintenance, PO 30 mg/m2 twice weekly (Abrams et al., 2009). Toxic effects include bone marrow suppression, mucositis and ulceration of the GI tract, and hair loss (Abrams et al., 2009).

3. 6-Mercaptopurine is an antimetabolites. The purine analogues mercaptopurine (6MP) is both converted to thioguanine nucleotides which inhibit purine synthesis and become incorporated into DNA (Makin, 2013). 6MP is used for the treatment of ALL- oral 6MP is given daily as the main component of maintenance treatment. Toxic effects are bone marrow suppression, nausea, vomiting, and mucositis (Abrams et al., 2009).

4. Cytarabine, as antimetabolites, is purine nucleoside analogues with anti-leukaemic effect (English, 2009). The pyrimidine analogue cytarabine is activated by conversion to ara-CTP which then inhibits DNA repair enzymes by competing with dCTP (Makin, 2013). Cytarabine is effective against acute leukaemia, both ALL and AML and is given by intravenous infusion daily 100 mg/m^2 for 7 days (Abrams et al., 2009). Intrathecal cytarabine is used as treatment and prophylaxis of CNS disease in AML (Makin, 2013). Cytarabine causes myelosuppression and mucositis, but also produces a febrile reaction, sometimes with muscle and joint pain. In high doses, it can be acutely neurotoxic and can cause acute conjunctival toxicity (Makin, 2013).

5. Cyclophosphamide is the alkylating agents. alkylating agents function through the covalent binding of an alkyl group to various molecules, most importantly DNA, where they form inter and intra DNA strand cross links that trigger cell death (Makin, 2013). Cyclophosphamide is widely used in the treatment protocols for ALL. Induction therapy, PO 1–5 mg/kg/d; IV 20–40 mg/kg in divided doses over 2 to 5 days. Maintenance therapy is PO 1–5 mg/kg daily (Abrams et al., 2009). Toxic effects, cyclophosphamide is nephrotoxic and has breakdown products that cause hemorrhagic cystitis.

6. Etoposide, as topoisomerase inhibitors, stabilizes the topoisomerase II DNA bonds leading to DNA strand breaks. Etoposide is part of the treatment protocols for AML (Makin, 2013). It is usually given by intravenous infusion daily over 1 to 5 days (English, 2009). The major toxicity of etoposide is myelosuppression and mucositis (Makin, 2013).

7. Doxorubicin, as antibiotics, interferes with topoisomerase function and leads to DNA strand breaks (Makin, 2013). Doxorubicin is part of the treatment of ALL and AML (Makin, 2013). It is usually given by infusion over not less than 1 hour and sometimes longer depending on protocol (English, 2009).Toxic effects are bone marrow suppression, alopecia, mucositis, GI upset, and cardiomyopathy (Abrams et al., 2009).

8. L-asparaginase,as asparaginase, is a bacterially derived enzyme that converts asparagine to aspartate. Normal cells are able to respond to this depletion of asparagine by synthesizing more but leukemic cells cannot up-regulate the enzyme responsible for asparagine synthesis (Makin, 2013). As a result asparaginase has

relatively selective action against blast cells. Asparaginase is a standard part of ALL treatment. It is usually given by intravenous infusion daily 1000 IU/kg for 10 days (Abrams et al., 2009). The main toxicity is allergic, as hypersensitivity reactions might be expected with a bacterial protein.

9. Corticosteroids, as steroids including prednisolone and dexamethasone, have anticancer effect against leukemic cells, and are an integral part of the management of ALL (Makin, 2013). Administration of prednisolone in leukemia protocol is given a daily dose as 40 mg/m^2 for 1 to 28 days then tapered off in 2 weeks (ThaiPOG, 2006). Dexamethasone 10 mg/m^2 /day PO is given for 1 to 21 then tapered off (ThaiPOG, 2006). Steroids induce apoptosis through binding to intracellular receptors and nuclear translocation. Apart from the usual side steroid effects of increased appetite and obesity, avascular necrosis (Makin, 2013).

Phases of chemotherapy

Although the specific approaches to patients in various risk groups and the terminology describing the phases of therapy may vary between clinical trials, modern leukemia treatment regimens divide therapy into five main phases: remission induction, the central nervous system (CNS) preventive therapy, consolidation, delayed intensification, and maintenance therapy (Margolin et al., 2011). However, intrathecal chemotherapy is given prophylactically to prevent relapse in the CNS through into three major phases: induction, consolidation or intensification, and maintenance as follows (Hutter, 2010).

Induction phase. The goals of induction therapy are to achieve a complete remission of leukemia, to preserve normal hematopoietic cells and to restore normal hematopoiesis quickly (Margolin et al., 2011). Remission can be verified within the first 28 days after the initiation of chemotherapy by sequential bone marrow aspirates and lumbar punctures (James, Nelson, & Ashwill, 2013). Children with leukemia who are treated with a four-drug induction consisting of vincristine, prednisone/ dexamethasone and L-asparaginase with intrathecal therapy attain complete remission rates of greater than 95% within 4 weeks (Margolin et al., 2011).

Children with leukemia normally take CNS prophylaxis with chemotherapy instilled intrathecally into the cerebral spinal fluid space during a lumbar puncture (Makin, 2013). The goal of this treatment is to accomplish effective CNS treatment while reducing neurotoxicity (Seibel, 2008). Children with CNS involvement at diagnosis (cerebrospinal fluid specimen with $\geq$ 5 WBCs/mm^3 with lymphoblasts present and/or cranial nerve palsied) are treated with intrathecal therapy and subsequent radiation. This is usually accomplished by weekly or biweekly intrathecal therapy along with systemic drugs including high-dose methotrexate, 6-mercaptopurine, dexamethasone, L-asparaginase, cyclophosphamide or cytarabine (Seibel, 2008).

Consolidation phase.The next phase of treatment following the induction phase is called consolidation or intensification therapy. The goal of consolidation therapy is to maintain remission eradicating any residual leukemic cells and to prevent relapse in the CNS. This phase of therapy is essential for all patients with leukemia, but there is no consensus on the best regimens and their duration (Pui, Mullighan, Evans & Relling, 2012). The consolidation phase usually takes 12 weeks. The chemotherapy in this stage consists of 6-mercaptopurine, cyclophosphamide, cytosine arabinoside, and methotrexate. When the absolute neutrophil count (ANC) is higher than 1,000% and the platelet count is higher than 100,000/ul, treatment is started with the administration of a combination of cyclophosphamide, cytosine arabinoside, and 6-mercaptopurine in addition to high dose methotrexate which is already given in high risk ALL (Pizzo & Poplack, 2011).

At the present time, the intensity of the post induction period changes, but all patients receive some forms of intensification following achievement of remission and before starting the continuous maintenance therapy (Makin, 2013). Reinduction therapy or delayed intensification most often uses drugs which are the same to those used during induction and consolidation. It may also use intermediate-or high-dose methotrexate, or different drug combinations with the extended use of high-dose L-asparaginase or combinations of all of these (Seibel, 2008).

