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RESEARCH ARTICLE

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

George Zhu
Institute of Oncology, Tehran University of Medical Sciences, Tehran, Iran.

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***Address for Correspondence:**
George Zhu, Institute of Oncology, Tehran University of Medical Sciences, Tehran, Iran. E-mail: *sansan4240732@163.com*

Abstract

Objective: Traditional systems of medicine all over the world even traditional medicine and cancer have been using plants and plants products for therapeutic intention. The purpose of these retrospective trials is to assess the clinical efficacy of chemotherapy in conjunction with TCM for a broad variety of cancers.
Methods: Total 75 patients with available cancers were concluded in the study during September1993 – May 2018. The sex ratio of male: female was 50:25 respectively. The mean age at onset was 46.9 years (range 10-79 years. All patients were treated with different dosage of various chemotherapy in combination with TCM or traditional medicine alone. The basic chemotherapeutic regimen consisted of vincristine (VCR, 1-2 mg/week)、cyclophosphamide (CTX, 200-1, 000mg/week), mitomycin C(MMC, 2-4 mg/week) and 5-fluorouracil (5-Fu,250-500 mg/day). The detail prescription of TCM varied among a broad variety of carcinomas. The criteria of complete remission (CR) and/or partial remission (PR) is according to the rules where physicians have in common with in clinics. In 75 cases, the CR was obtained in 33(44%) advanced cancers, a short CR in 11(14.7%) cases, PR in 25 (33.3%) cancers, stable disease in 6 cases. 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.*
Results: Among those long-term survivors, 31 carcinomas obtained in disease-free survival over 5 years, 20 cancers were survival over 10 years, the longest four patients over 25 years.
Conclusion: In this study, it was experienced that a CR was a pivotal influencing factor in those longest survival patients, and traditional medicine was also recommended. Down regulating 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, target therapy, traditional medicine.

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 to the protocol of chemotherapy in conjunction with recent targeting oncogenic receptor[1-14], traditional medicine (TCM) and/or adoptive immunotherapy (LAK cells, TIL therapy)[15,16]. The experience in Ugandan children with Hodgkin's disease has been excellent and in a study of 14 adults with stage I and II Hodgkin's disease, mostly clinically staged, 13 patients (93%) achieved CR with combination chemotherapy and all were in CR 11 to 94 months after the completion of treatment[17]. Another, a disease-free survivors of 5 years (56.5-59.3% versus 22-24.3%) and 10 years (48.9%) was remarkably higher rate in those breast cancers with stage III following surgery plus chemotherapy than only surgery. More promising, in large trials of 48 HER2-positive early breast cancer patients, targeting the adjuvant trastuzumab treatment demonstrated highly favorable outcome. Five year overall survival rates and disease-free survival rates were 95.8% and 93.8% respectively[19]. Recently, neratinib was recently approved by FDA for extended adjuvant treatment of

ER+/HER2+ breast cancer[20]. Systemic chemotherapies and combined regimens are currently available, provide palliation and prolong survival. In particular, high-quality clinical trials on TCM in cancer are generally lacking, except for Kampo medication for Japanese cancer patients[21,22], arsenic trioxide (As_2O_3) in the role of acute promyelocytic leukemia[23] and cantharidin in treatment of liver cancer[24]. This paper will attempt to place in proper interpretative review from those patients with cancers under remission in this group.

MATERIALS AND METHODS

Total 75 patients with available cancers were concluded in the study during September 1993- May 2018. The sex ratio of male: female was 50:25 respectively. The mean age at onset was 46.9 years ranging from 10 to 79 yrs. 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, 44.0 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 tumors 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 oral cancer 1, epidermoid carcinoma 1, replapsed 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, 1-2 mg/wk), cyclophosphamide (CTX, 200-1, 000 mg/wk), mitomycin C (MMC, 2-4 mg/wk) and 5-fluorouracil (5-Fu, 250-500 mg/day). In addition, the additional drug adriamycin (ADM, 20 mg/wk) in lymphoma and metastatic breast cancer, demethyl cantharidin in liver cancer and cisplatin (DDP) or interleukin-2(PHA/gefitinib) in lung cancer. The detail prescription of TCM varied among a broad variety of carcinomas. The criteria of complete remission (CR) and/or partial remission (PR) is according to the rules where physicians have in common with in clinics.

Complete remission (CR): there was no more tumor or tumor complete regressed in patients for at least 1 month;

Partial remission: the tumor decreased by more than 50% in patients for at least 1 month;

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[25,26] and lung cancer[27,28] were previously described.

