

Research article

Influence of endurance exercise on the risk of pneumonia and fever in leukemia and lymphoma patients undergoing high dose chemotherapy. A pilot study

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Abstract

Pneumonia and fever are common side effects of high dose chemotherapy (HDC). The positive influence of physical activity on physiological and psychological parameters in cancer patients has been demonstrated in several studies. In this non-randomized controlled pilot study we investigated the infection and pneumonia risk in 36 high dose chemotherapy patients undergoing a supervised endurance exercise program. Eighteen patients exercised for at least 3 weeks, starting with initiation of chemotherapy. These patients in the intervention group were compared with 18 patients who were matched by disease (leukemia/lymphoma), sex, age, risk factors, therapy protocols and did not take part in the exercise intervention. Leukemia and lymphoma groups were evaluated separately. In the leukemia group significant higher pneumonia rates could be observed in the control group ($p = 0.040$) when compared to the intervention group. Further an almost significantly higher risk ($p = 0.061$) of developing a pneumonia and fever was detected in the control group. In this pilot study, we gained first important positive experiences in possibly preventing pneumonias and fever through endurance training. Due to the non-randomized study design and small sample size the results are limited yet not irrelevant. RCTs with larger sample sizes are necessary to prove these findings.

Key words: Exercise, chemotherapy, cancer, pneumonia, fever, activity.

Introduction

With an incidence of 60-100%, infections and fevers are the most prominent side-effects in high dose chemotherapy (HDC) patients during aplasia (Kuderer et al., 2007). Although infections are the leading cause of treatment-related mortality in cancer patients, the reason for infections is only known in 30-50% of all cases. The risk of infection correlates with the time spent in aplasia, leading to a mortality risk of 2.8-5.7% (Kuderer et al., 2007; Link 2004; Link et al., 1994). Aside from high risk factors such as gram negative bacterial sepsis and aspergillosis, pneumonia has a relative risk of 2.23 in HDC patients (Kuderer et al., 2006). Another consequence of aplasia and its associated infection risk is a prolonged hospital stay, which leads to a poorer prognosis for the patient and

higher economic costs for the healthcare systems (Battaglini et al., 2009).

The positive influence of a moderate exercise program on physical and psychological parameters in cancer patients has been demonstrated in several studies. Both, changes in cytokine patterns (Gomez et al., 2011; Pedersen, 2011), NK-cell-activity, and toxicity (Maltseva et al., 2011; Wang et al., 2009) as well as in pain, fatigue, and quality of life (Adamsen et al., 2009; Baumann et al., 2010; Battaglini et al., 2009; Hayes et al., 2004) have been observed. While the positive effects of physical exercise on psychological parameters are well proven, only few studies focus on clinical and physiological outcomes. Influences on leucocytes and hospital days have been observed and could probably impact the nosocomial infection risk (Dimeo et al., 1997; Dimitriu et al., 2005; Fairey et al., 2005; Lu et al., 2006).

The primary objective of this pilot study was to investigate the influence of a supervised, moderate endurance exercise program which lasts for at least three weeks, on the incidence of non-fungal, nosocomial pneumonias and fevers in patients undergoing HDC. Secondary outcomes were changes in neutrophile- or leukocyte-counts as well as the absolute time spent in the hospital.

Methods

Subjects

From March 2008 until July 2009 36 patients participated in this matched-pair pilot study which was conducted at the University Hospital of Cologne, Department of Hematology and Oncology. Patients were included if they received leukemia or lymphoma chemotherapy treatment, had to be older than 18 years and give written consent prior to the intervention for scientific data evaluation. Exclusion criteria were severe co-morbidities, such as cardio-vascular diseases (New York Heart Association III-IV), a partial or global respiratory insufficiency, orthopedic handicaps, or an autoimmune thrombocytopenia or anemia that rule out regular physical activities. Platelet values under $10.000/\mu\text{l}$, hemoglobin values above $9\text{g}\cdot\text{dl}^{-1}$, fever above 38°C , infections, emesis, diarrhea, or ongoing administration of chemotherapy excluded patients from testing and training. Patients were included in the study during chemotherapy, yet at different stages of medical treatment. However, all subjects were involved at the beginning of their aplasia-related inpatient treatment. 18 patients took part in a moderate endurance exercise pro

Table 1. patient characteristics.