Maintenance phase.Maintenance therapy is the longest therapy phase for leukemia and generally continues for 2 to 3 years of continuous complete remission (Margolin et al., 2011). Usually, after the initial induction and consolidation phases

of chemotherapy are complete, a maintenance phase begins. Maintenance chemotherapy usually consists of a lower dosage of chemotherapy given orally and possibly intravenously to maintain remission and prevent recurrence of the leukemia (James et al., 2013). Chemotherapeutic agents are vincristine or prednisone pulses given monthly, and intrathecal methotrexate given every three months, oral 6-mercaptopurine given daily and weekly oral methotrexate given weekly. (Pizzo & Poplack, 2011; Devita, Hellman, & Rosenberg, 2008).

Thai national protocol for treatment of childhood leukemia. In Thailand, the treatment of childhood cancer differs between institutions due to limitations in personnel, budget, drugs and medical devices. There is also a difference in response to treatment of Thai patients compared with other countries. In 2006, the Board of Thai Pediatric Oncology Group (ThaiPOG) developed a national protocol for the treatment of leukemia in children which was coordinated with several institutions including King Chulalongkorn Memorial Hospital, Ramathibodi Hospital, Phamongkutklao Hospital, Maharaj Nakorn Chiang Mai Hospital, Siriraj Hospital, Srinagarind Hospital, Queen Sirikit National Institute of Child Health, and other hospitals under the Ministry of Public Health. The practical protocol is that cancer in children is controlled and treated by a pediatrician. (Thai Pediatric Oncology Group, 2006).

Presently, the Thai treatment protocol for acute leukemia has two categories. The first protocol is used for children with Acute Non Lymphoblastic Leukemia (ANLL), and the second protocol is used for children with Acute Lymphoblastic Leukemia (ALL) in both low and high risk groups (intermediate-risk). The low risk group (or so-called standard-risk) refers to the children aged 9 or below who have a WBCs count less than 50,000/mm^3. The high risk group refers to the children age 10 or above who have a WBC count 50,000/mm^3 or greater. Patients are classified as very high risk if they have any of the following features: hypodiploidy with less than 44 chromosomes, and induction failure (Schultz, Pullen, Sather et al., 2007).

Side Effects and Complications of Chemotherapy

Side effects of chemotherapy. Side effects of chemotherapy may occur as a result of toxic agents or bone marrow suppression which results in a decrease in red blood cells, white blood cells, and platelets. After myelosuppressive treatment for 10

to 14 days, patients normally experience the most impact of bone marrow suppression.Many agents carry unique toxicities affecting specific organs or tissues such as cardio toxicity associated with the anthracyclines; hemorrhagic cystitis associated with cyclophosphamide and ifosfamide; peripheral nephrotoxicity from vincristine, cisplatin, and paclitaxel; nephrotoxicity from cisplatin and ifosfamide; and ototoxicity from cisplatin and coagulopathy from L-asparaginase (Adamson, Bagatell, Balis, & Blaney, 2011). However, common side effects in children with cancer receiving chemotherapy include nausea, vomiting, mucositis, fatigue, taste change, diarrhea, alopecia, neutropenia, thrombocytopenia, and anemia (Chordas & Graham, 2010). The prevalence, physiology, and treatment of these various side effects are described as follows.

Nausea and vomiting. Chemotherapy-induced nausea and vomiting (CINV) are categorized into acute, delayed, and anticipatory types depending on the onset of the symptoms (Marloney, 2010). Acute CINV normally begins within 1 to 2 hours after receiving chemotherapy, peaks in the first four to 6 hours, and lasts 24 hours. Delayed CINV is usually present 24 hours after chemotherapy, lasts up to 5 days or more, and mostly involves cisplatin, carboplatin, and high-dose cyclophosphamide usage (Marloney, 2010). Lastly, anticipatory CINV commonly occurs before starting the next cycles of chemotherapy (Dewan, Singhal, & Harit, 2010; Marloney, 2010).

Mucositis. The use of Methotrexate in high doses destroys epithelial cells in the oral cavity, especially in children because they have a higher mitotic rate of child's gastric mucosa. Hence, they develop more severe mucositis cases than adults. (Hockenberry, 2004). Mucositis is a toxic inflammatory response to the drug which is present with focal or diffused erythematous burn-like lesions or ulcerations from the mouth to the anus or entire gastrointestinal tract (McCulloch, Hemsley, & Kelly, 2013). Subsequently, the symptom causes pain, burning, bleeding in the oral cavity and risk of infection (Hockenberry, 2004).

Fatigue. In the days following chemotherapy administration, fatigue normally occurs together with other symptoms (Erickson at al., 2010). Fatigue is described as physical and mental exhaustion that consists of general fatigue, physical fatigue, activity fatigue and motivation fatigue by many authors (Molassiotis, Sylt, & Diggins, 2007; Woodgate, Degner, & Yanofsky, 2003). However, the definition of fatigue has

also been described variously as a ‘persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning and can be described in terms of perceived energy, mental capacity and psychological status’; and ‘a profound sense of being tired or having difficulty with movement such as arms and legs, or opening eyes which is influenced by environmental factors particularly hospitalization’ (McCulloch et al., 2013).

Taste change. A child’s foods may taste more salty, bitter or metallic during the course of treatment (Children’s Cancer & Leukaemia Group, 2012). Furthermore, chemotherapy has various impacts on the level of sensitivity of the taste and on the more subjective aspects of taste. The perception of sweetness, saltiness, sourness or bitterness may be distorted (Boltong & Keast, 2012).

Diarrhea. Diarrhea may become a serious problem for children with cancer (Maloney, 2010). Many factors such as intestinal epithelial cytotoxicity, inflammation, ulceration, and increased bowel wall permeability from chemotherapy cause the diarrhea (Norradechanont, 2004; Cronin, O'Connor, Lohan, Keane, Roche, Bruzzi, & Murphy, 2009). Several chemotherapeutic agents including daunorubicin, cytarabine, etoposide, doxorubicin, cyclophosphamide, vincristine, and methotrexate have been associated with enterocolitis (Gray, Ooi, Tran, Traubici, Gerstle, & Sung, 2010). Diarrhea causes dehydration which requires further hospitalization, and in severe cause, it can bring about a delay of therapy. Furthermore, infection is the number one cause of acute diarrhea. Either an early onset and late onset, can be present with diarrhea within the first four hours and second week of chemotherapy administration, respectively, and this can be a self-limiting symptom (Maloney, 2010).

