Clinical Efficacy and Timing of Influenza Immunization in Cancer Patients Receiving Chemotherapy

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Abstract:

Background: Cancer patients who are immunocompromised due to the nature of their malignancy or treatment with chemotherapy, are at increased of developing complications related to influenza infections. While the influenza vaccination has been shown to be safe in immunocompromised patients, recommendations regarding when to vaccinate patients with cancer are inconsistent, and there are currently no guidelines in place to guide clinical decision-making. This review seeks to assess the efficacy of the influenza vaccine and the proper timing of its administration to immunocompromised adult patients due to cancer. Methodology: A literature search was done of studies that assessed humoral seroconversion after vaccination and clinical effectiveness of the influenza vaccination in immunocompromised cancer patients. The studies included patients with solid tumors, hematological malignancies, and those who were post hematopoietic stem cell transplant. Results: The literature indicates chemotherapy patients generally showed decreased immune response to vaccination, when compared to healthy patients who had not been treated with chemotherapy. However, the aforementioned cancer patients did show adequate seroconversion and patients vaccinated early in their chemotherapy cycle (Day 4-5) as opposed to later (Day 16) had a greater serological response to the influenza vaccinate. Conclusion: The influenza vaccine has been confirmed to produce adequate overall antibody response in

chemotherapy patients and to be safe and effective. However, literature indicates it should generally be given early in relation to the chemotherapy cycle to achieve maximum effectiveness. The data supporting this assertion is limited, and the topic requires further study. In view of this, clinicians should consider the potential benefits of influenza immunization for patients being treated with chemotherapy.

Table of Content

Introduction:

Influenza is an acute respiratory condition affecting both the upper and lower respiratory tracts. It occurs globally with annual epidemics that result in 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths annually (1). The Influenza viruses, specifically Influenza A, B and C strains, can cause significant epidemic infections leading to acute respiratory issues with significant morbidity and mortality. Influenza A and B are the most prevalent of the viruses, generally occurring with seasonal epidemics between late fall and early spring, while Influenza C results in a lower frequency of infections among the general public. Influenza A can be further categorized into subtypes based on two viral surface glycoproteins: hemagglutinin and neuraminidase. Influenza vaccines contain antigens of these specific proteins and attempt to stimulate the body's production of anti-bodies against the viral proteins to promote a faster immune response upon infection. Influenza A's hemagglutinin and neuraminidase are constantly mutating; therefore the vaccine requires annual updating to be effective. Current influenza vaccinations are available as trivalent and quadrivalent inactivated vaccines containing three to four strains of the influenza viruses. Since the viruses are inactivated and non-pathological, vaccine administration poses no risk of infection to the patient. When the vaccine matches the circulating influenza strains, protection rates can be as high as 70-90% in patients less than 65 years old (2). Reactions to the vaccine have included minimal transient local reactions, such as mild swelling and discomfort at the site of vaccination. Further, fever and malaise have been known to occur, without any other systemic reactions to the vaccination, in both patients with and without cancer (3)(4). Patients infected with influenza will present with a variety of symptoms, most notably

fever, myalgia, headache, cough, chills, nasal congestion, and sore throat. Pneumonia is the most typical major complication, of which secondary bacteria pneumonia is the most common form. Primary influenza pneumonia is also a severe complication, however it is far more rare. Other complications of influenza infections include otitis media, bronchiolitis in children and exacerbations of chronic respiratory disease. Non-respiratory complications include febrile convulsions, Reye's syndrome (an acute encephalopathy presenting with fever, vomiting, fatty infiltration of the liver, disorientation, and coma, which occurring mainly in children and usually following a viral infection), neurological sequelae and myocarditis (5).

