ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2013 May 10; 4(2): 29-57

Baishideng Publishing Group
www.wjgnet.com

WJCO World Journal of Clinical Oncology

A peer-reviewed, online, open-access journal of clinical oncology

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WJCO World Journal of Clinical Oncology

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Volume 4 Number 2 May 10, 2013

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INDEXING/ABSTRACTING		*World Journal of Clinical Oncology* is now indexed in PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.
FLYLEAF	I-III	Editorial Board

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Quarterly

World Journal of Clinical Oncology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjco@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
May 10, 2013

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-4333/g_info_20100722172206.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
wjco@wjgnet.com
doi:10.5306/wjco.v4.i2.29

World J Clin Oncol 2013 May 10; 4(2): 29-42
ISSN 2218-4333 (online)

EDITORIAL

Molecularly targeted therapies for advanced or metastatic non-small-cell lung carcinoma

Soley Bayraktar, Caio M Rocha-Lima

Soley Bayraktar, Departments of Medical Oncology, Mercy Cancer Center, Ardmore, OK 73401, United States
Caio M Rocha-Lima, University of Miami and Sylvester Comprehensive Cancer Center, Miami, FL 33124, United States
Author contributions: Both authors contributed equally to this work.
Correspondence to: Soley Bayraktar, MD, MBA, Departments of Medical Oncology, Mercy Cancer Center, 1220 Hall street, Ardmore, OK 73401, United States. soley.bayraktar@mercy.net
Telephone: +1-580-5042781 Fax: +1-580-2206118
Received: March 7, 2013 Revised: April 9, 2013
Accepted: April 17, 2013
Published online: May 10, 2013

Abstract

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related death in both men and women in the United States. Platinum-based doublet chemotherapy has been a standard for patients with advanced stage disease. Improvements in overall survival and quality of life have been modest. Improved knowledge of the aberrant molecular signaling pathways found in NSCLC has led to the development of biomarkers with associated targeted therapeutics, thus changing the treatment paradigm for many NSCLC patients. In this review, we present a summary of many of the currently investigated biologic targets in NSCLC, discuss their current clinical trial status, and also discuss the potential for development of other targeted agents.

Key words: Non-small cell lung cancer; Molecular targeted therapy; Vascular endothelial growth factor; Epidermal growth factor receptor; Tyrosine kinase inhibitors; BRAF; Anaplastic lymphoma kinase

Core tip: Targetable molecular abnormalities have not yet been identified in approximately 80% of non-small-cell lung cancer patients. In addition to anaplastic lymphoma kinase, epidermal growth factor receptor, vascular endothelial growth factor targeted therapies, the results from ongoing trials will determine if the newer targeted agents will be incorporated into clinical practice.

Bayraktar S, Rocha-Lima CM. Molecularly targeted therapies for advanced or metastatic non-small-cell lung carcinoma. *World J Clin Oncol* 2013; 4(2): 29-42 Available from: URL: http://www.wjgnet.com/2218-4333/full/v4/i2/29.htm DOI: http://dx.doi.org/10.5306/wjco.v4.i2.29

INTRODUCTION

Non-small-cell lung cancer (NSCLC) remains a therapeutic challenge. Despite some progress, it remains the leading cause of cancer-related death in the United States in both men and women. The estimated incidence of NSCLC is 226160 cases with 160340 deaths in the United States in 2012. The 5-year survival rates for advanced and metastatic NSCLC are only 24% and 4%, respectively[1].

The core drug and backbone of treatment in locally advanced and metastatic settings of NSCLC has been a platinum agent. In a large randomized clinical trial, Schiller *et al*[2] compared the efficacy of three commonly used regimens (cisplatin and gemcitabine, cisplatin and docetaxel, carboplatin and paclitaxel) with that of a reference regimen of cisplatin and paclitaxel. No significant difference in survival was observed among the four commonly used regimens, although the regimen of carboplatin and paclitaxel had a lower rate of toxic effects than the other regimens. On the basis of these results, Eastern Cooperative Oncology Group had chosen carboplatin and paclitaxel as its reference regimen for future studies; and it is still the most commonly used taxane-platinum combination in the United States[3] which produces 15%-32% objective response rates (ORR), with 7.9-10.6 mo median overall survivals (OS)[4-6].

Further attempt at subclassification is now accepted as a standard of care; separating squamous cell carcinoma from adenocarcinoma and large-cell carcinoma as the distinction carries implications for prognosis and treatment decisions. For example, a phase Ⅲ study in patients with advanced NSCLC treated with cisplatin plus pemetrexed (an inhibitor of purine and pyrimidine synthesis), showed no improvement in tumor response rate and survival over cisplatin plus gemcitabine for all histologies; however, an improvement in survival was noted in the non-squamous histology subset while a decrement in the squamous histology subset was observed[7]. Due to safety concerns observed in the phase Ⅱ trial, the addition of bevacizumab to carboplatin/taxol was subsequently studied in phase Ⅲ trial and improved efficacy was observed in patients with non-squamous histology (ORR, 35%; OS, 12.3 mo)[5].