Alopecia. Sixty five percent of cancer patients experience Chemotherapy-induced alopecia (CIA) (Cash, 2001). The cause of CIA is from direct damage to the hair matrix cell and when hair loss occurs, patients can lose their self image and self esteem (Cash, 2001; Paus & Cotsarelis, 1999). Since chemotherapy damages cancer cells, it also harms normal cells or tissues of hair follicles, the functions of vasculature and sebaceous glands. This can result in change of color or texture of hair such as being darker or lighter, thicker or curlier (Hockenberry, 2004; Choi et al., 2014; Luanpitpong & Rojanasakul, 2012; Selleri, Seltmann, Gariboldi, Shirai, Balsari,

Zouboulis et al., 2007; Amoh, Li, Katsuoka, & Hoffman, 2007). Children with leukemia normally require high-dose conditioning to chemotherapy and such treatment has the side effects of alopecia about 1.5 months after the first dose of chemotherapy and was sustained until about 2 months after that. Furthermore, hair regrowth started about 3 months after chemotherapy ceased and lasted for 7 months, approximately (Choi, et al., 2014). The risk of permanent CIA increased with specific chemotherapeutic agents such as high-dose busulfan, cyclophosphamide, and carboplatin (de Jonge, Mathot, Dalesio, Huitema, Rodenhuis, & Beijnen, 2002; Tallon, Blanchard, & Goldberg, 2010). In contrast, the previous study suggested that hair density fully recovers after chemotherapy (Paus, Haslam, Sharov, Botchkarev, 2013)

Neutropenia. The side effect of cytotoxic chemotherapy in children with cancer is neutropenia which usually occurs with the first cycle of chemotherapy (Castagnola et al., 2007; Caggliano, Weiss, & Rickert, 2005). After the administration, a short term of neutropenia lasts less than 10 days; whereas, a long term exceeds 10-14 days (Lehrnbecher, Varwig, Kaiser, Reinhardt, Klingebiel, & Creutzig, 2004). The ANC is calculated by multiplying the white blood cells (WBCs) count by the total number of bands plus segmented (mature) neutrophils (Brundige, 2010). However, when neutropenia is present, there is a decrease in the number of circulating neutrophil granulocytes and phagocytic WBCs which engulf and destroy microorganisms, (Brundige, 2010). There are various definitions of neutropenia from institutions, ranging from an ANC of less than 500 % to one of less than 1500 cells/mm3 (Seth & Bhat, 2011). In general, an ANC at or below 500 indicates high risk rates for developing infection, an ANC of 500 to 1,000 indicates a less severe risk and with an ANC of 1,000 to 1,500 there is low risk for infection(Camp-Sorrell, 2005).

Thrombocytopenia. Thrombocytopenia in children with leukemia is usually due to myelosuppression from chemotherapy (Doyle, 2010). A normal platelet count in adults and children ranges from 1500,000 to 450,000/mm^3. Platelets normally survive for 7 to 10 days in circulation before being removed by the spleen (Brundige, 2010a). Thrombocytopenia is defined as a platelet count of more than two standard deviations below the mean of the general population, or less than 150,000/mm^3

(Brundige, 2010a). It commonly occurs 7 to 21 days after administration of chemotherapy (Yarbro, Frogge, & Goodman, 2004).

Anemia. The low red blood cell (RBC) count is frequently the initial cause is the leukemia itself. The condition may deteriorate during the beginning stage of treatment because of the chemotherapy (American Cancer Society, 2013). Chemotherapy brings about dose-related marrow suppression by damaging the DNA and decreasing the numbers of RBC progenitors, which also causes anemia (Bryant, 2009). Consequently, the incidences of anemia may range from 20% to 60% at the time of the diagnosis of cancer and reach as high as 60% to 90% during treatment (Buckner & Maxon, 2004; Capo & Waltzman, 2004). Anemia symptoms include fatigue, lethargy, tiredness, or lack of energy (Lyman et al., 2005). The child may be tired, pale with accelerated breathing because of a decrease in the capacity to carry oxygen. The red blood cell count will be low contributing to fatigue and being easily tired in childhood anemia (Potts & Mandleco, 2012). Anemia is commonly encountered in children receiving chemotherapy. This is usually due to chemotherapy related myelosuppression, but can also be related to malignant infiltration of bone marrow, radiation, viral suppression, blood loss, and nonspecific processes (Rizzo et al., 2002). The use of erythropoietin is a treatment option for children with chemotherapy-associated anemia and a hemoglobin concentration <10 g/dL (Rizzo et al. 2002). Thus, children with leukemia receiving chemotherapy need high rates of oncologic care, which impedes the complication of anemia becoming less life threatening.

Complications of chemotherapy. Bone marrow suppression, including infection, bleeding, and severe anemia are common complications of chemotherapy. Seven to 10 days after the administration, bone marrow suppression usually occurs and it takes normally 3-4 weeks to have a complete recovery (Ball & Bindler, 2003).

Infection. Infections lead to substantial morbidity and mortality in neutropenic patients (Roongpoovapatr & Suankratay, 2010). This symptom is a serious complication among children with neutropenia. The clinical presentation may not be clearly recognized because the defense mechanism to inflammation is abnormal. (Crawford, Dale, & Lyman, 2004). Children with an ANC < 200 % and severe prolonged neutropenia, are at high risk for sepsis, pulmonary infections, and

life-threatening gastrointestinal (Brundige, 2010). The predisposal factors causing bacteraemia and sepsis in this group of children can be the presence of an indwelling central line and the concurrent loss of the mucosal integrity of the gastrointestinal tract.

Bleeding. Bleeding can occur if platelets are reduced in number or defective in function (Brundige, 2010a). Platelets are crucial for normal blood clotting. Clinical bleeding brought on by thrombrocytopenia is not a usual factor until the platelet count goes lower than 100,000/mm^3. Serious spontaneous bleeding is rare unless the platelet count is lower than 10-20,000/mm^3 (Brundige, 2010a). Complications from thrombocytopenia vary from asymptomatic to mild bleeding characterized by conditions from ecchymosis and petechiae through disruptive epistaxis and gingival bleeding to life-threatening GI or intracranial hemorrhage (Schwartzberg, 2013).

S***evere anemia***. The intensity of therapy and previous receiving of myelosuppressive therapy, are important factors in the incidence and severity of chemotherapy-induced anemia (Wu, Aravind, Ranganathan, Martin, & Nalysnyk, 2009). Anemia is graded as mild (Hb 10 g/dL to lower limit of normal), moderate (Hb 8 to lower 10 g/dL), severe (Hb 6.5 to lower 8 g/dL), or life threatening (Hb less 6.5 g/dL) (Schwartzberg, 2013). The percentage of patients with more severe, grade moderate to severe anemia, also increased with increased use of chemotherapy cycles (Ludwig et al., 2004). The usual recommended triggers for transfusion are a hemoglobin count of 6-7 g/dL and no signs of imminent marrow recovery, or hemoglobin > 7 g/dL in a child who is symptomatic (i.e., decreased energy, fatigue, pallor, headache, tachypnea, tachycardia and/or gallop, and inability to take part in normal activities of daily living) (Steele 2003).

Uncertainty in Illness Theory

Mishel (1981, 1988) developed a middle-range nursing theory based on knowledge of nursing combined with knowledge from other disciplines, processes and clinical phenomena for practical experience and the theory of stress and coping formulated by Lazarus and Folkman (1984). The original Uncertainty in Illness Theory' was expanded to address uncertainty during the diagnosis and treatment

stages of an illness or in a condition that had a determined downward trajectory. Uncertainty refers to a cognitive state of lack of form or structure to the events occurring in a specific illness conditions (Mishel, 1988),

Mishel (1988) defined uncertainty as an inability to determine the meaning of illness-related events. The decision maker was unable to assign definite values to objects and events and/or unable to accurately predict outcomes because sufficient clues were lacking (Mishel, 1990). The Mishel Uncertainty in Illness Theory provides an explanation as to how patients cognitively process illness associated with stimuli and then create meaning for this illness. Uncertainty, the inability to structure meaning, develops when a patient does not formulate a cognitive schema in which to deal with his/her illness. A cognitive schema is the patient's subjective interpretation of illness, treatment and hospitalization and it has 4 dimensions: (1) ambiguity concerning the state of the illness, (2) complexity regarding treatment and systems of care, (3) lack of information about the diagnosis and seriousness of the illness and (4) unpredictability of the course of the disease and prognosis (Mishel, 1988; 2014). Uncertainty in illness is influenced by antecedents including stimuli frame and structure provider (Figure 1).