Influenza A and B infection rates are generally highest in children, however it is a cause of significant mortality and morbidity in all individuals with reduced immune systems (6). This population includes patients with hematological malignancies, solid tumors who are undergoing systemic chemotherapy, and post hematopoietic stem cell transplant patients. After chemotherapy is administered, a drop is generally seen in the level of antibodies that were previously induced with vaccination. Consequently, these levels can reach a non-protective state resulting in increased vulnerability to viral infections (7). In cancer patients, the risk of bacterial infections is higher than that of viral infections, due to the main immune deficiency of neutropenia. However, notably, the rates of influenza related complications are higher in these patients compared to the general population (6). There are two major causes for the increased risk of infection seen in patients receiving chemotherapy or other immunosuppressive medications. The malignancy itself can have a directly immunosuppressive effect, which is most notable in relation to hematological malignancies. Secondly, modalities of treatment for malignancies often induce

immunosuppressive effects (8). The cytotoxicities of chemotherapy are targeted towards rapidly proliferating tumor cells. However, these cytotoxic effects also impact the host's proliferating cells and inevitably impair hematopoiesis. The adverse effects of chemotherapy on immune cells are highly variable depending on the chemotherapy regimen and length of time it is used. Since, the full and efficient function of the immune system depends on the rapid proliferation of cells is it adversely affected by cytotoxic therapies that target rapidly proliferating cells. Therefore, immunocompromised patients are also at increased risk of post-influenza infections that include secondary bacterial pneumonia, otitis media, sinusitis, further deterioration of chronic respiratory and cardiac issues, all of which increase rates of mortality (9). This hospitalization and mortality risk of influenza is elevated in cancer patients, with an estimated age-specific rates for influenza-related hospitalization and death of 219 and 17.4 per 100,000, respectively for patients age<65 years old. For patients 65 years or age and older the risk is higher at 623 and 59.4, respectively (10). While both hematological and solid tumor malignancies increase the risk of influenza infection, those at highest risk are patients who have undergone allogenic bone marrow transplant. Among these patients, episodes of graft-versus host disease (GVHD) further compounds the risk of infection for these patients (11). Patients who have impaired lymphocyte function are in a lower risk category such as individuals living with chronic lymphocytic leukemia (CLL), multiple myeloma, and possibly patients being treated with an anti-lymphocyte antibody (12). Overall, hospitalization rates for influenza related issues are four times higher for cancer patients relative to the general population, and influenza- related mortality is ten times higher (10). In addition, it can be speculated that the presence of symptoms and complications

related to influenza may prolong the time in between chemotherapy treatments, which negatively impact remission rates and patient outcomes.

At present, there are no evidence-based guidelines for the vaccination of cancer patients undergoing chemotherapy, and conflicting reviews of the subject have provided variable recommendations. The Center for Disease Control and Prevention (CDC) recommends influenza immunization for high-risk populations, which include healthcare providers, the elderly, and people who are immunocompromised. Active immunization against various diseases has been shown to confer immunity in cancer patient at similar rates as in healthy individuals. Seroprotection, measured with hemagglutination inhibition assay (HI) greater than or equal to 40, can convey at least a 50% reduction in risk of influenza infection (13). In turn, this decreases severity and duration of infections, as well as reduces morbidity and mortality (14). However, despite the recommendations for vaccinating and availability of effective vaccines, vaccination coverage remains low in cancer patients that are undergoing chemotherapy (15). Although it is generally agreed upon that anti-influenza vaccines are safe in immunocompromised patients and should be given annually, there are conflicting ideas in regards to the efficacy and timing of vaccine administration in this population. Questions relating to the efficacy and proper timing of vaccination may be due, in part, to the generally low rates of vaccination in this population. In general, it is recommended to vaccinate before chemotherapy begins (16). However, research reflects various perspectives of when vaccination should occur during chemotherapy treatment. One study recommends vaccinating at least two weeks prior to chemotherapy and annually. The study notes also that if vaccination prior to