RESULTS

In 75 cancers, the rate of complete remission (CR) was achieved in 33(44%) advanced cancers. All CR patients with advanced cancers was survival over 5 years, 18 cancers was survival 10 years. Another, a short CR was obtained in 11 (14.7%) advanced cancers, the survival time varied from 20 months to 4 yrs. PR was obtained in 25(33.3%) patients with a broad variety of carcinoma, while 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. Basic characteristics of studied population were summarized in Table 1. During the schedule of drug administration, all patients were treated with the different dosage of 1 to 4 courses of various combination chemotherapy in conjunction with traditional medicine. In statistically analysis, one patient with nasophyaryngeal cancer, the diplopia and unable version 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 (8x5 cm) once obtained complete response as to an approach of 5% Fu of retinoic acid ointment. A short CR was achieved by the protocol of MFC (MMC; 5-Fu; Ara C/homoharringtonine, CTX) plus cantharidin or cinobufacini drug in 5 advanced gastric cancers. One of them was a long-term survivor for 6 yrs via mass incision and the combination of MFC with herbs *Scutellaria barbata d. don*. In view of cancer types, 10 lymphoma was setted to the major protocol of the combination conventional chemotherapy (COMA, 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 4 patients with thumb lymphadenopathy was treated by the use of antibiotics regimen in full dose with anti-inflammatory herbal tablets or immunotherapy lymphocyte transfer factor. In 12 HCC, 6 HCC were treated mainly by 5-Fu (500-1,000 mg/day) and TCM. 2 patients obtained CR through cantharidin and traditional medicine. The main protocol of TCM with adjuvant antibiotics regimen and low dose of dexamethasone was given in a primary liver cancer (AFP+, ascites +++, jaundice +++, liver tumor 3.2x3.0 cm). One acute promyelocytic leukemia complicated with metastatic liver cancer (7x4.5 cm) was in CR with all-trans retinoic acid (ATRA) and TCM. The detail prescription of TCM was mentioned before[25,26]. In the follow up, one HCC accompanied with colon polyps obtained complete remission via hapatectomy and targeting oncogenic receptor tyrosine kinase inhibitor sorafenib. Dose intensity has proven to be critical in maximizing chemotherapeutic efficacy for numerous human cancers. Eight other patients with cancers were in remission through small dosage of chemotherapy and TCM or traditional medicine (TCM) alone. There were 4 lung cancers, 1 gallbladder cancer, 1 cholangicarcinoma and 2 thyroid cancers. Among

targeting two metastatic lung cancer, one female with lung cancer was given the combination chemotherapy plus targeting oncogenic receptor EGFRv III 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 were less than 1 years 10 cases, 1 to 3 years 20 cases, over 3 to 5 years 12 cases, over 5 to 10 years 11 cases, over 10 to 20 years 13 cases, and over 20 years 7 cases. In differential types of 20 patients with over 10 years survivors, lymphoma occupied 8 cases (40%). Among 7 patients with over 20 years, lymphoma occupied 3 cases, metastatic breast cancer 2 cases and hepatocellular carcinoma 2 cases.

CASE REPORTS

A 55 years 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 (4x3 cm) enlargement in her left neck. A 3x5 cm 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 version 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 3years 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 surgery in a local hospital due to her tarry stools. At post-operatively, a rodent ulcer (5x4x2.8 cm) with harden border 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 MFC (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 4.5x3 cm, 2x3 cm, 2x3 cm 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 yrs.

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 70 g/l. Leukocyte count 160,000 (160x109/l) with 19% blasts and promyelocytes, 28.5% myelocytes and metamyelocytes. Platelet count was 375x109/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 120 mg, with CR again. She was survivor for near 8 years.

Table 1: Patient's characteristics.

