

## CHAPTER V

### DISCUSSION

The aims of this study were to look at the effect of chemotherapy on cardiorespiratory fitness and quality of life in newly diagnosed patients with advanced stage of SCLC and NSCLC. The majority of the study found that there was no significant differences of 6MWD, cardiovascular variables; except post-heart rate and post-fatigue were seen to increase significantly, PFTs (except  $PEFR_{\%predicted}$  increased significantly) and the core quality of life questionnaire items (EORTC QLQ C-30), whereas the supplementary module of quality of life questionnaire items (LC-13) showed hair loss and peripheral neuropathy increased significantly.

Although almost of these results were different from the hypotheses, most of these findings showed positive results to the patients in that chemotherapy did not deteriorate exercise capacity indicated by 6MWT, lung functions indicated by PFTs, cardiovascular variables and the majority of quality of life items. All details are described as follows:

#### 1. Exercise Capacity

The exercise capacity (6MWD) in this study showed no declined after patients received four courses of chemotherapy. The study finding differed from the study of Shin et al. and Kasymjanova et al, but was not very different from the latest study of Mohan et al. (Table 11).

**Table 11** The comparison of previous studies and the present study on exercise capacity.

Researcher [yr.]	Study design	Outcome	Result
Shin et al (2002)	3 cycles, advanced NSCLC	VO <sub>2max</sub>	↓ [Sig.]
Mohan et al (2008)	4 cycles, advanced NSCLC	6MWT	<u>No</u> change [Overall]
Kasymjanova et al (2009)	2 cycles, advance NSCLC	6MWT	↓ [Sig.]
Present study	2 cycle, 4 cycle, advanced NSCLC	6MWT	<u>No</u> change [Overall]

Shin et al. (45) investigated changes of cardiopulmonary exercise tolerance prior to four cycles of chemotherapy in eleven patients with locally advanced NSCLC, the results showed significant reduction of maximal oxygen uptake (VO<sub>2max</sub>, ml/kg/min, 17.9+/-2.6 : 12.6+/-6.1, <0.05). This result might possibly be explained in that the tumor did not respond to chemotherapy. The measurement of exercise capacity of Shin et al. was different from the present study as it used VO<sub>2max</sub> which is a maximal exercise test, whereas the present study used the 6MWT a submaximal test of exercise capacity. However, many studies show that 6MWT is appropriate in many conditions especially in case of pulmonary and cardiac diseases (81). Therefore, we chose the 6MWT for measuring exercise capacity. Moreover, the assessment time point in this present study was measured after four courses of

chemotherapy while the study of Shin et al. was done before the fourth course of chemotherapy, this might cause differences in results.

Kasymjanova et al. (47) studied advanced NSCLC patients' exercise capacity by using 6MWT, with 45 patients completing the study, the results showed a decreasing of 6MWD after patients received two courses of chemotherapy. Even though the study of Kasymjanova et al. (47) investigated the effect of chemotherapy after second courses of chemotherapy which differed from the present study that examined the second courses and also after four courses of chemotherapy, however 6MWD in the present study after a second course still did not show a decrease of 6MWD. By the 6MWD average pre-chemotherapy of Kasymjanova study was 462 meters and after a second course of chemotherapy declined to 422 meters; however, 462 meters at the pre-chemotherapy stage is not enough to explain that point was a ceiling effect, so the decreasing of 6MWD might be a negative effect from chemotherapy. Whereas, the average of 6MWD before receiving chemotherapy and after a second course of chemotherapy in this present study was 413 meters and 415 meters, respectively. Therefore, we could conclude that this finding might be positive in terms of chemotherapy and did not have enough serious effects to change the exercise capacity of patients.

Mohan et al. (16) studied 44 patients after four cycles of chemotherapy in advanced NSCLC, the results showed that increasing in 6MWD especially in group of good response but was not significant, however overall there was no change of 6MWD. The study of Mohan et al. (16) was quite similar to the present study showing no changes in 6MWD after four cycles of chemotherapy (Mean of 6MWD both pre and post chemotherapy = 331 meters). The researchers' explanation is the

same as previous study that it depends on the response to chemotherapy. The 6MWD in responder group was higher than non-responder group, but not significant. Therefore, the present study could explain in the same way that patients might respond to chemotherapy, even though we did not find how many. In addition, the reasons that explain why the 6MWD in the present study did not decline following the hypotheses, could be explained that the physical fitness level of patients before receiving chemotherapy was rather high, this is supported by the results of the core quality of life form (QLQ C-30) in part of functioning that five main items of functioning showed more than 80 percent. Moreover, 50% were working and others took exercise.