chemotherapy is not plausible, then vaccination can occur during the course of chemotherapy (17). However, the majority of chemotherapy regimens occur over the course of several months, and there is very little data directing practitioners as to when to vaccinate during these prolonged chemotherapy cycles, and additionally, whether the efficacy of the influenza vaccine is even supported by seroconversion after chemotherapy initiation. There is data that supports the idea that vaccination should occur as far as possible prior to chemotherapy initiation. However, this idea is currently based on a single study that took place over 30 years ago, and involved a very small sample size of only 11 breast cancer patients (3). As such, the research that has been done on this subject is of limited scope, and does not include other common cancers or hematological cancers, which have an increased disease burden on the immune response. While seroprotection is associated with at least a 50% reduction in risk of influenza infection, the optimal moment to administer the vaccine during a chemotherapy cycle has not been studied extensively.

This review will endeavor to answer the question of whether there is a most appropriate time to administer influenza vaccinations to cancer patients receiving chemotherapy, either before a treatment regimen is to begin or during the course of chemotherapy treatment. As, well the review will examine whether the serological response induced by the influenza vaccine in these patients indicates the efficacy of the vaccine in this population. This assessment will be based on studies of humoral serological responses to the vaccination itself, and will also examine clinical randomized controlled trials that identify the response to the influenza vaccination in particular cancer

populations, including patients with breast cancer, lung cancer, colorectal cancer, and hematological cancers. The aim will be to determine if there is an optimal point at which the influenza vaccination should be given in the context of the course of chemotherapy treatment, and to assess if there are differences relating to hematological versus solid tumor malignancies. Immunity evolves more heterogeneously over time in cancer patients as opposed to patients who have had stem cell transplants. Thus, challenges are present in attempting to determine the appropriate time to vaccinate the patient when comparing different patient populations. Considering the significance of both primary and secondary complications in cancer patients, and the expected diminished immune response to immunization, data on the effectiveness of influenza vaccination is needed in this population.

Methods:

Types of Studies:

Included in this literature review were randomized controlled trials (RCTs), cohort studies, and case control studies. Observational studies were also considered in order to holistically consider the empirical data on vaccine trials and their use in adults undergoing chemotherapy treatment for cancer. However, no observational studies were included in the final data.

Types of Participants:

Participants included adults 16 years of age and older with cancer. This included patients with solid tumor malignancies being treated with chemotherapy, hematological cancers, and individuals who had received autologous or allogeneic hematopoietic stem cell transplantation as treatment for cancer.

Types of Interventions:

Several studies were examined, and specific parameters around the intervention under study differed slightly. The first analysis looked at the time that the cancer patient and the healthy subject (control group) were vaccinated; therefore the intervention was the timing of vaccination in relation to the chemotherapy cycle. The second analysis assessed the overall degree of seroconversion and seroprotection in protecting against the virus. As such, the intervention was simply the vaccination of adult cancer patients receiving chemotherapy and comparing their response to that of healthy adults not receiving chemotherapy. Comparisons of different forms trivalent vaccinations and different vaccination seasons were not included in this review. Further, though the review included several types of cancer diagnoses there was no differentiation based on the types of chemotherapy regimes the patients were receiving.

Types of Outcomes:

In evaluating the timing of when the influenza vaccine is best given, as well as the resultant degree of seroconversion, influenza virus specific antibody titres were determined at specific time periods by measuring hemagglutination inhibition assays (referred to as "HI titre"). Virus-specific titres were assessed 3 weeks before vaccination, and up to 12 weeks after vaccination. For the purpose of comparing seroconversion in chemotherapy patients versus healthy individuals, adequate seroconversion was categorized as those who had a HI titre of equal to or greater than 40 (18).

Primary Outcomes: In the studies reviewed, measurements of HI titer were used as the primary outcome to evaluate seroconversion. Antibody titers of 40, or a 4 fold increase in titer was used as the primary outcome, as this is considered protective in healthy individuals without chemotherapy.

Secondary Outcomes: Secondary outcomes in the studies reviewed included hospitalizations for fever, acute respiratory infections, pneumonia, and infection related chemotherapy interruptions. These secondary outcomes are not examined in this analysis.

