

LONG TERM FOLLOW UP OF PATIENTS WITH ADVANCED CANCER FOLLOWING CHEMOTHERAPY AND TRADITIONAL MEDICINE (75 CASES)

Abstract

Objective: Traditional systems of medicine all over the world even traditional medicine and cancer have been using plants and plants products for therapeutic purposes. In search for effective strategies of cancer therapeutics, I had summarized in this group the retrospective study of cancers under remission, with chemotherapy in conjunction with plant medicine traditional medicine (TCM) .

Methods: 75 patients with available cancers were entered in the study during September 1993 - May 2018. The sex ratio of male:female was 49:26 respectively. The mean age at onset was 46.9 years (range 10-79 years) . The other benign neoplasias were not statistically included. The criteria of complete remission (CR) and/or partial remission (PR) is according to the rules where physicians have in common with in clinics.

Results: In 75 cases, the CR was obtained in 33 advanced cancers, a short CR in 11 cases, PR in 25 cancers, Stable disease in 6 cases. As to approach to the schedule of drug administration, all patients were treated with different dosage of chemotherapy in combination with traditional medicine (TCM) or traditional medicine alone. In differential types of 21 patients over ten years, lymphoma occupied 8 cases. And more, six advanced hepatocellular carcinoma were also successfully treated using chemotherapy in conjunction with TCM. In follow up, one HCC accompanied with colon polyps obtained CR via hepatectomy and targeting oncogenic receptor tyrosine kinase inhibitor Sorafenib. Among two lung cancer, one female with metastatic lung cancer was given targeting oncogenic receptor EGFR gefitinib therapy after the combination chemotherapy, which was stable disease for 8+months. CR can also be achieved in one advanced cholangiocarcinoma and one advanced gallbladder cancer through major protocol of TCM and the addition of small dosage of chemotherapy. A 62-year-old female with multiple myeloma obtained CR after low-dose thalidomide and plant medicine *Vinca rosea* (*Catharanthus roseus*). Traditional medicine consisted of *vinca rosea*, *asparagalus membranaceus*, *ophiopogon japonicus*, *asparagus*

cochinchinensis,angelica sinensis,poria cocos,coix lacryina jobi L. varma-yuen,solanum nigrum L,houttuynia cordata,scutellaria barbata d.don and oldenlandin diffusa roxb. Among those long-term survivors,31 carcinomas obtained in disease-free survival over 5years,21 cancers were survival over 10years,the longest four patients over 25 years.

Conclusion:In this study,I experienced that a CR was a pivotal influencing factor in those longest survival patients,and traditional medicine was also recommended.Downregulating oncogenic receptors may be useful paradigm and perspective in currently the third line setting of clinical target therapy and in rendering our better understanding of cancer biology.

Keywords:Cancer Chemotherapy Traditional medicine Target therapy

Introduction

Chemotherapy is a major skillful of cancer therapy.One of the most important advances in oncology has been increased acceptance of evidence that most patients with disseminated tumors were setted the protocol of chemotherapy in conjunction with targeting oncogenic receptor[1-17],traditional medicine (TCM) and/or adoptive immunotherapy(LAK cells,TIL therapy)[18,19].This paper will attempt to place in proper interpretative review from those patients with cancers under remission in this group.

Material and Methods

75 patients with available cancers were entered in the study during 1993-2017.All patients were in progressive when hospitalization.The sex ratio of male:female was 49:26 respectively.The mean age at onset was 46.9 years(range 10-79 years).Among age distribution,although there is some uncertain about the type distribution of cancers,It was found 38.1 years as the mean age at onset for lymphoma,44.4 years for liver cancer,while higher mean age at 60.1 years has been shown in lung cancer in this group.The clinical diagnoses in a broad variety of carcinomas consisted of metastatic nasopharyngeal cancer 5 cases,metastatic breast cancer 4,lung cancer 12,hepatocellular carcinoma(HCC) 12,stomach cancer 5,hematological malignancies 25 cases(acute leukemias FAB M1 type 2,M2 type 1,acute promyelocytic leukemia 1,chronic myeloid leukemia CML 2,chronic lymphocytic leukemia CLL 1,multiple myeloma 2,lymphoma 16),thyroid cancer 2,maxillary sinus carcinoma 1,carcinoma of