Stimuli Frame

Stimuli frame, a primary antecedent variable in the Uncertainty in Illness Theory (Mishel, 1988), directly affects the uncertainty in illness and consists of three components; symptom pattern, event familiarity, and event congruence as follows.

Symptom pattern. Symptom pattern is the degree to which symptoms occur with enough consistency to be perceived as having a pattern or configuration (Mishel, 1988). The ability to recognize symptom pattern decreases the vagueness of illness. Number, frequency, intensity, duration, and location of symptom are evaluated in symptom pattern appraisal. Individuals can predict and evaluate their illness more accurately when the symptom pattern is consistent.

Event familiarity. Event familiarity refers to the degree of familiarity with the illness, treatment, and the health care environment. It develops through a cognitive map built through personal experience encountered with the events over time and can influence uncertainty. Hence, uncertainty is lower when a person

encounters a new situation that they can correlate with their old experience. However, uncertainty is heightened when a person is faced with new illness related experiences, such as unfamiliar procedures or changes in the illness condition.

Event congruence. Event congruence refers to the consistency between the expected and the experienced in illness-related events. This can help a person understand the meaning of the situation and be able to predict the events that may occur in the future.

Structure Providers

Structure providers are the resources available to assist the person in the interpretation of the stimuli frame. Structure providers consist of credible authority, social support, and education (Mishel & Clayton, 2008) explained as follows:

Credible authority. Credible authority refers to the degree of confidence and trust in physicians and nurses which affect the uncertainty in illness. Trust and confidence in health professionals lead to a lower level of overall uncertainty. One of the most effective structure providers is the health care provider (Mishel, 1997). The health care provider can give information on causes, occurrence, and intensity of symptoms that enable a person to develop a cognitive schema and attach meaning to the symptoms in terms of their future impact.

Social support. Social support is proposed by Mishel's Uncertainty in Illness Theory to have both direct and indirect influence on uncertainty. The result of the direct influence from social support is the modification of ambiguity about the illness, treatment complexity, and unpredictability of the future (Mishel, 1988; Mishel & Braden, 1988). The indirect influence of social support is on the clarity of the symptom pattern (Mishel, 1998; Mishel & Braden, 1988).

Education. Education affects uncertainty in illness. Individuals with higher education are more likely to comprehend the information about the diagnosis, treatment, and nursing activities. This contributes to better constructing of meaning for the event and reducing uncertainty (Christman et al, 1988; Mishel, 1995).

In addition, cognitive capacity refers to the information-processing ability of persons for decision making. Each person will have this ability differently. The major path to uncertainty is through the stimuli frame variables. Patients who have

compromised cognitive capacity because of illness events will likely have reduced clarity and definition of the stimuli frame variables resulting in uncertainty. However in patients whose cognitive capacity is adequate, stimuli frame variables may still lack a symptom pattern or it may be unfamiliar on inconsistent because there is not enough information, the information is too complex, there is information overload or the information is contradictory. The structure provider variables then take effect to alter the stimuli frame variables by providing interpretation, meaning or explanation. These actions serve to structure the stimuli frame, thereby reducing or preventing uncertainty. (Mishel & Clayton, 2008).

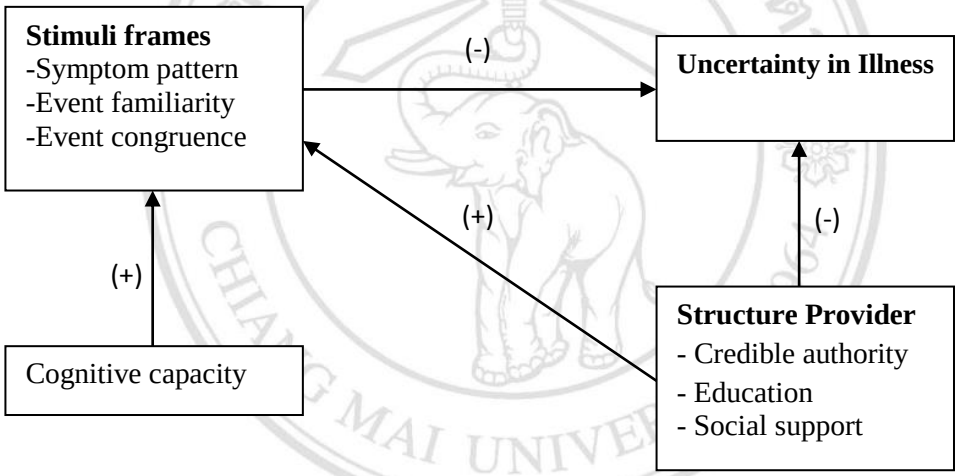

Figure 2-1 Model of factors influencing uncertainty in illness (Mishel, 1988)

Uncertainty in Illness Among Children with Leukemia

According to this theory, uncertainty is the inability to determine the meaning of an illness event. Uncertainty in illness of individuals occurs during the diagnostic and treatment phases in four forms: ambiguity regarding illness events, complexity about the treatment, lack of information about the diagnosis and the illness, and unpredictability of the health outcome.

Previous studies in Thailand demonstrated that children with cancer receiving chemotherapy experienced moderate to high levels of uncertainty in illness (Silapavitayatorn, Kantawang & Leuviiryakit, 2009; Tathong, Kantawang, & Sripusanapan, 2012). In addition, qualitative studies of children's experiences of cancer therapy explained that uncertainty was a major complaint of their cancer experience (Haase & Rostad, 1994; Weekes & Kagan, 1994).

Uncertainty in illness has long been recognized as a significant issue in childhood cancer (Cohen, 1993; Koocher & O'Malley, 1981). Most studies have identified uncertainty as an important aspect in cancer treatment for children. The previously cited qualitative studies suggested that uncertainty was a major theme in childrens' reports of their cancer experiences retrospectively about treatment, (Haase & Rostad, 1994) and coping strategies were used to deal with uncertainty (Weekes & Kagan, 1994). Both studies found continued uncertainty beyond the treatment period and the possibly of it for years beyond the end of treatment. The outcome for any individual child remains unpredictable, so hopes for long term survival are accompanied by enduring uncertainty. Similarly, the uncertainty about cancer has returned (Novakovic et al., 1996). The overall level of uncertainty remained unchanged across the adolescent with cancer continuum (Decker, Haase & Bell, 2007).