Cancer types	Cases No	Sex	Mean ages (years)	Treatment Protocol	Response following therapy	Duration of remission(years) < 1	1-3	> 3-5	>5-10	>10
Lymphoma	16	M14, F2	38.1(13-66)	COMA(10)*, Radiotherapy**(1), prednisone(1), Immunotherapy(4)	CR(10)*, short CR(2), PR(4)	1	3	2	1	9
HCC	12	M10, F2	44.0(26-63)	a.5-Fu(250-1,000 mg/day), VCR,CTX,MMC,TCM b. Cantharidin, TCM c. hepatectomy, sorafenib	CR(8), Short CR(2), PR(1), stable disease(1)	1	4	1	3	3
Lung tumors	12	M8,F4	60.1(40-79)	a. COMF, TCM; b.DDP, etoposide, IL-2/gefitinib; c.CTX,5-FU, antitumor capsule; d.TCM alone	CR(2), short CR(2), PR(3), stable disease (5)	4	3		3	1
NPC	5	M3, F2	51.4(38-75)	a. VCMF, TCM b.CTX, 5-FU, TCM	CR(1), short CR(1), PR(3)		1	3	1	
MBC	4	F4	31.3(25-41)	a. COMF, TCM b.COP, TCM	CR(3),PR(1)			1		2
Stomach cancer	5	M2, F3	42.3(35-500	a.MFC, TCM; b.CTX, 5-FU, antitumor capsule	CR(1),short CR(2),PR(2)	1	3		1	
AML	3	M2, F1	4, 18, 20	DA**, HA, TCM	PR(3)	3				
APL	1	M	31	ATRA 80mg/day; H 1 mg x 5 days; TCM	CR	1 died of relapsed APL				
CML	2	M1, F1	33, 62	Busulfan, TCM	CR (1), short CR(1)			1	1	
CLL	1	M	58	Chlorambucil, TCM	CR	1 died of stomach cancer				
MM	2	M1, F1	60, 63	Thalidomide, pred, TCM	Short CR(1), PR(1)		1	1		
Epidermoid cancer	1	F	72	5% FU of retinoic acid ointment	PR		1			
Thyroid cancer	2	F2	54, 60	TCM alone	CR(2)			1		1
Bile cancer	1	F	65	CTX,5-FU,TCM	CR					1
Cholangio-carcinoma	1	M	72	MFC（MMC, 5-FU, CTX）, TCM	CR	1 died of intestinal cancer				
Others***	7	M5,F2	57.5(44-69)	COFP, COMMB, TCM	CR(1), PR(6)		1	2	1	3

Note: HCC: hepatocellular carcinoma; NPC: metastatic nasopharyngeal cancer; MBC: metastatic breast cancer; AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; CML: chronic myeloid leukemia; CLL: chronic lymphocytic leukemia; MM: multiple myeloma; COMA:CTX, VCR, MMC, ADM; COMF: CTX, VCR, MMC/ADM, 5-FU; VCMF:VCR,CTX, MMC/DDP; 5-FU; COP: CTX, VCR, pred; COFP:CTX, VCR, 5-FU, PHA, Pred; DA:DNR, 45 mg/m^2, Ara-c 100 mg/m^2; HA: homoharringtone 1mg x 5 days, ara-c 50 mg, intramuscle, twice a day; MFC:MMC,5-FU, Ara-c/H,CTX; COMMB: CTX, VCR, MMC, MTX, Bleomycin; ATRA: all-trans retinoic acid; Pred: prednisone; TCM: traditional medicine; M:male; F:female. *: cases number; **: treatment in another hospital; ***include oral cancer 1, relapsed vulva cancer 1, laryngeal cancer 1, maxillary sinus carcinoma 1, carcinoma of mandibular sinus 2, and metastatic bone tumor 1.

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 ascites+++, gallbladder was dilation, 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 15years.

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 red ulcer patches. CR can be achieved by use of antibiotics regimen in full dose and combination chemotherapy (VCR, CTX, 5-Fu, MMC), the tumors was 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 cholangio carcinoma on September 2, 2004. He had a history of bad cough two months ago, followed by a progressive general jaundice, conspicuous weight loss, and 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, combinatiion 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 *Prunella vulgaris, Traxacum, honeysuckle, Ophiopogon japonicas, Asparagus, mussels, 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 118x109/l. The patient complained of his leukocytosis (67-97x109/l) for more than one month duration. He was treated with hydroxycarbamide in another hospital and leukocytosis declined to 27x109/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) 123.88x109/l. The leukocyte differential count: 9% segmented neutrophils, 90% small lymphocytes. The platelet count 131x109/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 112g/l, WBC 13.6x109/l, plt 128x109/l. On May 5 and July 28, 2011, Hb 104-112g/l; WBC 9.54-10.1x109/l, with a leukocyte differential count of 26.2% mature neutrophils and 63.8% lymphocytes; plt 101-112x109/l respectively. Bone marrow aspirates on May14, 2011 revealed normal cellularity. Bone marrow differential count: 34% myeloid, 31.2% erythoid, 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 7.3x109/l with 70% mature neutrophils and 28% lymphocytes; plt 188x109/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. The traditional combination chemotherapy program for lymphomas of favorable histologic type has been CVP (CTX, VCR, Pred) given at 21-days intervals[29]. Cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) were used in the NCI study for patients with nodular mixed and nodular histocytic lymphomas[30]. More intensive CVP programs with the addition of Adriamycin or bleomycin, or both, known as BACOP or CHOP-bleo, resulted in overall complete remission rates for patients with diffuse lymphomas ranging from 48% to 89%[31-34]. The NCI program of this 5-drug program, complete remission rates with these approaches has ranged from 48% to