In addition to making distinction in cytotoxic chemotherapy based on histology, over the past decade, a large number of studies have been published that aimed to target the molecular abnormalities implicated in NSCLC tumor growth, invasion, metastasis, angiogenesis and resistance to apoptosis. Currently, detection of the presence of mutations involving the epidermal growth factor receptor (*EGFR*) gene and fusion of the N-terminal portion of the protein encoded by echinoderm microtubule-associated protein-like 4 (*EML4*) gene with the intracellular signaling portion of the receptor tyrosine kinase encoded by anaplastic lymphoma kinase (*ALK*) gene - that is, EML4-ALK - has become routine in many centers because patients having tumors harboring such alterations benefit from novel targeted inhibitors as part of their treatment regimen. This review describes some of the important developments and targeted agents that have been tested in clinical trials; and the potential future biologics in the treatment of advanced or metastatic NSCLC.

MOLECULARLY TARGETED THERAPIES IN ADVANCED OR METASTATIC NSCLC

EGFR inhibition

EGFRs are a group of transmembrane proteins that regulate key processes in the cell, such as proliferation, division, migration, and differentiation. This family has 4 different members: EGFR (HER1 or ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4); all of which share a similar structure[8]. Upon binding to its ligands, EGFR induces receptor homo- or hetero-dimerization and results in the activation of an intracellular tyrosine kinase domain. Receptor activation cause downstream signaling events through activation of the Ras/Raf/MEK/MAPK and PI3K/AKT/mTOR pathways that regulate cell proliferation, differentiation, and survival[9]. The two most common EGFR mutations are short in-frame deletions of exon 19 and a point mutation in exon 21[10]. Tumors with EGFR mutations occur at a higher frequency in East Asians than in non-Asians (30% *vs* 8%), in women than in men (59% *vs* 26%), in never-smokers than in ever-smokers (66% *vs* 22%), and in adenocarcinoma than in other NSCLC histologies (49% *vs* 2%)[11]. In the United States, activating EGFR mutations are estimated to occur in 15% of patients with primary lung adenocarcinoma[12].

Monoclonal antibodies against EGFR: Cetuximab is a chimeric monoclonal antibody against EGFR. One of the first phase Ⅱ studies assessing combination chemotherapy with cetuximab (cisplatin or carboplatin and gemcitabine with or without cetuximab) showed an increased ORR, progression-free survival (PFS), and OS in the cetuximab group[13]. A similar phase Ⅱ study in which cisplatin and vinorelbine were administered with or without cetuximab also showed enhanced survival indices in the cetuximab arm[14]. However a subsequent large phase Ⅲ trial investigating paclitaxel or docetaxel and carboplatin, with or without cetuximab in 676 patients with NSCLC did not find any notable differences in PFS or ORR[15].

The recently published FLEX study demonstrated that adding cetuximab to cisplatin-based chemotherapy resulted in a small but significant improvement in median OS in patients with advanced NSCLC [11.3 mo *vs* 10.1 mo; hazard ratio (HR): 0.87; $P = 0.04$][16]. A retrospective analysis of FLEX data showed that 31% of patients with high EGFR expression, adding cetuximab increased the median OS from 9.6 to 12 mo (HR: 0.73; $P = 0.011$)[17]. Ultimately, a meta-analysis looking at the four trials in which 2018 previously untreated NSCLC patients were analyzed concluded that cetuximab improved OS and ORR regardless of the presence of EGFR mutations[18]. In accordance with the above results, a more in-depth analysis of these subgroups in phase Ⅲ trials revealed that specific activating mutations in the tyrosine kinase domain of the *EGFR* gene were associated with sensitivity to gefitinib but not to cetuximab[19]. In addition, no significant cetuximab treatment-specific correlations between EGFR or K-RAS mutation status and PFS, OS, or ORR were observed in the phase Ⅲ trials[20,21]. Therefore, we can conclude that EGFR or K-RAS mutations may not be useful as biomarkers in cetuximab therapy. At present, a number of clinical trials are still evaluating the efficacy of cetuximab in combination with other treatment modalities in combination with tyrosine kinase inhibitors (TKIs), and other chemotherapeutic drugs. Most of these trials are also assessing biomarker status that could be predictive or prognostic in value.

EGFR-Tyrosine kinase inhibitors: EGFR-TKIs are small molecules administered orally and are subdivided in reversible, gefitinib and erlotinib, and irreversible, afatinib on the basis of their straight binding with the specific site of the EGFR intracellular domain. These drugs inhibit the phosphorylation and tyrosine kinase activity of the intracellular adenosine triphosphate (ATP)-binding domain of the EGFR through competitive binding to this site, and were initially investigated in unselected patients reporting contrasting results depending on the type of population/enrolled in each study. However, the discov-

ery that response to EGFR-TKIs is associated with the presence of activating EGFR mutations in NSCLC has led to the design of clinical trials in which patients were selected on the basis of the EGFR mutational status. Almost all patients who respond to EGFR-TKIs have been shown to carry activating mutations usually found in exons 18 through 21 of the TK domain of EGFR, and are either point mutations or in-frame small deletions or insertions[22]. Although more than 250 mutations of the EGFR have been described up to now, two mutations, one single point mutation in exon 21, the L858R, and a series of small in-frame deletions in exon 19 account for approximately 90% of all EGFR mutations.