Two participants was excluded because they felt tired and had lung effusion after they received two courses of chemotherapy, this might be the effect of chemotherapy. Therefore, we could not determine that chemotherapy did not affect exercise capacity because all above mentioned reasons might counterbalance from the adverse effect of chemotherapy. Therefore, finally the 6MWD after four courses of chemotherapy did not decline than after receiving the second course and prior to receiving chemotherapy.

## **2. Cardiovascular variables response to 6MWT**

Previous studies (16, 45, 47) investigated the effects of chemotherapy on exercise capacity (6MWT) but there are no papers about the cardiovascular variables after the test such as heart rate, blood pressure, oxygen saturation percent, dyspnea level and fatigue level. Mostly cardiovascular variables in the present study have a good response after 6MWT such as systolic blood pressure and oxygen saturation

percent did not decline, whereas heart rate, dyspnea level and fatigue level were increased. At the same time, if compared between all the three times measurements, the result showed a significant increase of post-heart rate and leg fatigue after fourth and second courses of chemotherapy including the percent change of maximum heart rate tended to increasing after the final assessment.

### **2.1 Pre-heart rate**

Pre-heart rate increased after the fourth courses of chemotherapy, but not significantly. Previous studies stated in the same direction that chemotherapy could directly and indirectly affect patients and these ranged from mild to severe adverse effects to cardiovascular systems (32, 34, 36, 37, 39, 73). In addition, chemotherapy can destroy bone marrow and lead to poor levels of oxygen in blood circulation (48, 50), finally causing anemia. In addition, some studies stated that many compensatory mechanisms that responded from anemia e.g. increase in pulse rate, cardiac output, peripheral vasodilatation, and blood flow, enhanced oxygen unloading, increased of respiratory rate in an effort to improve blood oxygenation (48). Therefore, the increasing of pre-heart rate in present study supported prior studies which might be the effect of chemotherapy.

### **2.2 Post-heart rate and percent changed of maximum heart rate**

Post-heart rates before receiving chemotherapy, after second and after fourth courses of chemotherapy were  $100.75 \pm 11.90$ ,  $106.92 \pm 14.82$  and  $116.00 \pm 17.10$  bpm, respectively. The differences between 1<sup>st</sup> vs 3<sup>rd</sup> and 2<sup>nd</sup> vs 3<sup>rd</sup> increased significantly. Chemotherapy might make patients feel more easy tired and fatigued, therefore heart rates of patients increased after receiving four courses of chemotherapy. Therefore, this might be explained as an effect of chemotherapy, and is supported with many

previous studies that chemotherapy could directly and indirectly affect the cardiovascular system of patients (32, 34, 36, 37, 39, 48, 50, 73). Moreover, if transformed pre-heart rate and post-heart rate to percent changed of maximum heart rate, the results show a tendency to increase after four courses of chemotherapy. This result might the effect of chemotherapy as well.

### **2.3 Percent of oxygen saturation**

After 6MWT, no patients had a drop of percentage oxygen saturation. Moreover, there were no significant changes of oxygen saturation percent after four courses of chemotherapy both pre-test and post-test. These results indicated that we could do the 6MWT in this patient group even though all them were in advanced stage of disease safety and with no drop of oxygen saturation percent. In addition, chemotherapy might not effect oxygen saturation percent after receiving chemotherapy.

### **2.4 Blood pressure**

If compared between pre-test or post-test of systolic blood pressure, it showed increase after 6MWT in all three measurements and diastolic blood pressure also increased after 6MWT, except in the second measurement when there was a decrease of diastolic blood pressure after 6MWT. In addition, there were no changes in pre-test systolic, pre-test diastolic, post-test systolic and post-test diastolic readings after patients received their second and fourth courses of chemotherapy, respectively. All of these results showed no adverse effects on both systolic and diastolic blood pressure after 6MWT.

