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Research Article

Synthetically Treatments and Analyses, for Old Age Advanced Lung Adenocarcinoma

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ABSTRACT

Purpose: To identify clinical treatment and feature of old age advanced lung adenocarcinoma. Using raised advanced lung adenocarcinoma clinical treatment level.

Materials and Methods: Between January 2018-July 2018. 52 patients more than 60 old-years with advanced lung adenocarcinoma were divided 5 groups, with different treatment method. After all group patients were treated, compared survival rates.

Results: Total group 52 patients survival rate, 1 years 88%, 2 years 70%, 3 years 38%, 4 years 34%, 5 years 23%. Median survival time 30 months. Surgical-operation-radiotherapy-chemical therapy-TKI therapy group survival rate: 1 years 100%, 2 years 100%, 3 years 57%, 4 years 35%, 5 years 35%, 6 years 21%. 10 years 14.2%, 15 years 7%, Median survival time 54 months. Chemical-TKI therapy group survival rate: 1 years 100%, 2 years 61%, 3 years 38%, 5 years 27%. Median survival time 28 months. Single TKI therapy group survival rate: 1 years 67%, 2 years 17%, Median survival time 14 months. Radiotherapy-chemical-TKI therapy group survival rate: 1 years 100%, 2 years 78%, 3 years 22%. Median survival time 29 months. Single chemical therapy group survival rate: 1 years 20%, Median survival time 8 months. Chemical-TKI therapy group compared single TKI therapy group $u=0.28$ $p<0.01$, $\alpha=0.05$. Chemical-TKI therapy group compared radiotherapy-chemical-TKI therapy group $p<0.1$, $\alpha=0.05$ without statistics meaning. Chemical-target-therapy group compared surgical operation-radio therapy-chemical-TKI therapy group $0.2<p<0.1$, $\alpha=0.05$. Without statistics meaning single TKI therapy group compared single chemical therapy group $p<0.05$, $\alpha=0.05$. Radiotherapy-chemical therapy-TKI therapy group compared single target therapy group $p<0.01$, $\alpha=0.05$. Had statistics meaning. Radiotherapy-chemical therapy-TKI therapy group compared surgical operation-radiotherapy-chemical-TKI therapy group $0.2<p<0.1$, $\alpha=0.05$ without statistics meaning.

Conclusion: For old aged advanced lung adenocarcinoma patients, surgical operation were best way. For no-surgical operation patients, according to patient's physique, pathological-phase, choose radiotherapy, chemical therapy, TKI therapy and synthetically therapy. For had a long survival time, enhanced quality of life, had a reality clinical significance.

Keywords: Lung adenocarcinoma; Chemical-radiotherapy-TKI therapy; Synthesized treatment

INTRODUCTION

Lung cancer was first death rates and first incidence of cancer in Chinese at present [1]. The lung adenocarcinoma was first high pathological type, holding 53.13%. Second were squamous cancer (24.51%), small cell cancer (14.95%), large cell cancer (0.06%) in lung adenocarcinoma, male: female=1:1.5. The adenocarcinoma of lung was most easy occurred in female and

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no-smoking patients. Squamous cancer patient smoke-rates were highest. Adenocarcinoma smoke-rates were lowest. Which originate bronchial mucosa, only small parts come from big bronchial glandular mucosa [2]. With the growth of age, incidence of lung cancer increasing gradually, about 30% lung cancer patients had been advanced age in diagnosis [3]. Now the treatment of the lung adenocarcinoma mainly were synthesized method, included surgical therapy, radiotherapy, chemical therapy, TKI therapy. In recent years, TKI therapy under the spotlight attracts much attention. The article from January 2018 to July 2018. China Shan-xi Bethune hospital tumor staff treated 52 lung adenocarcinoma patients with more than 60 years-old, after synthesized treatment, given a reviewed analyze.