Matching parameters	Exercise group	Control group
Diagnosis	AML: 7, ALL: 2, HL: 3; NHL: 6	AML: 7, ALL: 2, HL: 3; NHL: 6
Sex	9 males, 9 females	9 males, 9 females
Age	46.11 years (SD=16.22)	45.22 years (SD=15.21)
Chemotherapy Protocol Subgroups	Leukemia chemotherapy protocol: 11 Lymphoma chemotherapy protocol: 7	Leukemia chemotherapy protocol: 11 Lymphoma chemotherapy protocol: 7

Abbreviations: AML= acute myeloid leukemia; ALL= acute lymphoblastic leukemia; HL= Hodgkin Lymphoma; NHL= non-Hodgkin lymphoma

gram conducted on a stationary bicycle. Further 18 patients from the clinic registry that were matched by sex, age, therapy protocol, stage, risk profile (complete days of aplasia), and disease served as a control group. The matching procedure was completed by a scientific member of the university hospital in two phases. Primary matching variables were disease, therapy protocol, sex and age (Table 1). In a second phase we tried to ascertain patients with similar stages and risk profiles. Controls did not participate in any exercise program, yet received the usual physiotherapeutic care, consisting of passive and active mobilization with low intensities, if necessary. Due to the fact that chemotherapy protocols lead to subsequently longer periods of aplasia with different recommendations for antibiotic or antimycotic prophylaxis, we performed a subgroup analyses (Cheson et al., 2003; Scherrer et al., 1994). The first group was defined as “lymphoma chemotherapy protocol”, including medical chemotherapy protocols which normally lead to an aplasia time of less than 7 days. The second, “leukemia chemotherapy protocol” group describes those protocols in which aplasia lasts longer than 7 days (Table 1). This pilot study was approved by the ethics committee of the University of Cologne, Germany (No. 07-241).

Diagnosics and exercise program

To determine a standardized exercise load the intervention group underwent a modified WHO endurance test on a cycle ergometer. All measurements were taken by a sport therapist. Starting with 25 Watt, the applied load increased by 10 Watt every 2 minutes (Baumann and Bloch, 2010). The test was stopped as soon as the patient reached a heart rate of 180 beats minus the patient’s age. 80% of that achieved watt load was defined as the patient’s exercise load for the stationary bicycle training (Baumann et al., 2010; Elter et al., 2009). The heart rate was measured with a Polar pulse watch. Patients exercised three times per week for 20 to 30 minutes over a period of three weeks. All exercise sessions were supervised by a therapist. The patients’ perception of the endurance intervention was to be “slightly strenuous”, which was determined by means of a RPE-scale (ratings of perceived exertion, Borg Scale) (Borg, 1998). Patients did not receive any other exercise instructions. Diagnostics and exercise sessions were interrupted if patients reached blood pressure values above 170/100 mmHg or heart rates over 180 bpm minus the patient’s age. The supervised exercise program, as well as the performance diagnostics, was conducted on a stationary training bicycle (Variobike 550 Ergoline, Bitz, Germany).

Statistics analyses

Statistical analyses were performed using SPSS 17.0. Nominal data such as non-fungal and nosokomial pneumonias and fevers were counted in all patients during their time in aplasia. In order to compare the two groups, the Fisher’s exact test was chosen because we obtained incidence smaller than five. A p-value of < 0.050 was defined as statistically significant for $\alpha = 5\%$. For significant results we calculated the relative risk. In case data did not show a normal distribution, we used the Mann-Whitney U test to compare the mean days with neutrophile-, leukocyte values and days spent in the hospital. Additionally we used the Mann-Whitney U test in a subgroup analysis of 22 patients receiving a leukemia chemotherapy protocol and 14 patients receiving a lymphoma chemotherapy protocol.