mandibular sinus 2, laryngeal carcinoma 1, gallbladder cancer 1, cholangiocarcinoma 1, metastatic melanoma 1, epidermoid carcinoma 1, relapsed vulvar cancer 1, and other metastatic sternal and spinal (T12) tumor 1 respectively. All other benign neoplasias were not statistically included. The basic chemotherapeutic regimen consisted of vincristine (VCR)、cyclophosphamide (CTX)、mitomycin C (MMC) and 5-fluorouracil (5-Fu). In addition, the additional drug adriamycin (ADM) in lymphoma and metastatic breast cancer, demethylcantharidin in liver cancer and PDD or cisplatin or interleukin-2 (PHA) in lung cancer. The criteria of complete remission (CR) and/or partial remission (PR) is according to the rules where physicians have in common with in clinics. Stable disease: the tumor decreased by less than 50% or increased by no more than 25% in patients. Disease progression: the tumor increased by more than 25% in patients, or new lesions emerged. The efficacy was evaluated according to the survival time from the day when patients were at onset. The clinical data for liver cancer [20,21] and lung cancer [22,23] were previously described.

Results

In 75 cancers, the rate of complete remission (CR) was achieved in 33 advanced cancers. All CR patients with advanced cancers was survival over 5 years, 18 cancers was survival 10 years. Among 7 patients with over 20 years, lymphoma occupied 3 cases, metastatic breast cancer 2 cases and hepatocellular carcinoma 2 cases. In differential types of 21 patients with over 10 years survivors, lymphoma occupied 8 cases (38.1%). Another, a short CR was obtained in 11 advanced cancers, the survival time varied from 20 months to 4 years. PR was obtained in 25 patients with a broad variety of carcinoma, and three patients (1 malignant lymphoma, 1 carcinoma of mandibular sinus, 1 metastatic tumor of bone) had survival 12, 18+ and 11+ years respectively, implicating a longer survivor in patients the survival with tumours. Otherwise, stable disease was 6 cases in this group.

During the schedule of drug administration, all patients were treated with the different dosage of 1 to 4 courses of combination chemotherapy in conjunction with traditional medicine. In statistically analysis, one patient with nasopharyngeal cancer, the diplopia and unable vision in his eye were recovered to "normal" visual acuity following the combination chemotherapy of VCMF (VCR, CTX, MMC and 5-Fu) plus traditional medicine. A patient with rodent ulcer (8x5cm) once obtained complete response as to

an approach of 5%Fu of retinoic acid ointment. A short CR was achieved by the protocol of FAM or FMC (5-Fu;Ara-C/homoharringtonine;MMC;CTX) plus cantharidin in 5 advanced gastric cancers.One of them was a long-term survivor for 6 years via mass incision and the combination of FAM with herbs *Scutellaria barbata d.don*.

In view of types of cancer,10 lymphoma was setted into the major protocol of the combination conventional chemotherapy (VCR,CTX,MMC or ADM) in conjunction with traditional medicine which to relieve the chemotherapeutic toxicity,and reinforced the efficacy of chemotherapy.One lymphoma was regressed only by prednisone (200#) .Another 2 patients with thumb lymphadenopathy was treated by the use of antibiotics regimen in full dose with anti-inflammatory herbal tablets.

In 10 HCC,a therapeutical protocol was mainly by 5-Fu,cantharidin and TCM. 2 patients with CR was achieved through cantharidin and traditional medicine.In the follow up,one HCC accompanied with colon polyps obtained complete remission via hapatectomy and targeting oncogenic receptor tyrosine kinase inhibitor sorafenib.

Eight other patients with cancers were also in remission through small dosage of chemotherapy and TCM or traditional medicine (TCM) alone.There were 4 lung cancers,1 gallbladder cancer,1 cholangiocarcinoma and 2 thyroid cancers.Among targeting two metastatic lung cancer,one female with lung cancer was given the combination chemotherapy plus targeting oncogenic receptor EGFRvIII gefitinib,which was stable disease for 8+ months. Thyroid cancer was placed on the primary use of traditional medicine.The crude herbs consisted of *sargassum,tangle,Oyster (mussels)* ,*Poria cocos,Ophiopogon japonicus,Prunella vulgaris,Taraxacum,Scrophularia ningpoensis,Cremastra appendiculata,Trichosanthes Kirilowii,Sophora subprostrata,Houttuynia cordata,Scutellaria barbata d. don and Oldenlandia diffusa roxb.*

The survival times in those patients with remission in this group were less than 1 years 10 cases (acute leukemias 3 cases,metastatic lung cancer 3,liver cancer 1, stomach cancer 1,laryngeal carcinoma 1,and malignant mesothelioma 1) ,1 to 3 years 21 cases,over 3 to 5 years 11 cases,over 5 to 10 years 10 cases,over 10 to 20 years 14 cases,and over 20 years 7 cases.