Search Methods:

A review of the MEDLINE/PubMed database included articles published between 1964 and 2015. Search results were filtered for randomized control trials, observational studies, and clinical trials only. Search terms used were, "cancer", "adult", "chemotherapy", and "influenza vaccination". An initial search, using these previously identified parameters identified 240 publications. Of the 240 publications retrieved, studies were chosen for analysis based on the inclusion criteria of this review; which were patients were over the

age of 16, had received chemotherapy treatment, and were diagnosed with a solid tumor or hematological malignancy, and/or had undergone allogenic bone marrow transplantation. Of these selected studies, five focused on the evaluation of the serological response to influenza vaccination in chemotherapy patients, and three assessed the timing of vaccination administration. Six studies focused on solid tumor malignancies and two included hematological malignancies.

Results:

Comparison 1: The comparison between early and late immunization in relation to day of chemotherapy cycle and the seroconversion thereafter.

This study had survey population of 136 patients which were included in the analysis. The sample consisted of patients with breast cancer, colorectal cancer, and hematological malignancies. Of the 76 breast cancer patients studied, overall serological response was adequate. There was a statistically significant response in patients vaccinated early in the chemotherapy cycle versus those vaccinated later. In the two studies that specifically examined breast cancer, day 4 & 5 of chemotherapy were defined as the early vaccination dates, while day 16 was chosen in both studies as the late chemotherapy cycle vaccination. In both the studies, it was identified that there was a statistically significant higher response in patients who received vaccination at the early date rather than late. In the first study that compared day 5 versus day 16, geometric mean titres were 69.3 versus 27.4 (H3N2), 76.4 versus 17.5 (H1N1) and 34.4 versus 26.0 (B/Brisbane), respectively (19). In the 18 patients with colorectal cancer, overall serological response was also adequate, but concluded there were no statistically significant differences established between the responses to vaccines received at day 5 versus day 16. Geometric mean titres post vaccination on day 5 versus day 16 were 170.1 versus 192.4 (H3N2), 233.0 versus 280.8 (H1N1) and 62.6 versus 75.9 (B/Brisbane), respectively (19).

In a second study examining vaccination timing in breast cancer patients, 38 patients participated. 20 subjects were assigned to the early vaccination group (Day 4) and 18 to the late vaccination group (Day =16). The 38 patients were compared to 21 healthy

individuals with no malignancy or chemotherapy. Overall, the patient group had a lower serological response to the vaccination compared to the healthy control group. Results also showed that patients vaccinated at day 4 had higher antibody titres than patients vaccinated at day 16, but the difference in these post vaccination titres was not found to be statistically significant. Geometric mean titres post-vaccination for day 4 versus day 16 were 63.7 versus 29.5 (H3N2), 28.2 versus 19.6 (H1N1) and 29.8 versus 16.0 (B/Brisbane), respectively (20).

The third study examining vaccine administration timing in chemotherapy patients sampled of 42 patients of which 21 were diagnosed with lymphoreticular neoplasms, and 21 with solid tumor malignancies. The patients were randomized into two groups which differed in relation to the timing of immunization. One group received influenza immunization at the time of chemotherapy administration and the second group received vaccinations between courses of chemotherapy treatments. Results showed that 50% of patients immunized during chemotherapy administration showed seroconversion, which is significantly less than the 93% seroconversion rate observed in patients immunized between chemotherapy courses. Consequently, the study's recommendation is to immunize between courses of chemotherapy (3).