Results

The mean age was 46.11 years in the intervention group (SD=16.22) and 45.22 years (SD=15.21) in the controls.

Training

Patients in the intervention group exercised 2-3 times per week ($M = 2.4$, $SD = 0.66$) at a mean intensity of 47 Watt (Median: 50 Watt, $SD = 14.5$). On average the patients worked out for 23 minutes per session (Median: 25 min, $SD = 7.9$). The mean age in the leukemia group was 49.25 ($SD = 8.81$) years and in the lymphoma group was 49 ($SD = 17.82$) years.

Pneumonia and fever

Regarding the entire sample size non-fungal, nosokomial pneumonia could be observed in two patients of the intervention group and seven patients of the control group (Table 2). Fever was diagnosed in eleven individuals of the intervention and 16 patients of the control group. These differences between exercise and control group were not significant ($p = 0.061$).

Table 2. Pneumonia and fever incidence in the intervention and the control group.

Pneumonia	intervention	control	total
no	16	11	27
yes	2	7	9
total	18	18	p = .061
Fever	intervention	control	total
no	7	2	9
yes	11	16	27
	18	18	p = .061

The subgroup results show, that almost all patients in the leukemia chemotherapy protocol group had fever, whether they exercised or not (Table 3). In contrast, only one patient that exercised and five patients that did not exercise had fever in the lymphoma chemotherapy protocol group. Even though no significant difference could be determined in the occurrence of fever, we observed a tendency in favor of the intervention group ($p = 0.051$). With a p value of 0.040, pneumonias occurred significantly more often in those individuals of the leukemia chemotherapy protocol group that did not exercise. Thus patients of the control group had a 3.5 higher relative risk for pneumonia infection. Only two individuals of the exercise group experienced pneumonia, whereas seven control group patients were affected. In the lymphoma group, no pneumonia incidences could be detected.

Table 3. Pneumonia incidence in the leukemia chemotherapy protocol group and fever incidence in the lymphoma chemotherapy protocol group.

Pneumonia	intervention	control	total	relative risk
no	9	4	13	
yes	2	7	9	
total	11	11		$p = .040^*$ 3.50*
Fever	intervention	control	total	relative risk
no	6	2	8	
yes	1	5	6	
total	7	7		$p = .051$

*significant

Blood counts, days spent in hospital

There were no statistically significant differences between the intervention and the control group in the mean days of leucopenia and neutropenia (Table 4). Similar results were observed for the absolute time spent in the hospital.

Discussion

In this probably first pilot study regarding the influence of physical activity on fever and non-fungal, nosocomial pneumonia risks in hematological cancer patients during aplasia, we observed no significant differences between the intervention and the control group. However regarding the subgroup analysis we were able to detect a statistically significant exercise benefit in terms of a reduced pneumonia risk in patients treated with a leukemia chemotherapy protocol. A supervised endurance exercise program seems to positively influence the pneumonia incidences in patients undergoing a leukemia chemotherapy protocol. These results underline the findings of Baumann et al. (2010) who proved a beneficial effect of physical exercise on pneumonia incidence in patients during bone marrow transplantation. Although all subjects showed typical