## 2.5 Dyspnea level and leg fatigue level

If compared between pre-test or post-test of dyspnea and fatigue on each time measurement, the result demonstrated that participants in all three measurements felt more tired and had more leg fatigue with scores ranging from 0 to 4, patients feelings range from a little bit tired up to somewhat strong tired. These findings support that 6MWT is the sub maximal test of exercise capacity (81). Moreover, there were no changes of pre-dyspnea, post-dyspnea, pre-leg fatigue and post-leg fatigue, excepted post-leg fatigue after the second course of chemotherapy showed increase. This can be explained as same as the increasing of post-heart rate as it might be a negative effect from chemotherapy and make patients feel more easy tired.

Therefore, overall, the findings of this study can be summarized that we could apply used of 6MWT in these patients group with safety even though the participants were in advanced stage of disease but they did not have any serious on heart rate, oxygen saturation percent, blood pressure, dyspnea and leg-fatigue levels.

## 3. Pulmonary function test

Many variables of pulmonary function tests were examined, the results merely showed  $PEFR_{\%predicted}$  increased significantly after four courses of chemotherapy, whereas the other variables did not see any significant changes. These results were in contrast to the hypotheses and some previous studies as show in Table 12.

**Table 12** The comparison of many previous studies and present study on PFTs.

Researcher [yr.]	Study design	Result
Pinson& Klastersky (1998)	3 cycles of NSCLC & SCLC	Resp. → ↑ FEV <sub>1</sub> and VC Non-resp. → <b>No</b> change
Maas et al. (2003)	3 cycles, stage IIIA/B NSCLC [NCT]	Overall → ↑ FEV <sub>1</sub> and FEV <sub>1</sub> /VC [Sig.]
Leo et al. (2004)	3 cycles of, stage IIIa NSCLC	Overall → ↑ FEV <sub>1</sub> and FVC [Sig.]
Mohan et al (2008)	4 cycles, advanced NSCLC	Overall → <b>No</b> change
Present study	2 cycle, 4 cycle, advanced NSCLC	PFTs → <b>No</b> change [except PEFR <sub>%predicted</sub> ]

Pinson and Klastersky (44) studied the effect of chemotherapy after the first three cycles of chemotherapy, the result showed statistically non-significant improvement of FEV<sub>1</sub> and VC in responders group and stable values in non-responders group, however this study design differed from the present study. Maas et al. (43) studied the effect of three cycles of chemotherapy within one month neoadjuvant, the result showed significant increases of FEV<sub>1</sub> and FEV<sub>1</sub>/VC. Nevertheless, the participants of Maas et al. studied in stage IIIa/b of NSCLC which was different from the present study. Leo et al. (42) investigated stage IIIa of NSCLC treated by induction chemotherapy with three cycles of chemotherapy, the result showed significant increase of FEV<sub>1</sub> and FVC. This study was similar to Maas et al.



The latest study by Mohan et al. (16) which the design study was as same as the present study examined the effect of standard chemotherapy after first four cycles in advanced NSCLC, the result showed improved lung function in responders group and decline in non-responder group but not a significant change in both groups, nevertheless overall did not change pulmonary function. Therefore, the findings of present study were similarly the study of Mohan et al. (16) with no significant changes of mostly variables.

Researchers in all previous studies explained that the increase of pulmonary function variables is dependent on the response to chemotherapy. If patients responded to the treatment, the pulmonary function variables are also improved, on the other hand, the pulmonary function variables declined if the tumor did not respond to chemotherapy. Therefore, the increasing of variables in this present study could assume that the tumor had responded to the chemotherapy. In addition, many patients can stop smoking that might also improve of pulmonary variable and supported the study of Leo et al that the increasing of pulmonary variables might cause from the patients can stop smoking (42).

The findings of present study was quite opposite to the hypothesize that expected that PFTs would declined after completing four courses of chemotherapy because many previous studies demonstrated that a side effect of chemotherapy would be destruction of lung properties (35). In addition, many lung problems were associated with chemotherapy such as acute pneumonitis, adult respiratory distress syndrome (ARDS), progressive pulmonary fibrosis, pleural disease, and hypersensitivity reaction. Moreover, many pathologic patterns are observed by a biopsy method after chemotherapy (35). Previous studies show that chemotherapy

could be directly involved in reducing patients daily activity (32, 34) and limit physical function (48, 50). Therefore, all of these reasons might affect pulmonary function are decreased after chemotherapy.

Conversely, the results showed no decline in these variables and tended to increase. Therefore, the effect of chemotherapy might not affect lung properties of patients in the present study, and the patients might not have any serious side effects from chemotherapy which supported by the result of QoL and many patients still could do many physical activities, continue work and take exercise.