Article Title	Selected Population	Time of Vaccination in Chemotherapy Cycle	Measure of Efficacy	Response	Outcomes
Serum antibody response to influenza virus vaccination during chemotherapy treatment in adult patients with solid tumors.	Breast Cancer Patients (n = 38) Colorectal Cancer Patients (n = 18)	Early = day 5 of chemotherapy cycle (n = 20) Late = day 16 of chemotherapy cycle (n =18)	HI titre ≥40	GMT: 63.7 vs. 29.5 (early vs. late, H3N2), 28.2 vs. 19.6 (early vs. late, H1N1), 29.8 vs. 16.0 (early vs. late, B/Brisbane).	Significantly lower in patient group vs. controls; early group had higher antibody titers vs. late group for breast cancer patients, however not significant for colorectal cancer patients
Response to influenza virus vaccination during chemotherapy in patients with breast cancer	Breast Cancer Patients (n = 38) Healthy Population (n=28)	Early = day 4 of chemotherapy cycle (n = 20) Late = day 16 of chemotherapy cycle (n =18)	HI titre ≥40	Day 4 vs Day 16 were 63.7 versus 29.5 (H3N2), 28.2 versus 19.6 (H1N1) and 29.8 versus 16.0 (B/Brisbane)	Patients vaccinated at day 4 have higher antibody titres compared to vaccination at day 16; the difference in post-vaccination titres is not statistically significant.
Influenza Immunization of Adult Patients with Malignant Disease	Solid Tumor Patients (n=21) Lymphoreticular Malignancy Patients (n=21)	Early = day 1 of chemotherapy cycle In between chemotherapy = 7, 10, & 14 (depending on chemo cycle)	Fourfold or greater increment in HI antibody titer	Immunized at time of chemotherapy – 50% seroconversion. Immunized in between chemotherapy – 93% seroconversion	Individuals with malignant disease should be immunization between chemotherapy courses.

Table 1: The comparison between early and late immunization in relation to day of chemotherapy cycle and the seroconversion thereafter.

Comparison 2: Influenza immunity in vaccinated patients receiving chemotherapy compared with those in the vaccinated healthy adult

A total of five studies were reviewed comparing levels of vaccine-mediated influenza immunity in healthy adults and cancer patients undergoing chemotherapy. These studies revealed that the serological response to the influenza vaccines was lower in cancer patients being treated with chemotherapy than in healthy individuals. However, patients receiving chemotherapy still produced a protective serological titre, defined as HI > 40.

The first study reviewed included a sample of solid tumor breast cancer patients. The study looked specifically at the humoral response to immunization in these patients compared to healthy adults. In the study, 89% of influenza vaccinated breast cancer patients had an adequate serological level of response (HI titre > 40), compared to healthy adult subjects, who demonstrated 95% response rate (11).

A second study evaluated the humoral responses to the 2009 influenza vaccine in adults with lymphoid malignancies. A total of 40 individuals participated in the study, and were divided into two groups, receiving either one (day 0) or two doses (day 0 & day 21) of the vaccine. Of these patients, 30% who received the single dose demonstrated an adequate response (HI titre > 40). However, only 5% of patients that received a second dose at day 21 obtained an adequate response. Titres were also measured at day 42 for all participants, which showed that 30% of the study participants had achieved an adequate humoral response (21).

The third study used assessed immunological impacts of the influenza vaccine on 38 adult breast cancer patients and 28 healthy adults. The study compared different influenza vaccination strains and their efficacy. The adequate response (HI titre > 40) for H3N2, H1N1, and Brisbane were 37%, 26%, and 24% respectively for the breast cancer patients, while the healthy control group had a response of 67%, 76%, and 57% respectively (20).

The fourth study reviewed analyzed the effects of influenza vaccination in 58 colorectal cancer patients receiving chemotherapy and 27 patients not receiving chemotherapy. Overall, the level of adequate immune response, measured as a HI titre > 40, was 70%. More specifically, colorectal cancer patients receiving chemotherapy had an immune response of 69% compared with a 74% response for colorectal cancer patients not receiving chemotherpay. While the chemotherapy patients did demonstrate a lower level immune response to vaccination, the study concluded that vaccination is still recommended for this vulnerable population (22).