Several studies have demonstrated that children are affected by uncertainties inherent in the illness experience. Findings of Stewart (2003) from systematically studying children's uncertainty demonstrated that children and adolescents aged 9 to 12 years undergoing cancer treatment describe illness situations in which they felt "unsure." Their rich descriptions yielded a conceptualization of uncertainty consistent with Mishel's (1988) categorization of uncertainty as novelty, complexity, ambiguity, and unpredictability. The children with cancer, including leukemia, undergoing treatment and receiving chemotherapy, reported a high level of uncertainty during the time of cancer diagnosis through the early stage of treatment (Stewart, 2005). A study of Silapavitayatorn (2008) shows that most of the children with cancer receiving chemotherapy, aged between 8 and15 years, reported having uncertainty in illness at a moderate level (93.3%) and a few reported having uncertainty in illness at a low level (6.7%) . Another recent study of uncertainty in illness among children with leukemia

and lymphoma receiving chemotherapy (Tathong, Kantawang, & Sripusanapan, 2012) found that the majority of them reported having uncertainty in illness at a moderate level (85.2%) and a few reported having uncertainty in illness at a high level (14.8%). Thus, uncertainty about the cancer illness is a major concern of children with cancer and appears predominantly in the initial diagnosis and treatment periods.

Patients with chronic diseases, like cancer, continuously and persistently live with uncertainty, which can harm their physical, social, spiritual and mental states, and daily activities (Mishel, 2014). This uncertainty in illness leads to psychological distress among children with cancer (Neville, 1998) and subsequent problems with their ability to cope with illness-related stress, and decreases their ability to take care of themselves (Stewart et al., 2010). Similarly, previous studies showed that increased uncertainty correlated with increased mood disorders (Lin, Chiang, Acquaye, Vera-Bolanos, Cahill, Gilbert, & Armstrong 2013) and reduced effectiveness of patients' coping and quality of life (Kurita, Garon, Stanton, & Meyerowitz, 2013; Parker et al., 2013). Moreover, childhood cancer patients who lack the capability of coping and uncertainty management may be at risk for the development of posttraumatic stress symptoms (Lee, 2006), thereby decreasing their well-being.

Thus, nurses should be aware of uncertainty in illness of children with leukemia undergoing chemotherapy and its consequences, and provide nursing interventions to reduce that uncertainty. However, there has been no intervention for reducing uncertainty in illness of these children. The intervention in any form will be effectively developed only if predictivg factors of uncertainty in illness are clearly identified.

Measuring uncertainty in illness among children with cancer

From existing studies in nursing research, two instruments have been developed to measure uncertainty in illness for children by using self-administered questionnaires as follows:

Children's Uncertainty in Illness Scale (CUIS). The CUIS is a 23-item self-report measure of the child's perceived uncertainty about the course, prognosis, and treatment of their illness. (Mullins & Hartman, 1995). The CUIS is an adapted

version of the MUIS-Community Form (Mishel, 1997) that was revised to be developmentally appropriate for children and adolescents and is designed to be used across the spectrum of children with chronic illness. The CUIS addresses four components of illness uncertainty: ambiguity, lack of clarity, lack of information, and unpredictability. Children are asked to respond on a 5-point Likert scale ranging from 1 (very true) to 5 (very false). The total score is obtained by summing up the score across all items, with higher scores indicting higher uncertainty in illness. This measure has previously been used for American children between the ages of 9 and 18. The CUIS has revealed good internal consistency reliabilities across a number of chronic illness with Cronbach's alpha ranging from .88 to .93 (Hartman, Mullins, Hoff, & Chaney, 2001; Hoff, Mullins, Chaney, Hartman, & Domek, 2002;White et al., 2005; Pai, Mullins, Drotar, Burant, Wagner, & Chaney, 2007; Steele, Aylward, Jeasen, & Wu., 2009). It was used for Thai children with cancer and showed Cronbach's alpha of .85 and .92 (Tathong et al., 2012; Silapavitayatorn, 2008).

The Uncertainty Scale for Kids (USK). The USK is a 22-item, 4-point ordinal self-reporting scale, which indexes the frequency with which children with cancer experience illness-related uncertainty (Stewart, et al., 2010). Children are asked to respond on a 4-point Likert scale ranging as 1 (never), 2 (sometimes), 3 (most of the time), or 4 (always). Higher scores refer to higher uncertainty in illness. In its initial psychometric evaluation with 72 children undergoing cancer treatment, the USK demonstrated strong internal consistency (Cronbach's alpha=.95), 1-week test-retest reliability (r= 64, p=.005), and its discriminant validity was supported with lower scores among children treated with less complex regimens (chemotherapy alone, $\overline{X}$ = 44.4, SD= 14.2, vs. in combination with surgery and/or radiation, $\overline{X}$ = 55.8, SD= 15.0, t (63) = 3.06, p= .003).

In this study, the researcher used CUIS in assessing uncertainty in illness because CUIS is the most well-known scale on child uncertainty. Moreover, psychometric properties of this instrument were accepted in several studies indicating its quality. The CUIS has also been improved continuously and has been used to assess uncertainty in illness among children with chronic illness at an international level in various studies. Therefore, this is a suitable tool for this research.

Factors Relating to Uncertainty in Illness Among Children with Cancer

The research review is organized accordingly to stimuli frame and structure provider, the antecedents of uncertainty in illness theory, and other factors influencing uncertainty in illness as follows:

Symptom Pattern

Symptom pattern is the degree to which symptom occurrence has enough consistency to be perceived as having a pattern (Mishel, 1988). Studies that address the process of identifying symptoms of a disease or condition of illness are classified as addressing symptom pattern (Mishel, 2014). The process of receiving chemotherapy among leukemic children requires that a symptom pattern exists and can be labelled as an illness or a condition. In the UIT, absence of the symptom pattern is associated with uncertainty (Mishel, 1988; 2014).

Tathong, Kantawang, and Sripusanapan (2012) examined factors influencing uncertainty in illness among children with cancer receiving chemotherapy and found that the overall stimuli frame included all three components: symptom pattern, event familiarity, and event congruence; was a predictor of uncertainty in illness and could explain variance in uncertainty in only 4.9% (R^2=.049, β =.220, p< .05). The other empirical studies focus on one aspect of symptom pattern such as symptom experience and symptom severity. Symptom experience has a strong, direct and positive impact on uncertainty in patients with head and neck cancer (β = .81, p<.001) (Detprapon, Sirapo-ngam, Mishel, Sitthimongkol, & Vorapongsathorn, 2009). Symptom experience is influenced by the patient's perception and response to symptom occurrence and symptom distress. Symptom occurrence is the frequency, duration, and severity of the symptom (Detprapon et al., 2009). Severity of illness is one aspect of symptom pattern. Studies that focus on the influence of severity of illness on uncertainty are classified as those that address the theoretical link between symptom pattern and uncertainty. Several studies of adult populations have shown that severity of illness is a predictor of uncertainty in patients, including patients in the acute or treatment phase of illnesses such as cancer (Detprapon et al., 2009;

Galloway & Graydon, 1996; Hilton, 1994;), cardiovascular disease (Christman et al., 1988; Kang, 2006), chronic illness such as pain in fibromyalgia (Johnson, Zautra, & Davis, 2006), parents of critically ill children and children recently diagnosed with cancer (Santacroce, 2002; Tomlinson, Kirschbaum, Harbaugh, & Anderson, 1996), and college students aged from 18 to 22 years old with asthma (Wolf- Christensen, Isenberg, Mullins, Carpentier, and Almstrom ,2008). Most studies found that severity of illness was positively associated with uncertainty. According to the uncertainty in illness theory, the nature of the severity presents difficulties depicting a symptom pattern about the extent of the illness, resulting in uncertainty.