#### **4. Quality of life questionnaires (EORTC QLQ C-30 and LC-13)**

The hypothesis in this study expected that overall, the majority items of the QoL and symptoms of patients after four courses of chemotherapy will not be greater than patients who received two courses of chemotherapy and pre-received first course of chemotherapy, respectively. Even though many of studies showed QoL improved after chemotherapy by relieved of many of symptoms (18-20), however the latest study of Mohan et al. showed that QoL was no change after four courses of chemotherapy even though many of symptoms were improve (16). In addition, many studies showed that chemotherapy can cause of many side effects both physical and psychological problems and related to the limitation of physical function, finally the QoL of patient those who completed four course of chemotherapy will not be greater than after two courses and before first course of chemotherapy.

Whereas, the result showed most of QoL items included the core questionnaires (EORCE QLQ C-30) and supplementary module (LC-13) did not have any QoL items significantly changed, except hair loss and peripheral neuropathy

items increased significantly after two and four courses of chemotherapy. Moreover, all of QoL items did not have any trends of change after the final assessment. These results contrasted to many prior studies that commonly show improvements on global QoL and relief on some symptoms and worsening in other symptoms (Table 13).

**Table 13** The comparison of many previous studies and present study on QoLs.

Researcher [yr.]	Study design	Result
Fernandez et al. (1989)	2 cycles, advanced NSCLC	QoL → ↑ [Sig.], symptoms → ↑/↓
Bircan(2003)	3 cycles, advanced NSCLC & SCLC	QoL → ↑ [Sig.], symptoms → ↑/↓
Mohan (2008)	4 cycles, advanced NSCLC	Resp./non Resp. → QoL → ↑ [Sig. of physical, psychological, social] Overall → QoL [no change], ↑ Some of symptoms [Sig.]
Sumitra (1999)	Pre/ 3 <sup>rd</sup> mo and post 2 mo, advanced NSCLC [compared BSC + chemotherapy & BSC]	QoL → ↑ [Sig.] [BSC+chemotherapy] compare with BSC
Jirawan (2007)	Pre/ post 1,2 mo, advanced NSCLC	QoL → ↑ [emotion, sig] / ↓ physical and function [not sig]
Present study	2 cycle, 4 cycle, advanced NSCLC	C-30; → <b>No</b> change LC-13; → ↓ Hair loss, PN [Sig.]

For instance, the study of Fernandez et al. (19) indicated that 75% of patients with advanced NSCLC improved QoL after having received the first two cycles of high-dose chemotherapy and had also improved in some of symptoms and declined in others. Bircan et al. (18) investigated after first three cycles of advanced NSCLC and SCLC as the result showed improved global health status and decreased many symptoms such as pain, haemoptysis, dyspnea and coughing; however, alopecia, sore mouth, nausea and vomiting increased with chemotherapy. Whereas, the review study by Paesman (17) and Fallowfield and Harper (15) showed improvement in QoL after chemotherapy, including the studies in Thailand by Thongprasert et al. studied in advanced NSCLC between those receiving best supportive care and best supportive care plus at least two courses of combination chemotherapy there was an improvement of QoL in chemotherapy group only. While the study of Santisevee (20), showed a tendency to increase QoL scores, especially in the dimension of emotional well being which is statistically significant whereas the physical and functional well being were not significantly decreased after chemotherapy. Therefore, all previous studies concluded that chemotherapy could relieve many symptoms of patients, and the overall QoL also showed improvements. However, this present study was seem similar to the study of Mohan et al. (16) that overall there was no significant improvement of QoL.

In addition in part of QLQ C-30, the symptoms that had higher scores than other symptoms at first measurement were fatigue, dyspnea, pain and financial problems. After the final measurement, all of these problems remained, so these might cause of overall of QoL was no change like many previous studies (15, 17-19). However, in all five functioning items at the first measurement showed higher than

80%, after the final measurement all of five functioning items still showed more than 80 %, these results indicated that all patients have a very high level of functioning, in addition as above mentioned that many patients can work, do many physical activity or even exercise, therefore, these might counterbalance the adverse effect of chemotherapy and finally after four course of chemotherapy was no decline than after second course and before first course of chemotherapy, respectively.