MATERIALS AND METHODS

Patient

52 cases lung pathological diagnosed of lung adenocarcinoma patients, between from January 2018 to July 2018. Shan-xi Bethune hospital tumor staff China after synthesized treatment 52 lung adenocarcinoma patient. With more than 60 years-old, given a reviewed analyze. The inclusion criteria were as follows:

- Pathological diagnosis of lung adenocarcinoma
- Karn of sky performance score>60
- Adequate organ function (white blood cell>4.0×10/L)

Neutrophil>2.0 × 10/L; hemoglobin>90 g/L; platelet>100 × 109/L; aspartate aminotransferase/alanine transaminase<2.5 upper limit of normal; Ccr>60 mL/min); (4) Routine evaluations were performed on patients, including physical examination, electrocardiography, chest and abdominal Computed Tomography (CT) with contrast and bone scan and so on.

Lung adenocarcinoma patients were divided 5 groups.

- Surgical therapy plus radio therapy plus chemical therapy plus TKI therapy group, Radiotherapy plus chemical therapy plus TKI therapy group.
- Chemical therapy plus TKI therapy group.
- Single TKI therapy group.
- Single chemical therapy group.

Whole group male 23 cases, female 29 cases, whole group ages: 60-70 years old 29 cases. 70-80 years old 15 cases 80-86 year's old 8 cases. Whole cases though fluoroscopy-guided bronchoscopy or chest-surgical operation or supraclavicular lymph nodes took the pathological tissue or pleural fluid fund cancer cell.

The pathological tissue included well-differentiated adenocarcinoma and poorly-differentiated-adenocarcinoma. Lung adenocarcinoma-pathology-stages: Surgical synthetically group were Ⅱ-Ⅲ a stages patients, others groups were Ⅲ b-Ⅳ stages patients. Tread method surgical operation method: Thoracotomy-lung-excision, thoracoscope-lung-excision. Radiotherapy method: used 6 MVX-linear-accelerators. Chemical therapy method:

- Pemetrexed plus carboplatin or Cisplatin or Lobaplatin or Nedaplatin.
- Docetaxel plus Lobaplatin or Platin or Bevacizumab.
- CTX plus Carboplatin or Cisplatin or VP-16 or Vinorelbine.

Above method used 4-6 weeks periods or more than. For malignant pleural fluid used pleurectomy plus cisplatin or paclitaxel and TNF. For brain metastases cases, used surgical brain-operation or three-dimensional orientation-radiotherapy, chemical therapy TKI therapy. TKI therapy method: Before TKI therapy, tumor prompted gene mutation and inspect done. Included EGFR gene, ALK gene and Ros, Ret, Metexon 14 and BRAF, V600E and so on, after rebuild positive, first generation medicine used TKI therapy: Gifitinib, Erlotinib, and Lcotinib Hydrochloride, after above drugs resisted. Second generation TKI gave, Apatinib, Mesylate. After above drugs resisted. Third generation TKI given Erlotinib or Osimertinib, Mesylate.

Effect evaluated

Followed way used telephone. Followed to 2019.8.30 followed rates 100%. After diagnosed lung adenocarcinoma cancer, all case survival time began to count.

Statistics method

Using Kaplan-Meier way calculated survival time two-samples compared-way using rank sum test-wilcoxon comparison method, Log rank-way calculated survival-rates-curves discrepancy. All statistical tests in our study were 2-tailed. $p<0.05$ was considered to represent statistical significance.

Ethical statement

At our hospital, all patients signed informed consent prior to treatment, including their consent to treatment and clinical information for further prognostic analysis. This study was approved by the Research Ethics Committee of Shan-xi Bethune hospital, Taiyuan City, Shanxi Province, China (Table 1).

RESULTS

Different groups therapeutic outcome are shown in Table 1.

Table 1: Therapeutic outcome of 52 cases lung adenocarcinoma.

Groups	Cases	Median survival time	Survival rate (100%)				P Value
		(month)	1 Year	2 Year	3 Year	4 Year	
Single chemical therapy	5	8	20	0			1 group comparison 2 group<0.05
Single TKI therapy	6	14	67	17	0		2 group comparison 3 group <0.05
Chemical-TKI therapy	18	28	100	61	38	27	3 group comparison 4 group > 0.05
Radiotherapy-chemical- TKI therapy	9	29	100	78	22		
Surgical operation-radiotherapy chemical-TKI therapy group	14	54	100	100	57	35	5 group comparison 4 group > 0.05
Complete group	52	30	89	70	38	23	