signs of an infection, including fever, the significant higher risk for pneumonia in the control group leads to the conclusion that physical exercise may have a preventive effect in these patients. A possible preventive effect could lead to a decrease in mortality during aplasia in this collective (Dimeo et al., 1997). Supervised endurance training supports antibiotic and antimycotic prophylaxis. Therefore it could play an important role and serve as a simple supportive method to prevent pneumonia in the clinical routine. Aside from the more intensive ventilation level during endurance exercise and the strengthening of respiratory muscles, which may hinder pathogenic germs from persisting in the respiratory tract, the systemic influence (Teasell and Dittmer, 1993), e.g. on NK-cell activity, NK-cell toxicity (Maltseva et al., 2011; Wang et al., 2009) and cytokine patterns (Pedersen, 2011) may explain the effects of targeted physical exercise. However, these are assumptions, since studies focusing on the preventive effect of exercise on pneumonia risk in cancer patients have not been completed. The preventive effect of a moderate exercise program on the infection risk of the upper respiratory tract has been proved in several studies (Gleeson, 2007). This exercise-induced protection is associated with exercise intensity related concentrations of salivary IgA (Allgrove et al., 2008). Whether this effect also has an influence on pneumonia risk is still unclear. A small numbers of studies report an increased pneumonia risk in obese people and during immobilization, although a significant correlation to physical activity could not be detected. In addition these studies, physical activity were neither defined nor supervised (Baik et al., 2000; Murugan and Sharma, 2008; Neuman et al., 2010; Teasell and Dittmer 1993). The higher fever rate in the leukemia chemotherapy protocol group compared to the lymphoma chemotherapy protocol group may be explained by the fact that these individuals experienced a longer time in aplasia and a longer hospital stay, which raises the probability of an infection (Battaglini et al., 2009). These presumptions should also be kept in mind regarding pneumonia risk.

The major limitation of our trial is the small sample size and that patients were not compared in a randomized fashion. A second limitation may be the fact that we only included patients who were able to exercise for at least three weeks during their hospital stay. The fitness status and exercise history of the patients were not documented. Thus, we potentially recruited a sample of individuals which had better preconditions. Nevertheless, matching partners were carefully selected and the medical status prior to treatment seemed to be comparable. Possible confounders which may have had an impact on our results need to be considered. A major risk for nosocomial

Table 4. Total days spent in hospital, and days with severe neutropenia or leucopenia in the leukemia chemotherapy protocol and the lymphoma chemotherapy protocol subgroups. Data are means (\pm SD).

Leukemia protocol (n=22)	Hospital days	Neutropenia days	Leukopenia days
IG	64.8 (12.6)	35.0 (13.8)	31.9 (11.9)
CG	69.8 (14.1)	36.4 (11.7)	28.0 (12.6)
Lymphoma protocol (n=14)	Hospital days	Neutropenia days	Leukopenia days
IG	41.7 (4.1)	5.1 (2.8)	4.1 (3.8)
CG	40.9 (3.2)	5.3 (3.5)	5.4 (3.0)

No significant differences between IG and CG.

infections in hospitals is the missing hand-disinfection of patients and personal. In clinical practice the compliance with hand disinfection is often low and could increase the infection rate by up to 40 % (Kampf and Löffler, 2010). Hygienic factors could have had an influence on our results, which indicates the difficulty to conduct a trial with the aim to reduce pneumonia.

Conclusion

Taken together, our results must be seen as a preliminary therapeutic experience, which has to be confirmed. In addition to that these results underline the need to carefully select patient subgroups and should be considered in the future. Despite the above mentioned limitations, we were able to gain valuable insights and probably for the first time describe clinical benefits of an exercise intervention on pneumonia and fever risk in leukemia and lymphoma patients in a pilot study. If further trials confirm our findings, a moderate exercise program should be recommended to all HDC patients, not only because of its positive psychological effects but also important physiological benefits which might reduce mortality (Adamsen et al., 2009; Baumann et al., 2010; Battaglini et al., 2009; Hayes et al., 2004; Dimeo et al., 1997).

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Key points

- Infections are the leading cause of treatment-related mortality in cancer patients.
- We gained first important data in possibly preventing pneumonia and fever during chemotherapy through exercise.
- Due to the non-randomized study design and small sample size these findings are limited.

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