Case reports

A 55-year-old woman was diagnosed as having metastatic palatum cancer on November 6, 1993 when she presented with tumors both in her cavity of the mouth and neck lymphadenopathy. On examination revealed 2 lymph nodes (4x3cm) enlargement in her left neck. A 3x5cm mass was found in her palate molle which was covered over uvula palatina. Moreover the left side of her face also had a thumb lymph nodes palpable. Cures can be achieved by use of combination chemotherapy (VCR, CTX, 5-Fu, phytohemagglutinin, PHA) and in 18 years later she died of recurrent episodes of oral cancer.

A 43-year-old man entered the hospital due to his metastatic nasopharynx cancer on July 4, 1995. At first onset he developed symptoms of marked headache, right neck lymphadenopathy (thumb size). The patient received no radiotherapy. With the relief symptoms of headache and regression of his lymphadenopathy, the diplopia and unable vision in his eye were recovered to "normal" visual acuity under the combination chemotherapy of VCMF (VCR, CTX, MMC, 5-Fu) with the addition of TCM. He obtained a 3 years survivor.

A 35-year-old woman was admitted to the hospital because of her relapsed gastric cancer, with recurrent fever for one month duration. In March, 1996 she was undergoing the operation in a local hospital due to her tarry stools. At post-operatively, a rodent ulcer (5x4x2.8cm) with harden border (margin) was detected in lesser curvature of the stomach, accompanied with adjacent metastatic lymph nodes. NHL was diagnosed according to her stomach tissue specimens. The definitive diagnosis of her malignant tumor was based on a provincial tumor hospital. She had a past history of tuberculosis. CR was obtained after small dosage of FMC (5-Fu, MMC, CTX) in combination with cinobufacini intravenously, oral daily demethylcantharidin and traditional herbs. As an outpatient, she had continued to traditional herbs *Scutellaria barbata d. don*. She was a long-term survivor for 6 years and died of tuberculosis (type IV).

A 58-year-old man was diagnosed as having malignant lymphoma on April 29, 1997. He presented his past history of lymph node palpable (a pea size) in right neck region 8 years ago. Later in 1995, a gradually increased thumb lymph node was palpable, accompanied by his left neck metastasis. At physical examination, on

admission, showed 4.5x3cm, 2x3cm, 2x3cm palpable lymph node in right neck and a 2x3cm lymph node in left neck region. Lymphoma was diagnosed according to his lymph node aspirates. He obtained remission following combination chemotherapy (CTX and 5-Fu) in conjunction with traditional medicine. He was stable disease with tumors for 12 years survivor.

A 75-year-old woman entered the hospital due to her metastatic nasopharynx cancer in June, 1997. On admission she presented with anemia following melena, fatigue and weakness. A thumb lymph node behind her right ear was palpable. CR was obtained through TCM and small dosage of chemotherapy (CTX and 5-Fu), and enlarged lymph node was disappeared. She was a 4 years survivor. Traditional medicine consisted of *Prunella vulgaris*, *asparagalus membranaceus*, *rehmannia glutinosa*, *ophiopogon japonicus*, *lyceum chinenses*, *centipede*, *cantharides*, *scutellaria barbata d. don*, *oldenlandin diffusa roxb.*

A 71-year-old man was admitted to the hospital on December 29, 1997 because of the relapse of his lymphoma for 2 months duration. He once obtained partial remission (PR) using chemotherapy in another tumor hospital. CR was obtained by the main protocol of TCM with small dosage of chemotherapy (CTX, 5-Fu). TCM consisted of *asparagalus membranaceus*, *ophiopogon japonicus*, *asparagus*, *coix lachryma*, *paris polyphylla*, *pseudobulb of appendiculate cremastra*, *trichosanthes kirilowii*, *indigowoad leaf*, *scutellaria barbata d. don*, *oldenlandia diffusa roxb.* He was a survivor of 7 years.

A 62-year-old woman entered the hospital because of her chronic myelocytic leukemia (CML) on October 21, 2000. She developed her distended abdomen and splenomegaly 6 months duration. On B ultrasound examination showed that spleen reached to umbilicus, with irregular liver scan. Hemoglobin concentration was 7.0g/L. leukocyte count 160,000 ($160 \times 10^9/l$) with 19% blasts and promyelocytes, 28.5% myelocytes and metamyelocytes. platelet count was $375 \times 10^9/l$. Bone marrow aspirations revealed marked hypercellularity with myeloid hyperplasia. Blast forms (blast and promyelocytes) constituted approximately 19.6% of all cells, and immature myelocyte and metamyelocytes occupied 28.5% of all cells. Megakaryocytes was hyperplasia. The diagnosis of CML with accelerate stage was made. CR was obtained after busulfan in conjunction with TCM. She was in satisfactory health until 4 years before admission. When she was found to be

splenomegaly. At that time, WBC 120x10⁹/l. The high percentage of blast cells corresponded to the beginning of her relapse. Oral busulfan was administered in the following a total dose of 120mg, with CR again. She was a survivor for nearly 8 years.