In the fifth and final study included in the review, 59 lung cancer patients were evaluated. Only 41 patients participated in the final study due to 18 participants demonstrating immunity to the applicable strains of influenza prior to vaccination. 32 of the 41 patients (78%) fully responded to vaccination with inactivated influenza vaccine, achieving a HI titre >40 (14).

Article Title	Selected Population	Measure of Efficacy	Response	Outcomes
Humoral immune response after vaccination against influenza in patients with breast cancer	Breast Cancer Patients (n=9) Healthy Population (n=19)	HI titre >40	89% vs. 95% in controls	Vaccination recommended
Evaluation of 2009 pandemic H1N1 influenza vaccination in adults with lymphoid malignancies receiving chemotherapy or following autologous stem cell transplant	Lymphoid Malignancies/BMT Patients (n=40) Only one dose (n=20) Two doses (n=20)	HI titre >40	30% 1 dose and 5% 2 doses at 21 days. Both 30% at 42 days	Patients with lymphoid malignancies did not achieve seroconversion rates in healthy subjects despite a second dose. Despite suboptimal seroconversion influenza vaccination should continue to be recommended.
Response to influenza virus vaccination during chemotherapy in patients with breast cancer	Breast Cancer Patients (n = 38) Healthy Population (n=28)	HI titre ≥40	Patients: H3N2 37%, H1N1 26% Brisbane 24% Control H3N2 67%, H1N1 76%, Brisbane 57%	Patients on chemotherapy have significantly lower responses to influenza virus vaccination compared with healthy controls. Vaccination recommended
Serological immune responses to inXuenza vaccine in patients with colorectal cancer	Colorectal Cancer Patient receiving chemotherapy (n = 58) Colorectal Patients not receiving chemotherapy (n = 27)	HI titre ≥40	69% immune response for patient on chemotherapy and 74% for those that were not on chemotherapy	Colorectal cancer patients receiving chemotherapy mount an immune response to the influenza vaccination. Vaccination recommended.
Seroconversion after influenza vaccination in patients with lung cancer	Lung cancer patients (n=59)	HI titre ≥40	79% seroconversion	Response rate is similar to healthy individuals. Vaccination recommended

Table 2: *Comparison 2: Influenza immunity in vaccinated patients receiving chemotherapy compared with those in the vaccinated healthy adult*

Discussion:

The presence of a malignancy and the chemotherapies used to treat them can lead to immunosuppression in cancer patients. This includes the suppression of cell mediated and humoral immune responses, creating increased vulnerability to common infections, including influenza, in these individuals. Through research, the provision of influenza immunizations to cancer patients receiving chemotherapy has been consistently demonstrated to be safe (23). However, the debate continues over the overall effectiveness of the vaccines in this patient population. In reviewing the literature on this topic, it was found that serological response to immunization and timing of vaccination in relation to the chemotherapy was a primary focus of investigation. A literature search revealed only a small number of relevant primary research papers that revealed several key points regarding influenza immunization in cancer patients being treated with chemotherapy. In patients being treated for solid tumor malignancies, there seems to be an adequate serological response when vaccinated for influenza. This was demonstrated in patients with solid tumor malignancies including breast, lung and colon cancer (14,20,24). Most research on immunization in adult cancer patients has focused on those presenting with solid tumors, not hematological malignancies. Therefore, a lack of data on immunization on hematological malignancies exists and leaves uncertainty on the efficacy of vaccinations in this patient population. Only one study focused on hematological cancer, by evaluating influenza immunization in lymphoma patients. Although this research revealed a lack of serological response in these chemotherapy patients, vaccination was still recommended (21). This study indicated rates of seroconversion and seroprotection were similar between treatment groups. However,

researchers acknowledged that the small sample size limits the potential to evaluate the actual benefit of a second dose of the vaccine. While a second dose may be anecdotally beneficial, evaluating the effectiveness of second doses of seasonal influenza vaccination tend to show minimal to no improvement in the seroconversion rates (25). The low seroconversion rate seen in the lymphoma study included in the review is consistent with previous studies involving patients with hematological malignancies (11). The study discusses other variables which may provide an explanation for this. For example, pre vaccination B-cell levels in these lymphoma patients were assessed, and it was noted that patients with the lowest pre-vaccination levels also had the lowest serological response to vaccination (21). Again, this may be due to the lack of data, as the authors pointed out, or due to the specific pathology of the hematological malignancy.