94%[33]. The use of chemotherapy to treat stomach cancer has no firmly established standard of care[35]. Some drugs used in stomach cancer treatment have included: 5-Fu (fluorouracil), doxorubicin (Adriamycin), mitomycin C and most recently oxaliplatin, irinotecan in various combination. The relative benefits of these different drugs, alone or in combination, are unclear[36]. There are evidences supporting that clinical researches are exploring the benefits of giving chemotherapy as adjuvant therapy for surgery to destroy remaining cancer cells[37]. In recent analyses of definitive surgery followed by adjuvant radio chemotherapy (5-Fu/leucovorin LV regimens) for patients with gastric cancer, Liu and Ahmed reported that 59.3% (48/81) patients survived >3 years, 18.5% (15/81) patients survived 5 or more years[38]. Eighteen out of 81(22.2%) patients are still alive with a medium survival of 142 months (57-196 months). More recent, treatment with HER2 inhibitor, trastuzumab, has been demonstrated to improve overall survival in inoperable locally advanced or metastatic gastric carcinoma over expressing the HER2[37]. Oncogenic receptor HER2[39] is over expressed in 13-22% of patients with gastric cancer[40,41]. Tanz and colleagues 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[42].

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)[43-49]. 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)[49,50]. Four of whom were treated with EGFR TKI erlotinib with documented antitumor response for 5, 6, 8, and 20 months respectively[51]. An early EGFR TKI trial randomized patients with EGFR mutation positive stage IIIb or IV adenocarcinoma to treatment with afatinib or gemcitabine and cisplatin[6]. 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]. A symptomatic and radiologic clinical response was achieved using oral daily lapatinib at a dose of 1,000 mg in combination with intravenous weekly paclitaxel 80 mg/m^2, lately, trastuzumab initial dose of 8mg/Kg intravenously[52]. 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) [53,54]. 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.

Interesting, in an APL complicated with secondary HCC, It has been demonstrated previously that nuclear RARB has been shown to be rearranged as a result of insertion of HBV sequences[55]. Recent promising, these oncogenic receptor derivatives[23,56-58], in addition to pml/RARA, oncogenic TBL1XR1-RARB[59], and NUP98/RARG[60,61], and PML-RARG[62] were also detected in APL rare cases. The involvement of RARB may explain why the disappearance of malignant hepatic tumour cells via the use of ATRA agent. In this case, ATRA (80-100 mg/day) was resistance to the relapse episode. In the presence of genetic mutation in RARA LBD and the PML-B2 domain of PML-RARA, one explanation for ATRA resistance is that the N-CoR/SMAT-corepressor complex tightly interact with pml/RARA or PLZF, even under pharmacological concentration of ATRA, so that transcriptional de-repression cannot occur at RARA target gene promoter, ATRA binding LBD impaired, degradation of pml/RARA by proteasome pathway are inhibited[23,63]. Previous studies uncovered that the ATRA and 13-cis forms of retinoic acid, two isomers of RA, are equally effective inhibiting proliferation[64].

In addition, new emerging aberrant pml/ RARA in relapsed APL returned to act as a constitutive transcriptional repressor[1,23,58,63,77-92] by pertubing normal retinoid signaling and RAR function, suppressing (the blockade of) differentiation, possessing an altered specifity for DNA response element, these DNA recognition changes target a distinct set of "neoplastic" genes that differ from the genes normally targeted by normal RARA. In literature alternative strategy, an APL obtained CR after treatment with 13-cis retinoic acid first and repeated CR with ATRA in relapse[65]. And more, 80% (4/5) CR in newly APL and 33% (4/12) CR in relapsed APL were achieved after treatment with 9-cis retinoic acid (LGD1057) alone[66]. Nowadays, a lot of cohort trials, 61.5% (24/39) achieved CR using tamibarotene including 5 newly APL and 13 relapse APL twice or more[67-73]. Among 269 APL with CR underwent maintenance random, four year relapse-free survival rate was 84% (ATRA) and 91% (Tamibarotene). In 52 high risk patients, this became significant (50% for ATRA, 87% for tamibarotene)[72]. In comparative analysis among those relapsed APL[74], 80%(28/35) achieved CR and 22.86% CRm in tamibarotene-ATO versus 54.2% (19/35)CR with only 2.86-3.7% CRm in ATRA and ATO regimen[73]. Thus, Tamibarotene demonstrated more efficacy in both untreated APL patients and relapsed who have been treated ATRA and chemotherapy, especially as novel strategy in relapsed APL in Japan and others[74-76]. This is encouraging perspective.

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AUTHOR'S CONTRIBUTION

Zhu G: Writing original draft, review, methodology, data curation, literature survey, editing.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICTS OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this paper.

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