For LC-13, after the first measurement just dyspnea, coughing and pain were obviously higher than other symptoms, and after the final assessment, these symptoms remained. The symptoms presented after received chemotherapy was hair loss and peripheral neuropathy which showed significantly worse after second and final measurement. These result studied also support that why the overall of QoL was no change after received chemotherapy.

In summary, all results showed no decline of cardiorespiratory fitness, these result was not absolutely difference from the hypothesized, and if we look back to the conceptual framework of the study, we can imply that the participants in this study might not have any serious side effects from chemotherapy. Therefore, it did not enough to change both physical and psychological status of participants including did not change lung properties or cardiotoxicity. At the same time, the common side effects are fatigue and dyspnea, in this study there was no change of these symptoms after four courses of chemotherapy, and chemotherapy might not cause bone marrow deterioration and patients might not have anemia problem. However, the very importance things that might counterbalance from the side effect of chemotherapy was many patients can keep work, exercise and do many activities as before receiving chemotherapy. Therefore, all of these result caused the cardiorespiratory fitness of

the patients after four courses of chemotherapy was no greater decline than after second and before first course of chemotherapy, respectively. As same as the result of QoL items that were no change after four courses of chemotherapy because of chemotherapy could not alleviate many symptoms such as fatigue, dyspnea, coughing and pain, also other symptoms were present after the chemotherapy such as hair loss and peripheral neuropathy. Moreover, the QoL after four courses of chemotherapy was no greater decline than after second and before first course of chemotherapy, respectively, these could explain as same as the result of cardiorespiratory fitness.

## 5. Conclusion

The findings of this study conclude that chemotherapy did not much deteriorate cardiorespiratory systems including exercise capacity (6MWT) and pulmonary function after patients received four courses of chemotherapy. Therefore, cardiorespiratory fitness after four courses of chemotherapy did not greatly decline than after receiving the second course of chemotherapy and before they received the first course of chemotherapy. In addition, most of the cardiovascular variables did not change after four courses of chemotherapy, except post-heart rate and leg-fatigue increased after the 6MWT after the fourth and the second courses of chemotherapy, respectively. In addition, after patients finished 6MWT, none of the patients presented with serious problems, these indicated that 6MWT is appropriately used in this patient group even though the patients were in the advanced stage of the disease. For the QoL in part of the core questionnaire (EORTC QLQ C-30) were no changes of any items of QoL, as same as in part of the supplementary module (LC-13), except

hair loss and peripheral neuropathy was worse after four and second courses of chemotherapy.

Patients who had obvious problems at the first measurement including fatigue, dyspnea, pain, coughing and financial problems, after the final measurement these problems still were present, so chemotherapy could not alleviate these symptoms. Therefore, overall the majority of QoL items of patients was not changed after receiving four courses of chemotherapy and did not greater decline than after receiving the second course of chemotherapy and before received first course of chemotherapy, respectively.

## **6. Clinical application and future study**

Even though most findings of cardiorespiratory fitness displayed no decline after four courses of chemotherapy, and cardiovascular variables responded to 6MWT showed positive in results, however most of QoL items of patients did not change, in addition some symptoms were still present and other symptoms were present after chemotherapy. Therefore, health professionals need to pay attention and carefully use chemotherapy for treatment of advanced lung cancer. In addition, in the future health professionals may consider adding interventions during chemotherapy especially a specific exercise program which could counterbalance the side effects of chemotherapy, exercise might improve the cardiorespiratory fitness as well as the QoL items.

Consequently, we believe that patients could exercise even during or after chemotherapy because most patients still could do many activities even work, moreover, all participants still could finish the 6MWT at the final measurement and

did not have any adverse effects. However, any exercise program should be done at the appropriate time, within comfortable limits of each person and different from person to person.

### **7. Limitations and suggestions**

This study was limited to twelve participants who completed the study. However, in fact we had many patients who were considered for chemotherapy but they could not participate for reasons as follows; a) some patients were included in other studies, b) patients have a lot of procedures and tests, so these resulted in making the patients feel more tired and fatigued and c) the time for agreeing to join in the study was limited and too short. For future study, the oncologist should be more supported for the study, these might make the patients have more motivation to join in and the oncologist might be able to extend the time for the patients to decide on receiving the chemotherapy and to join the study. In addition, this research had only NSCLC, therefore we could not apply the findings to SCLC type.