Lack of clarification of the symptom pattern has resulted in a high level of uncertainty in illness (Mishel, 1988). Characterized by alternating remissions and worsenings, the unpredictable and consistent nature of the symptoms displayed hampers formation of a symptom pattern, which results in more ambiguity about the state of the illness. The study of Mishel and Braden (1988) showed that symptom pattern was significantly negatively related to uncertainty and ambiguity in women receiving treatment for gynecological cancer ($r = -.31$; $r = -.35$, $p < 0.01$, respectively). An additional analysis of the study in Thai children with leukemia and lymphoma undergoing chemotherapy found that symptom pattern was a predictor of uncertainty and could explain 9.2% of the variance in uncertainty ($R^2 = .092$, $\beta = .303$, $p < .01$) (Kantawang & Tathong, 2013) Thus, symptom pattern would influence uncertainty in illness of children with leukemia undergoing chemotherapy. In this study, symptom pattern from the stimuli frame based on Uncertainty in Illness Theory's antecedent was selected as a predicting factor.

Measuring symptom pattern. The Symptoms Pattern Scale can be quantified subjectively through a self- report. The Symptoms Pattern Scale was used to measure symptom pattern. It was a subscale of the Stimuli Frame of Children with Cancer Scale developed by Tathong and Kantawang (2011) based on the stimuli frame concept in Mishel's Uncertainty in Illness Theory (1988). It consisted of eight items with a three-point Likert scale type of responses (0 = disagree, 1 = agree, and 3 = strongly agree). The higher scores reflect that leukemic children perceive a more congruent symptom pattern. The Stimuli Frame of Children with Cancer Scale developed by Tathong and Kantawang (2011) has demonstrated good construct

validity (CVI = 0.85) and reliability (Cronbach's alpha = 0.81) (Tathong & Kawang, 2011).

Information Support

Information support, as a dimension of social support, is another major factor influencing uncertainty in illness, and has been argued to be more likely to directly affect uncertainty than other dimensions (Mishel, 2014). Sharing information with persons in their social network assists individuals to properly appraise symptoms, which results in lower uncertainty (Mishel, 1988). Children with cancer need information about their diagnosis, treatment and side effects, and care practices from health care providers (Till, 2004; Miller, 2012). They need information for problem solving and modifying their uncertainty.

Mishel (1988) conceptualized social support as affirmation support which is believed to influence uncertainty in illness directly by providing information to modify three forms of uncertainty: ambiguity about the illness, treatment complexity, and the unpredictability of the future. The indirect influence of social support is the decreasing of the uncertainty by helping individuals' clarify symptom patterns and promoting event familiarity and event congruence (Mishel & Clayton, 2008). Information support, according to House (1981), is the provision of advice, suggestions, and information for problem solving. Appraisal support is the provision of information for self-evaluation, such as feedback, affirmation, and social comparison (House, 1981). This information is often evaluative and can come from family, friends, co-workers, or networks.

A study on the relationship of social support and uncertainty in illness among children with systemic lupus erythematosus (SLE) aged 10-15 years found that there were high negative relationships between overall social support and illness uncertainty(r =-.746,p< .01) (Naruemandecha, 2008). However, previous studies of children and adolescents with cancer indicated a low to moderate level of the relationship or influence (Neville, 1998; Tathong, Kantawang, & Sripusanapan, 2012).

Uncertainty in illness of newly diagnosed children and adolescents with cancer was seen to be moderately negatively associated with social support (Neville, 1998). Neville (1998) studied the associations among perceived social support, uncertainty, and psychological distress of male and female adolescents recently diagnosed with cancer. Among the 60 adolescents were male and female, aged 14-22 years, who were recently diagnosed with a malignancy within the past 100 days and receiving outpatient treatment. The result showed an inverse relationship between perceived social support and illness uncertainty ($r = -.30$, $p < .01$).

In addition, the overall social support of Thai children with leukemia and lymhoma, aged 8-15 years, undergoing chemotherapy could predict only 4.4% of the variance in their uncertainty in illness ($R^2 = .044$, $p < .05$) (Tathong, Kantawang, & Sripusanapan,2012). This might be because, while only information support may have influenced uncertainty, the social support scale measured several types of social support, including emotional, esteem, information, and tangible support, which resulted in lessening its influence on the child's uncertainty.An additional analysis of this study found that only information support from parents, friends, nurses, and physicians was a predictor of uncertainty and could explain 10.4% of the variance in uncertainty of these children ($R^2 = .104$, $\beta = .326$, $p < .01$) (Kantawang & Tathong, 2013). The influence of social support by giving information from persons in the social network assists individuals in the understanding of illness events, which results in lower uncertainty (Mishel, 1988; Schapira, 2014).

Sources of social support among children with cancer. Important sources of support of children with cancer are parents and friends that have the same diagnosis and treatment (Haluska, Jessee, & Nagy, 2002; Trask, Paterson, Trask, Bares, Birt, & Maan, 2003**;** Gibson Aldiss, Horstman, Kumpunen, & Richardson, 2010). Social support may come from various sources such as professionals, the health care system, friends, relatives, family, God or social networks of the church, and community members (Fink, 1995; Rose, 1997). In this study, social support is considered as social support that is offered by family, peers and health care providers respectively. Enskär's study (1997) shows that family (especially parents) provides the greatest support for children with cancer. A survey conducted to compare social support from parents to other sources in adolescents of the ages 11 to18 who are at least a month

from diagnosis and not more than 1 year off treatment, found that parents were the major source of support and friends were rated next (Trask et al, 2003).

In addition, Haluska, Jessee, and Nagy (2002) examined perceived sources of support and levels of satisfaction with social support in adolescent survivors of cancer compared to healthy norms. The results show no difference in social support from friends between adolescent cancer survivors and healthy norms. However, adolescents with cancer had significantly higher levels of support from their parents. Similarly, children with cancer reported significantly higher social support from families, but not significantly different support from friends compared to norms (Brown, Madan-Swain, & Lambert, 2003). Hence, information support from parents and peers that are children with leukemia undergoing chemotherapy would influence their uncertainty in illness.

Informational support from health care providers as credible authorities was derived from Mishel's Uncertainty in Illness Theory (1988). Nurses, physicians, and other health care providers often are the trusted experts who help patients manage the illness experience (including uncertainty), especially through diagnosis and treatment decision-making. In uncertainty in illness theory, Mishel (1988) defined credible authority as the degree of trust and confidence patients have in health professionals. Health professionals have the ability to reduce uncertainty in illness by providing information. Children with cancer need information about their diagnosis, treatment and side effects, and care practices from health care providers (Decker, Phillips, & Haase, 2004; Till, 2004). However, the influence of information support from only health care providers on the uncertainty of children has not been reported. Only one study reported that information support from parents, friends, nurses, and physicians was a predictor of uncertainty in illness among Thai children with cancer (R^2=.104, β =.326, p< .01) (Kantawang & Tathong, 2013).