A 65-year-old woman was diagnosed as having gallbladder cancer in July 20, 2002. She developed symptoms of lancinating abdominal pain and intensive distended abdomen and tender with muscle defense in upper quadrants. On CT scan demonstrated that her gallbladder was dilated, with irregular thick cholecystic inner wall, and many nodules were found in the cavity of bile. She was given the combination of TCM with small dosage of 5-Fu and CTX drugs. Three months later, in view of improvement of her general symptoms, she obtained CR. She is in health during follow up of 15 years.

A 25-year-old man was admitted to the hospital on October 4, 2003 because of his relapsed malignant lymphoma. He complained of his enlarged lymph nodes once regression using herbs in 1997. He had a past experience of combination chemotherapy due to lymph node enlargement in bilateral neck, which was diagnosed as having malignant lymphoma (B cell type). In September, 2003, he developed his nasopharynx the markedly inflamed redness, swelling, and with obstruction. At physical examination revealed 5 firm lymph nodes to varying degree in size of a pea to a walnut in his left neck, and 2 palpable lymph nodes (1.5x2cm) in his right neck. A 3x4.5cm mass was found in his soft palate molle which was flecked with small redded ulcer patches. CR can be achieved by use of antibiotics regimen in full dose and combination chemotherapy (VCR, CTX, 5-Fu, MMC), the tumors were disappeared as like the mouth of health individuals. He was a 3 years of survivors.

A 72-year-old man was admitted to the hospital due to his jaundice cholangiocarcinoma on September 2, 2004. He had a history of bad cough two months ago, followed by a progressive general jaundice, conspicuous weight loss, no appetite and urine icterus. On CT examination showed his complete obstructive choledodus and his cholangiectasis due to the cause of obstructive tumor (1.5x2cm). He was given the treatment of antibiotics in full dose, combination chemotherapy (5-Fu, CTX, MMC) with TCM. CR was achieved two months later, and as an outpatient, he was to be continued the traditional herbs. Traditional medicine consisted of *astragalus membranaceus*, *ophiopogon japonicas*, *asparagus*, *poria cocos*, *lyceum chinenses*, *wheat*

sprout, salvia bowleyana, scutellaria baicalensis, Artemisia capillaries, gardenia jasminoides, hypericum japonicum, houttuynia cordata, scutellaria barbata d. don, oldenlandia diffusa roxb.

A 38-year-old woman was admitted to the hospital on September 26, 2004 due to palpable lymph nodes in her neck for 1+ year duration. One year before admission to the hospital she accidentally noted lymphadenopathy in her bilateral neck region, and lymph node enlargement regressed with unknown drugs. In July, 2003, she presented no efficacy following treatment because of her lymphadenopathy relapsed. When examined, there were 6 lymph nodes palpable in her left neck, with varied degree in size of a pigeon's egg to a pea or thumb size. Scrofula with caseous necrosis was diagnosed according to her lymph node aspirates. TB-Ab negative. Remission was obtained through anti-TB regimen in combination with TCM. TCM consisted of *traxacum, honeysuckle, ophiopogon japonicus, asparagus, muskels, coix lachryma, houttuynia cordate, scutellaria barbata d. don, oldenlandia diffusa roxb.* In the follow up, she was a 15 years survivor.