- Single chemical therapy group survival rate: 1 years 20%, median survival time 8 months. 2) Single TKI therapy group survival rate:1 year 67%, 2 years 17%, Median survival time 14 months compared single chemical therapy median survival time 8 months $p<0.05$, $\alpha=0.05$. Had statistics meaning.
- Chemical TKI therapy group survival rate: 1 year 100%, 2 years 61%, 3 years 38%, 5 years 27%. Median survival time 28 months compared single TKI therapy group median survival time 14 months. $u=0.28$ $p<0.01$, $\alpha=0.05$, had statistics meaning, compared radiotherapy-chemical-TKI therapy group median survival time 29 months. $p<0.1$, $\alpha=0.05$ without statistics meaning. Compared surgical operation-radiotherapy-chemical-TKI therapy group median survival time 54 months. $0.2<p<0.1$, $\alpha=0.05$ without statistics meaning.
- Radiotherapy-chemical therapy-TKI therapy group survival rate: 1 year 100%, 2 years 7 8%, 3 years 22%, Median survival time 29 months compared single TKI therapy group median survival time 14 months $p<0.01$, had statistics meaning.
- Surgical operation-radiotherapy-chemical-TKI therapy group survival rate: 1 year 100%, 2 years 100%, 3 years 57%, 5 years 35%. Median survival time 54 months, compared radiotherapy-chemical-TKI therapy group median survival time 29 months. $p<0.1$, $\alpha=0.05$ without statistics meaning (Figures 1 and 2).
- Complete group survival rate: 1 years 89%, 2 years 70%, 3 years 38%, 5 years 23%. Median survival time 30 months.

Different group cases survival-time-curves are shown in Figure 1 and Figure 2.

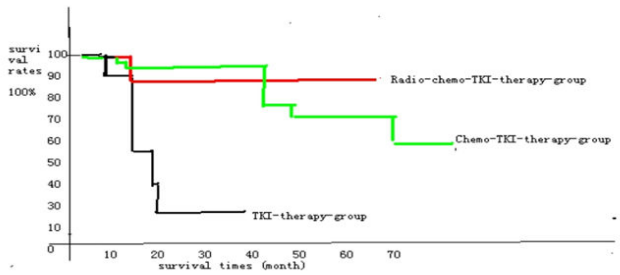

Figure 1: Comparison of survival-rates-curves of different treatment groups.

Comparison of survival-rates-curves of radio therapy-chemical therapy-TKI therapy-group, chemical therapy-TKI therapy-group and single TKI therapy-group (Figures 1 and 2).

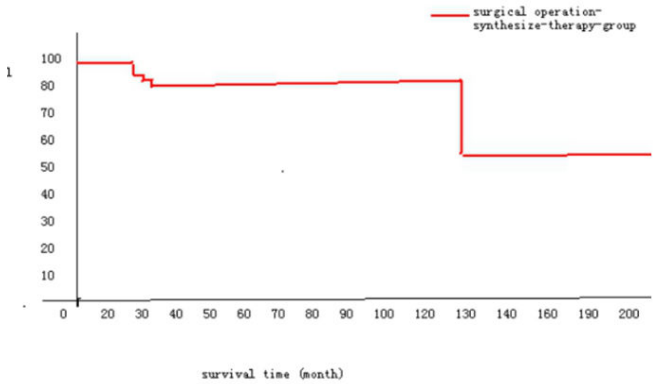

Figure 2: Survival-rates-curves of surgical synthesize therapy group.

- Survival-rates-curves of surgical synthesize therapy group.
- Total group 52 patient's survival rate, 1 year 100%, 2 years 70%, 3 years 38%, 4 years 34%, 5 years 23%. Median survival time 30 months.
- Surgical-operation-radiotherapy-chemical-TKI therapy group survival rate: 1 year 100%, 2 years 100%, 3 years 57%, 4 years 35%, 5 years 35%, 6 years 21%. 10 years 14.2%, 15 years 7%. Median survival time 54 months.
- Chemical-TKI-therapy group survival rate: 1 years 100%, 2 years 61%, 3 years 38%, 5 years 27%. Median survival time 28 months compared single TKI therapy group median survival time 14 months. u=0.28 p<0.01, α=0.05, had statistics meaning. Compared radiotherapy-chemical-TKI therapy group median survival time 29 months. p<0.1, α=0.05 without statistics meaning compared surgical operation-radiotherapy-chemical-TKI therapy group median survival time 54 months. 0.2<p<0.1, α=0.05 without statistics meaning.
- Radiotherapy-chemical therapy-TKI therapy group survival rate: 1 years 100%, 2 years 78%, 3 years 22%, Median survival time 29 months compared single TKI therapy group median survival time 14 months p<0.01, had statistics meaning.
- Single TKI therapy group survival rate: 1 years 67%, 2 years 17%, Median survival time 14 months compared single chemical therapy median survival time 8 months p<0.05, α=0.05 had statistics meaning.
- Single chemical therapy group survival rate: 1 years 20%, median survival time 8 months.