In addition, Naruemandecha (2008) found that the majority of adolescents aged 10 to 15 who were SLE (81.10%) reported receiving overall social support at a high level. For each dimension of their social support most of them reported receiving emotional, tangible, social network, esteem, and information support at a high level (97.80%, 82.20%, 75.60%, 72.20% and 68.90%, respectively). Parents were the largest source of the adolescents' emotional support (95%), esteem support

(77.56%), and tangible support (56.67%). Friends mostly reported as a social network (95.28%). Physicians were the largest source of information support (75.93%) and nurses were the second (51.48%). There were high negative relationships between child uncertainty and information support from various sources, including parents, friends, siblings, relatives, physicians, and nurses. Meanwhile, there were significant negative relationships between illness uncertainty and esteem, social network, tangible, and emotional support at a moderate level (r = -.581, -.520, -.494, and -.475, $p < .01$, respectively).

In conclusion, prior studies have revealed that information support from parents, friends, nurses, and physicians were a predicting factor of uncertainty in illness among Thai children with cancer receiving chemotherapy, and children with SLE. However those studies did not determine whether the support from each separate source was related to uncertainty. As information supports can be from various sources depending on the children's perception and preference, it is worthwhile to identify the source. Information supports from parents, peers, and health care provider were proposed to have association with the children's uncertainty in this study.

Measuring information support among leukemic children. From existing studies in nursing research, several instruments have been used to measure social support by using self – administered questionnaires. There are no instruments to assess social support, especially information support, among leukemic children. Tathong (2011) modified the Social Support among children with cancer from the Social Support of Adolescent with Chronic Illness Scale (Sangsuwan, 1998), which focused on the social support concept of Schaefer, Coyne, & Lazarus (1981) and Cobb (1976). It measures five subscales of social support including emotional, information, tangible, social network, and esteem support from family and friends. This scale consists of 22 items with a rating scale ranging from 1 (not at all true), 2 (less true) to 3 (very true). The average of social support scores is classified into levels of social support in three categories: low (22-36), moderate (37-51) and high (52- 66). The content validity index was evaluated by five experts and its value was 0.91. Also, the internal consistency coefficient was 0.86 (Tathong, 2011). This indicated good internal consistency. In this study, the researcher modified The Social

Support of Children with Cancer Scale to measure information support from health care providers, parents and peers.

Illness Related Knowledge

Illness related knowledge is another factor associated with the uncertainty of chronically-ill children. According to the Uncertainty in Illness Theory, cognitive capacity is the antecedent of uncertainty. Cognitive capacity refers to information – processing abilities which can allow the person to interpret the events in which illness occurs (Wallance, 2005). When the patient has access to information, knowledge is improved as is the ability to distinguish between uncertainty and certainty (Mishel, et al., 2009). Adolescents with cancer seek knowledge through the acquisition and processing of information. They will also have specific information and knowledge related to cancer. So, poor provision of information or lack of knowledge may lead to uncertainty (Decker, Phillip, & Haase, 2004). High levels of symptoms such as pain are associated with uncertainty when one does not know how to manage the symptoms (Johnson et al., 2006).

Naruemandecha (2008) conducted a correlational descriptive study to explain the relationships between knowledge regarding illness and illness uncertainty of Thai adolescents with SLE. The findings revealed a moderately negative relationship between knowledge regarding illness and illness uncertainty ($r = -.467$, $p < .01$).

The empirical evidence on the relationship between illness-related knowledge and uncertainty in illness of children with cancer is inconsistent. Stewart (2003) analyzed the relationship of age and cancer knowledge to children's uncertainty. The result indicated these two factors significantly predicted uncertainty ($F_{2, 69}=4.43$, $p=.02$) and accounted for 9% of its variance. Thus when age was held constant, children's cancer knowledge significantly and negatively predicted their level of uncertainty ($\beta=-2.65$, $p<.05$), such that lower cancer knowledge was associated with higher uncertainty. However, illness-related knowledge of Thai children with leukemia and lymphoma was not a predictor of uncertainty in illness (Tathong, Kantawang, & Sripusanapan, 2012). Thus, illness-related knowledge should be investigated for its predictability of children's uncertainty.

Measuring illness related knowledge. Illness related knowledge can be assessed by self-reporting subjective measurement. There are no instruments to assess disease knowledge, especially illness related knowledge among leukemic children. But only two instruments measured cancer knowledge in children with cancer as follows:

The Cancer Knowledge Scale. The Cancer Knowledge Scale (Stewart et al., 2010) consisted of 12 true-false statements to measure of how much children had been told about their cancer and treatment. They were instructed to answer each item to the best of their knowledge about cancer in children and the common side effects of treatment. Five of the items were true, and seven were false. The scale score was constructed by summing the number of correct answers for each subject. The content validity was determined by experts. The Kuder-Richardson 21 (KR-21) was .44, indicating that its internal consistency reliability was poor.

The Illness Knowledge of Children with Cancer Scale. The Illness Knowledge of Children with Cancer Scale (Tathong et al., 2012) consisted of 25 true-false questions representing the children's understanding of leukemia and lymphoma, side effects and complications of chemotherapy, and care practices. The higher the score, the higher would be the illness-related knowledge of children with cancer. The content validity index was .97 determined by 5 experts. The KR-21 was .98

The Illness Knowledge of Children with Cancer Scale was developed based on the Thai cultural context and it evaluated cancer knowledge especially, leukemia and lymphoma in children with cancer receiving chemotherapy. Also the psychometric properties of this questionnaire were accepted as good in content validity and reliability. In this study, therefore, the researcher modified the Illness Knowledge of Children with Cancer Scale to measure knowledge related illness among leukemic children receiving chemotherapy.

Parental Uncertainty

Parental uncertainty is an inability of parents or other family caregivers to determine meaning dealing with illness in a family member, specifically a child (Mishel, 1983; Santacroce, 2001). Parental uncertainty in a child's illness is

characterized by Mishel's Uncertainty in Illness Theory (Mishel, 1981). It is composed of four dimensions: (1) ambiguity about the child's illness state, (2) lack of information about the child's illness, its treatment, side effects, and management, (3) complexity in what information is known, the care system, and communication with health care providers and (4) unpredictability of a child's prognosis, ability to function and quality of life (Mishel, 1983). Therefore, parents feel more uncertain when their children's health status is full of ambiguity, complexity, and unpredictability. Childhood cancers do not have exact manners and markers of illness progression and they lack clear indicators of the seriousness of the illness. Hence, uncertainty among parents of children with cancer is increased (Tomlinson, et al., 1996; Stewart &Mishel, 2000).

The literature indicates empirical support for a link between parental uncertainty and child uncertainty (Stewart et al., 2010; Stewart & Mishel, 2000). Evidence has shown that parental uncertainty has demonstrated a significant main effect on uncertainty among children 8 to18 years of age who were undergoing treatment for any form of cancer (β=.27, $p < .05$) (Stewart et al., 2010). In addition, uncertainty in illness of children with chronic illness between 8 and 12 years of age was found to be a predictor of maternal uncertainty (β=.38, $p < .001$) (Page et al, 2011). A study of Fedele et al. (2011) found that parental uncertainty showed a significant effect on both parent's global distress and youth depressive symptoms. Moreover, according to White et al. (2005), parents' psychological distress was related to child-reported depressive symptoms in which the relationship was mediated by child illness uncertainty. Typically, the incidence of children with cancer may strengthen the link between parents' and child's psychological functioning (Okado, Long, & Phipps, 2014).