When analyzing the specific timing of vaccination in a patient being treated with chemotherapy, vaccination administration was evaluated relative to the day of the chemotherapy cycle. Despite the wide range chemotherapeutic regimens used, each with a unique protocol in terms of cycle length and timing of doses, studies defined the timing of vaccine administration as either “early” or “late” in the cycle. Only select studies that specifically examined the timing of influenza vaccination in relation to the chemotherapy cycle, however the consensus appears to be that vaccination early in the chemotherapy cycle provides better levels of seroconversion compared to when vaccinations are received later in the schedule (20). One study examining vaccination timing in breast and colon cancer patients found that there was a statistically significant difference in the level of antibody titres when compared with early vaccination (day 5) and late vaccination (day

16) in breast cancer patients, showing that early vaccination was favorable. However, the same trend results was not demonstrated in the group of colon cancer patients (19). The lack of differentiation may be in part to decreased sample size (n=18) or simply due to the nature of colon cancer and the differences in chemotherapies used. The recommendation in one study that was analyzed was to specifically immunize in between chemotherapy treatments. However, in analyzing the results of the study, it showed that adequate levels of seroconversion were best demonstrated when immunized on day 7, 10, and 14 of the chemotherapy cycle. This was in contrary to the other arm of the study, in which patients were immunized on day one of the cycle (3). This mildly contradicts previous studies which concluded that early vaccination is better. In summary, although most of the literature supports the concept of "early" vaccination, it s clear that additional scientific data must be obtained in order to reliably determine if there is an ideal time for cancer patients to receive immunizations for influenza.

This review has attempted to answer two questions. The first being what is the clinical efficacy of influenza immunization measured as a serum immune response, and secondly what is the ideal time at which the vaccination should be given in the chemotherapy cycle. In the literature, evidence exists for the clinical effectiveness of the influenza vaccination. However, little evidence has been compiled for when the most appropriate time to vaccinate within the chemotherapy cycle should be. The review found three studies that commented specifically on the timing of vaccination, therefore it is evident more research is needed to support a reliable, scientifically based conclusion. Further, due to the diversity of malignancies and different chemotherapies, it may be prudent to

evaluate and contrast hematological and solid tumor malignancies separately when more data becomes available.

Influenza immunization is an invaluable clinical resource, and when a good match between vaccine strains and circulating influenza viruses occurs, can produce a 70-90% rate of efficacy in the prevention of influenza in healthy adults (26). With adequate seroprotection, this can produce a reduction of influenza infection rates by at least 50% in the general population (13). If cancer patients receiving chemotherapy can obtain similar degrees of seroprotection to a similar degree, this will be beneficial in terms of reducing both morbidity and mortality. Vaccination of close personal contacts, adherence to proper hand hygiene, avoidance of ill contacts, and antiviral therapy for acute respiratory illnesses are also important interventions in reducing virus-related mortality and morbidity in cancer patients undergoing chemotherapy.

Conclusion:

Influenza infection remains a significant source of morbidity and mortality in cancer patients receiving chemotherapy. However, the data shows that, when properly vaccinated, it is possible for these patients to achieve a level of serological response that protects against the influenza virus. The data regarding the timing of administration of the vaccine to this population seems to support early vaccination. However the limited scope and amount of data make this inconclusive. Additional evaluation of this subject would be beneficial in developing evidence based guidelines for clinical practice, which would allow care providers to optimize patient outcomes by reducing influenza related illness and complications in this immunologically vulnerable population.

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