DISCUSSION

Now old aged advanced lung adenocarcinoma were death-rates very high diseases in China. For treatment method, more used synthesis-therapy. Through in early stages, surgical operation was realized. For recovered normal living. First method, Throat-tumor excision was an only cured method. But after lung adenocarcinoma diagnosed, most patients had been an advanced stages had not a changes for surgical operation. Although some patients were opereated, but 5 year survival rates curves only were 20%. Traditional radiotherapy, chemical therapy for survival-rates of old aged advanced lung adenocarcinoma with week physique patients were very lowed, many treatment methods were limited. Along with TKI therapy was applied for lung-adenocarcinoma, treatment method had had many new changes and new break though. Before TKI therapy, Tumor prompted gene mutation-rebuild and inspect done included EGFR gene, ALK gene and Ros, Ret, Metexon 14 and BRAF, V600E gene and so on. Patients for gene negative and no-used-TKI therapy may use Immunization-Inspect-Check Point-Inhibitor (ICI) and standard double medicine-treatment with platinum [4]. Recent years, how overcome and delayed EGFR, TKI drug-resistant, how TKI therapy achieved a maximization-effect always were a research hot spot. Except researched new TKI-drugs, TKI therapy plus chemical therapy also were a most commonly used method. Chen-yin reported, TKI therapy plus chemical therapy were most commonly used method. In FASTACT2 researches confirmed that patients with EGFR sensitive-sudden-changes-gene could were a TKI therapy plus chemical therapy sensitive-gained-advantage-groups. NEJ005 research pointed that TKI plus platinum-chemical therapy in equal time treatment compared interval time treatment were better. JMIT research further proved that gifitinib plus pemetrexed group may increase Progression Free Survival (PFS) 5 months, compared with single gifitinib group. To point out gifitinib plus pemetrexed may were a new method of first-line-treatment for EGFR sensitive- sudden-changes-gene in advanced no-small-cell-lung-cancer patients. In first clinical research phase III, no-small-cell-lung-cancer patients with EGFR sensitive-sudden-changes-gene, EGFR, TKI plus platinum and two drugs (pemetrexed or carboplatin) groups compared single gifitinib groups, whole 350 patients (combination group n=173 single group n=177), combination drug therapy Objective Response Rate (ORR) higher single drug therapy-ORR, respectively 16 months and 8 months (p<0.001), there were a obviously benefit from Over Survival (OS), respectively miss and 18 months (p<0.001). There was a win-win in NEJ009 combination-drug-therapy, Overall Survival (OS) and progression-free survival time (PFS) [5]. Basis experimental result analysis pointed out that after EGFR-TKI plus pemetrexed may increase killing tumor cell function of resistant drug, reduced tumor cells multiplication rate, induced necrosis and atrophy of the lesion [6]. Combined application of two kind's drugs also helped antagonizing mitochondrial activity in tumor cells which promoted cellular apoptosis and attained slow deterioration speed of illness and had stable progress of lesions [7]. Our groups chemical-TKI therapy group compared single TKI therapy group u=0.28 p<0.01, α=0.05. There was a statistics meaning. Chemical-TKI therapy group median survival time 28 months. Single TKI therapy group median survival time 14 months. Our group results also confirmed chemical-TKI-therapy excels single TKI therapy, accorded with above result. Provided a new solution in initial therapy for EGFR sensitive-sudden-changes-gene patients. While advanced no-small-cell-lung-cancer patients with accepted EGFR-TKI treatment had a drug resistant, stopped treatment, tumor would grow fast [8] occurred EGFR-TKI treatment drug resistant, patients with slow progress, at this moment, Pemetrexed may rise one year survival time. The 2 line use of pemetrexed showed superiority for EGFR-TKI-treatment drug resistant but in OS, compared Docetaxel no differentiate, without statistics meaning [9]. Zhang wen-yu reported: for TKI treatment failed cases, more than 2/3 failed lesions still located primary lesion plus radiotherapy had the potential to benefit. Shang-hai chest department hospital 145 patients with TKI treatment EGFR sensible changement IV stages NSCLC, 51 cases used total lesion plus radiotherapy, 55 cases used partial lesion radiotherapy, 39 cases no used lesion radiotherapy, result displayed that 55 cases used partial lesion radiotherapy had significantly superior to 39 cases no used lesion radiotherapy in survival time[10]. T790 M gene mutation was the most common drug resistance mechanism; there were 40%-60% T790 M gene mutation in drug resistance patients [11]. Wu yi-long reported; in II phase AURA extended research and AURA2 research, Oxiotinib every day 80 mg treated T790 M gene mutation patients, PFS were 12.3 months and 9.9 months. Compared pemetrexed plus platinum two drugs, Oxiotinib significant prolonged patient PFS, had more than 2 times (10.1 months: 4.4 months). Significant reduce 70% progress risk of disease risk ratio (HR=0.30, P<0.001) [12]. Lu sun reported: AURA3 research, Oxiotinib not only prolonged