Given the episodic disease trajectory, complex treatment regimens, and ambiguity surrounding prognosis and the disease course in chronic illness and treatment, parental uncertainty stands to be a key variable in predicting parent and child maladjustment. (Carpentier, Mullins, Chaney, & Wagner, 2006; Fuemmeler, Mullins, Marx, 2001; Maikranz, Steele, Dreyer, Stratman, & Bovaird, 2007). Apparently, parents who respond to their child's chronic illness with excessive concern or changes in their parenting practices may convey both verbal and nonverbal

messages to their child that they are vulnerable. Subsequently, their children might internalize these perceptions of vulnerability, which could then lead to extended levels of perceived illness uncertainty (Steele& Tripp, 1997). Collectively, these findings indicate that parental uncertainty could interfere with their capacity to provide information and support for their child's illness schema formation, and thereby increase the child's uncertainty.

Measuring parental uncertainty. The Parent Perception of Uncertainty Scale (Mishel, 1983) is designed to measure the uncertainty parents experience concerning their child's illness, the original adult form of the Mishel Uncertainty in Illness Scale (MUIS) (Mishel, 1981) was modified for this use. This instrument was composed of 31 items that consisted of four subscales as follows: (1) ambiguity, (2) lack of clarity, (3) lack of information, and (4) unpredictability. The scale was a 5-Likert scale from the truest to the least true. The explanation of the scale from 5 = the truest to 1 = the least true.

The construct validity of this scale was examined by the known group method. The three groups were comprised of 125 parents of children who were classified as medical patients. 90 parents of children classified as surgical patients, and 50 parents of children who had been classified as diagnostic. An analysis of the results indicated that parents in the "diagnostic" group had higher rates of uncertainty in illness than parents in the "medical" and "surgical" groups. These findings indicate support for the construct validity of the scale. For the reliability of the scale, the Cronbach's alpha of ambiguity, lack of clarity, lack of information, and unpredictability was 0.87, 0.81, 0.73, and 0.72, respectively.

In Thailand, the Parent Perception of Uncertainty Scale (PPUS) was translated into Thai by Suwan-o-sod (2004). The Cronbach's alpha reliability of the translated PPUS among 10 parents of children with cancer was 0.88. (Suwan-o-sod, 2004) and 0.85 (Maneerat, 2007). This indicated the good internal consistency.

Mishel's Uncertainty in Illness Theory (1988) has guided a considerable number of research projects into the experience of adults and parents of children with life- threatening illnesses, and recently has been applied in studies on children. The literature reviews and evidence based hypothesized models of the uncertainty in illness among leukemic children receiving chemotherapy was used as the study

framework. Six selected factors related to uncertainty in illness among leukemic children are illustrated in the theoretical framework of predicting factors of uncertainty in illness in this study.

Theoretical Framework

The theoretical framework for this study is based on the Uncertainty in Illness Theory (Mishel, 1988) and literature reviews on children's uncertainty in illness. Based on Mishel's (1988) theories, antecedents of uncertainty in illness include symptom pattern (stimuli frame) and information support from health care providers, information support from parents, and information support from peers (structure providers) and two influential variables include parental uncertainty and illness related knowledge which can influence uncertainty in illness of leukemic children.

Uncertainty in illness of children with leukemia undergoing chemotherapy is proposed to be influenced by symptom pattern, information support from health care providers, information support from parents, information support from peers, illness related knowledge, and parental uncertainty as follows: (1) when children are unable to interpret the symptom occurrence during a course of chemotherapy, or when the symptoms worsen and become unpredictable leading to high uncertainty; (2) information support from health care providers, parents, and peers would help in modifying illness ambiguity, treatment complexity, and unpredictability of the treatment result and clarify symptom pattern leading to low uncertainty; (3) illness related knowledge would assist the children to interpret their symptoms and illness related events resulting in low uncertainty and (4) parental uncertainty about their child's illness would interfere with their capacity to provide information support for the child's illness schema formation resulting in high uncertainty for children. The influences of these factors on uncertainty in illness among leukemic children receiving chemotherapy are illustrated in Figure 2.

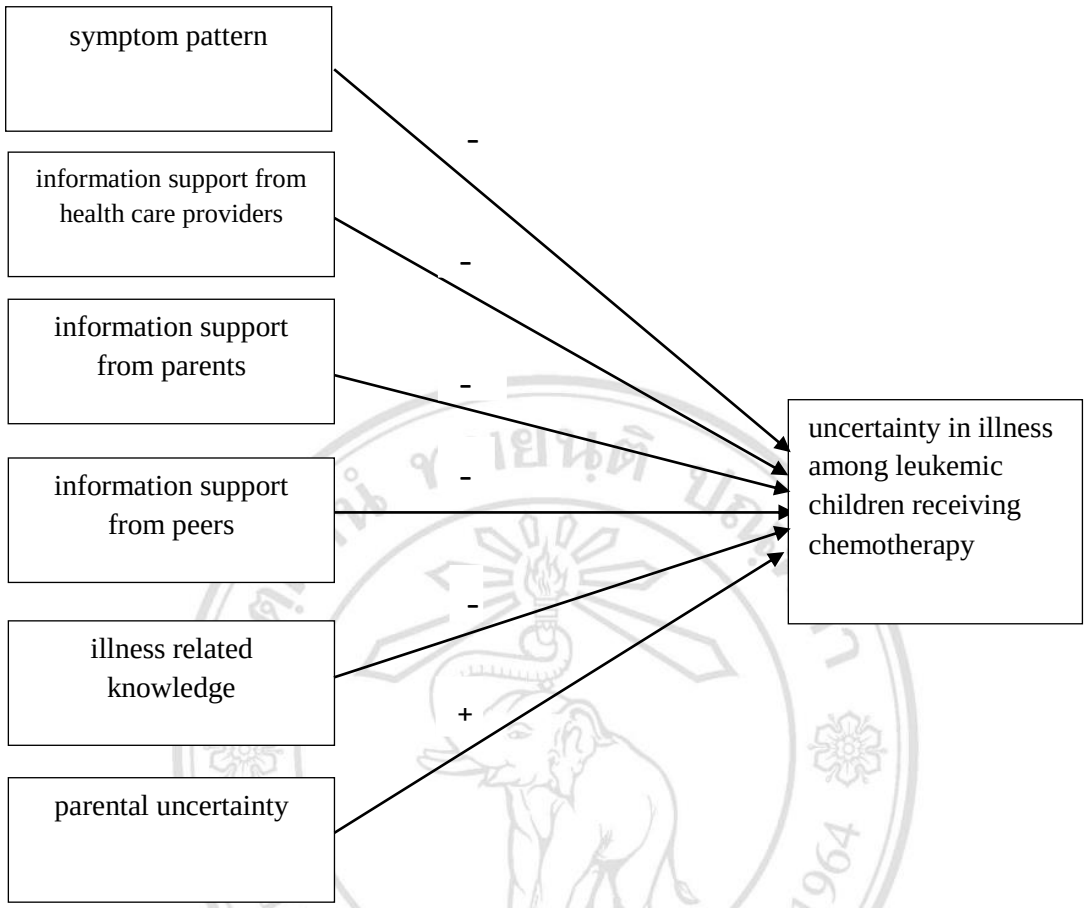

Figure 2-2 Theoretical framework of uncertainty in illness among leukemic children receiving chemotherapy