A 58-year-old man was diagnosed as having chronic lymphocytic leukemia (CLL) on January 16, 2011 because of recent leukocyte counts elevated to $118 \times 10^9/l$. The patient complained of his leukocytosis ($67-97 \times 10^9/l$) for more than one month duration. He was treated with hydroxycarbamide in another hospital and leukocytosis declined to $27 \times 10^9/l$. The most common physical signs revealed two thumb lymph nodes palpable in his left neck. Hemogram: Hemoglobin concentration (Hb) was $87 g/l$. leukocyte count (WBC) $123.88 \times 10^9/l$. The leukocyte differential count: 9% segmented neutrophils, 90% small lymphocytes. The platelet count $131 \times 10^9/l$. Bone marrow aspiration revealed hypercellularity. Bone marrow differential count: 14% myeloid, 7.2% erythroid, approximately 76.8% of predominant cell was small lymphocytes. The diagnosis of CLL was made. CR was obtained by the use of chlorambucil tablets and traditional medicine. On April 9, 2011, repeat hemogram: Hb $112 g/l$, WBC $13.6 \times 10^9/l$, plt $128 \times 10^9/l$. On May 5 and July 28, 2011, Hb $104-112 g/l$; WBC $9.54-10.1 \times 10^9/l$, with a leukocyte differential count of 26.2% mature neutrophils and 63.8% lymphocytes; plt $101-112 \times 10^9/l$ respectively. Bone marrow aspirates on May 14, 2011 revealed normal cellularity. Bone marrow differential count: 34% myeloid, 31.2% erythroid, 33.6% lymphocytes. As an outpatient, he

continued traditional herbs. He was well until on October 15, 2011 while an attack of stomach pain and tarry stools was admitted to another hospital. Routine hematologic studies at that time, Hb 69g/l; WBC $7.3 \times 10^9/l$ with 70% mature neutrophils and 28% lymphocytes; plt $188 \times 10^9/l$. Repeat bone marrow aspirates on October 15, 2011 revealed normal cellularity. Bone marrow differential counts: 50% myeloid, 21% erythroid, 27.5% lymphocytes. He died of another stomach cancer.

Discussion

In this study, a series of the long follow up of patients with cancers were reported. I experienced that a CR was a pivotal influencing factor in those longest survival patients, and traditional medicine was also recommended.

In our understanding of pathology of tumors development, and this might provide novel insights into the molecular and biologic field of clinical treatment including possible cancer therapy. Oncogenic EGFR mutations are found in 10% to 35% of lung adenocarcinomas, with predominants in a subset of patients with non-small cell lung cancer (NSCLC) [24-30]. These mutations, which commonly occur as either small in-frame deletions in exon 19 or point mutations T790M or L858R in exon 21 within the EGFR tyrosine kinase domain, confer constitutive activity and sensitivity to EGFR tyrosine kinase inhibitor (TKI) [30,31]. Konduri and colleagues [32] reported five patients with metastatic lung cancer whose tumors harbored EGFR fusion, most commonly RAD51, are recurrent in lung cancer. Four of whom were treated with EGFR TKI erlotinib with documented antitumor response for 5, 6, 8, and 20 months respectively. An early EGFR TKI trial randomized patients with EGFR mutation positive stage IIIb or IV adenocarcinoma to treatment with afatinib or gemcitabine and cisplatin, treatment with afatinib prolonged progression free survival to 11.0 months as opposed to 5.6 months with gemcitabine and cisplatin [7]. In the phase III trial of 419 patients with advanced T790M positive NSCLC with osimertinib vs platinum based therapy, progression free survival in the osimertinib group was 8.5 months, compared to the platinum-based therapy group at 4.2 months [6]. In Cuba, CimaVax-EGF, promising, an active vaccine targeting EGF as the major ligand of oncogenic EGFR, it is in use as a cancer therapy against non-small cell lung cancer (NSCLC) [33,34].

Serra[35] reported the clinical response of a lapatinib-based therapy in lung metastatic lesions of a Li-Fraumeni syndrome patient with oncogenic HER2V659E mutation and an EGFR-exon 20 insertion. A symptomatic and radiologic clinical response was achieved using oral daily lapatinib at a dose of 1,000mg in combination with intravenous weekly paclitaxel 80mg/m²,trastuzumab initial dose of 8mg/kg intravenously,and then followed by 6mg/kg every three weeks.In total,the clinical benefits lasted over 9 months.In a large trials of 48 HER2-positive early breast cancer patients,the adjuvant trastuzumab treatment demonstrates highly favorable outcome.Five year overall survival rates and disease-free survival rates were 95.8% and 93.8% respectively[36].Tanz and colleagues[37] reported two HER2 positive metastatic gastric adenocarcinoma who favorably responded to second line chemotherapy (FOLFIRI,irinotecan plus 5-Fu) with trastuzumab continuation following progressive disease to first line treatment containing trastuzumab,implicating trastuzumab continuation in metastatic HER positive gastric cancer is safe,practical and improve survival .Recently,neratinib was recently approved by FDA for extended adjuvant treatment of ER+/HER2+ breast cancer[38].In this study,we use gefitinib in keeping stable disease for 8+ months in a woman with lung adenocarcinoma,and using gefitinib in more patients are under investigation.

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