T790 M gene mutation patient's curative effect, but 3 levels or above adverse reactions incidences was lower 1%, totality 3 levels or above adverse reactions incidences only were 1/2 for double drugs chemical therapy group [13].

Brain was a most common distant transferred part in lung-adenocarcinoma. In first diagnosed time, there were 10%-15% brain metastases in advanced lung cancer patients. 30%-50% advanced lung cancer patients final occurred brain metastases. Brain metastases patients no been treated, median survival time 1 months and so on [14]. The later T stages and N stages, the higher brain metastases incidences in NSCLC. Brain metastases incidences in adenocarcinoma were a highest were a lowest in squamous cancer. EGFR gene mutation, ALK gene positive all were risk factors of brain metastases, EGFR gene mutation patients with operation excision were 3.5 times for EGFR wild type patients on brain metastases recurrent risk. ALK gene positive patients were 2 times ALK gene negative patients on brain metastases incidence [15]. Our radiotherapy-chemical-TKI therapy group (n=9), whole patients with a brain-metastases used radiotherapy included X-knife or γ-knife stereotactic brain radiotherapy and 6 MVX-linear-accelerator conventional radiotherapy. Brain-chemical therapy used temozolomide treatment and systemic chemical therapy, specific method in above. TKI therapy specific method in above. Our group radiotherapy-chemical-TKI therapy compared chemical-TKI therapy, $p<0.1$, $\alpha=0.05$ without statistics meaning. Chemical-target-therapy group median survival time 28 months, Radiotherapy-chemical-TKI therapy group median survival time 29 months. Wang wen-hui reported that brain-metastases were more common in no-small-cell-lung-cancer with sensitive-sudden-changes-gene. Now brain-radiotherapy plus TKI therapy were a research heat spot. But about the brain metastases correlational research in no-small-cell-lung-cancer with sensitive-sudden-changes-gene also were little [16] for their prognosis. Radiotherapy and radiotherapy plus TKI therapy for brain were worth a discussion [17]. Pai et al. passed though cytological and animal test, achieved a conclusions that EGFR-TKI treatment plus radiotherapy may had 2-3 times increase to ALK rearrangement cell lines apoptosis [18,19]. Sun also achieved a similar conclusions in cytological and animal test, namely ALK-TKL plus radiotherapy group compared any one single treatment group had a very strong inhibition for tumor [20]. Research findings, crizotinib plus radiotherapy group compared single crizotinib group in brain focus Objective Response Rate, (ORR) mTTP had a significant improvement (18%: 33%; 7 months:13.2 months) other small sample research also showed that crizotinib plus brain-radiotherapy group for single crizotinib group had a high free-Progression-Survival Time (PFS), 7 months: 3-4 months [21]. IVEN other research also showed that crizotinib plus brain-radiotherapy group Free-Progression Survival Time (PFS) reached 27 months [22]. In addition Crizotinib plus brain part treatment was a good factor of PFS in prognosis [23]. Johung et al. research findings 90 ALK rearrangement cell lines NSCLC brain-metastases patients given radiotherapy (WBRT or SRS) plus crizotinib, median survival time reached 49.5 months [24]. Gerber other research also showed that 110 patients with brain metastases in NSCLC were respectively accepted first EGFR-TKI sequential therapy, first WRBT sequential therapy and first SRS sequential therapy. Result displayed SRS + EGFR-TKI group survival time 64 months, first accepted WRBT, survival time were 35 months. First accepted EGFR-TKI, survival time were 26 months. First accepted WRBT brain lesion no-progress time were longer to first EGFR-TKI group (24 months: 16 months). First accepted EGFR-TKI or SRS group progress lesion main were in-of-brain lesion as well as first accepted WRBT group progress lesion main were out-of-brain lesion (P=0.004), showed first WRBT sequential therapy for controlled in-of-brain lesion were better [25]. Our radiotherapy-chemical-TKI therapy group median survival time 29 months, accord with above result. Wu yi-long research pointed that single first generation EGFR, TKI effect were superior traditional whole-brain radiotherapy in EGFR sudden-changes-brain-metastases patients [26] for the brain metastases. In second generation, third generation ALK-TKL treatment. Ascends series confirmed that ceritinib effect for brain metastases in 0RR may achieved 62.5% curative effect, may had free-Progression Survival Time (PFS) 8.2 months. Ascend-1-reaserches: 19 cases with sudden-changes-gene-brain-metastases were divided radiotherapy plus ceritinib group and single ceritinib group, showed that two group controlled rates in brain Disease Controlled Rates (DCR) and (ORR) were no different, showed that Ceritinib for brain-metastases controlled rates and effect and reactions not relied on radiotherapy but fewer samples, also wanted more prospective researches and proved [27]. AURA3-reaserches for osimertinib with brain-metastases patients, osimertinib group compared chemical therapy group had a notable extended (PFS) 11.7 months for 5.5 months, had a higher Central Nervous System (CNS) objective remission rates, 70% for 31%. BLOOM-researches showed that osimertinib for brain-metastases patients had a delight well-activity and well-tolerance but these effect and reactions only were fewer samples, also wanted more samples researches and proved [28].

Our surgical operation therapy radiotherapy chemicaltherapy T KI therapygroup, survivalrate: 1 years 100%, 2 years 100%, 3 yea rs 57%, 4 years 35%, 5 years 35%, 6 years 21% 10 years 14.2%, 15 years 7%. Median survival time 54 months. Surgical operation therapy was a best method for lung adenocarcinoma. Wang Chang-li reported that II-III stages for lung adenocarcinoma-patients after the surgical operation, Given Erlotinib treatment, and survival rate 2 years 81%, 3 years 54%. Compared given chemical therapy group survival rate, 2 years 44%, 3 years 19.8%, median survival time increased one times [29] Wu yi-long adjuvant-research pointed that NSCLC patients for whole tumor excision II-III a stages (N1-N2), EGFR positive 222 patients, 2 years-gifitinib-therapy group superior to vinorelbine plus cisplatin group. In median survival time (PFS) 28.7 months: 18.0 months 3 yeares (DFS) rates are 34%: 27% compared chemical therapy group, gifitinib-therapy group safety better [30]. After surgical operation, for lung adenocarcinoma, given a synthesize-treatment and TKI-therapy for prolong survival time were better method. Our group result accord with above result.

CONCLUSION

In summary, for old aged advanced lung adenocarcinoma patients, surgical operation was a most useful method. For no-surgical operation patient, Adopted to three-dimensional-orientation-radiotherapy and chemical therapy, TKI therapy and immunization therapy and so on. It had an important clinical significance that according to patient different physique, conditions, pathological stages, different methods and synthesized therapy methods adopted, for prolong survival time, enhanced the quality of life.

CONFLICT OF INTEREST

This research received no grant from any funding agency in the public commercial or not-for profit sectors. The authors declare that there is no conflict of interest.

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