Erlotinib: EGFR mutations have been defined "activating" and "sensitizing" and both definitions are correct. In fact, EGFR mutations lead to increased response of the EGFR to exogenous growth factors, thus producing a more significant and more persistent activation of intracellular signaling pathways, resulting in increased cell proliferation and survival. On the other hand, the mutant receptor is more sensitive to EGFR-TKIs as compared with wild type EGFR, since lower concentrations of drugs are required to inhibit its phosphorylation. Retrospective analyses have demonstrated that patients with EGFR mutations have high ORRs to EGFR-TKIs in any line of treatment[23]. These findings sustain the hypothesis that tumors with EGFR mutations are addicted to the EGFR pathway, *i.e.* depend on these pathways for their growth. In agreement with this hypothesis, tumors with EGFR mutations have shown to homogeneously carry this molecular alteration in all tumor cells[24]. As discussed above, erlotinib was first studied in unselected patients with NSCLC, and a subsequent analysis of the patients who had experienced dramatic tumor responses were found to have the activating mutations in the kinase domain of EGFR[25]. The response rate was as high as 81% in patients harboring EGFR tyrosine kinase domain mutations, but less than 10% in patients with wild-type EGFR[26]. The OPTIMAL trial was the first phase Ⅲ study directly comparing erlotinib with standard chemotherapy in the first-line setting of advanced NSCLC in Chinese patients with an activating EGFR mutation. That trial showed a PFS of 13.1 mo with erlotinib compared with 4.6 mo with gemcitabine-carboplatin chemotherapy (HR: 0.16; 95%CI: 0.1-0.26; $P < 0.001$)[27]. An updated analysis also showed median PFS of 13.7 mo *vs* 4.6 mo; HR: 0.164; $P < 0.0001$[28]. A second trial called EURTAC, the first to involve a Western European population, randomized patients to a platinum-based doublet chemotherapy regimen (docetaxel-gemcitabine) or to erlotinib in patients with an EGFR activating mutation. Patients treated with erlotinib experienced a PFS advantage (9.7 mo *vs* 5.2 mo; HR: 0.37; 95%CI: 0.25-0.54)[29]. Based on these results, erlotinib was approved as a first-line treatment in patients with advanced or metastatic NSCLC harboring the EGFR mutations.

Recent phase Ⅱ/Ⅲ trials have shown single agent activity of erlotinib in the second-line setting in either selected or unselected patients with metastatic NSCLC[30,31]. In the TITAN phase Ⅲ trial, the efficacy and tolerability of second-line erlotinib was compared with either pemetrexed or docetaxel in 425 patients with advanced NSCLC who were treated with first-line platinum doublet chemotherapy and had disease progression during or immediately after chemotherapy. The second-line erlotinib was associated with a similar median OS duration to pemetrexed or docetaxel in patients with advanced NSCLC (5.3 mo *vs* 5.5 mo; HR: 0.96 in the overall population; 95%CI: 0.78-1.19). Similarly, there was no difference in OS between the treatment groups (HR: 0.85; 95%CI: 0.59-1.22) in 149 patients with EGFR wild type tumors[32].

The phase Ⅲ SATURN trial examined erlotinib as maintenance therapy after platinum-based chemotherapy. That trial met the primary endpoint of significantly longer PFS in patients treated with erlotinib (12.3 wk) than in patients receiving placebo (11.1 wk; HR: 0.69; 95%CI: 0.58-0.82; $P < 0.0001$). The overall response rate was 11.9% in the erlotinib arm compared with 5.4% in the placebo arm ($P = 0.0006$)[33]. Importantly, the benefit of erlotinib maintenance on PFS and OS was also seen in EGFR wild-type patients (HR: 0.78, 95%CI: 0.63-0.96, $P = 0.0185$, and HR: 0.77, 95%CI: 0.61-0.097, $P = 0.008$, respectively).

Gefitinib: Two large phase Ⅲ studies highlighted the role of gefitinib in tumors harboring EGFR mutations[34,35]. In IPASS trial, the efficacy of gefitinib was compared with carboplatin/paclitaxel in previously untreated never-smokers and light ex-smokers with advanced pulmonary adenocarcinoma. Of 1217 enrolled patients, OS was similar for gefitinib and carboplatin/paclitaxel (HR: 0.90; 95%CI: 0.79-1.02; $P = 0.109$) in overall, or in EGFR mutation-positive (HR: 1.00; 95%CI: 0.76-1.33; $P = 0.990$) or EGFR mutation-negative (HR: 1.18; 95%CI: 0.86-1.63; $P = 0.309$) subgroups. Of importance, PFS was significantly longer with gefitinib for patients whose tumors had both high *EGFR* gene copy number and EGFR mutation (HR: 0.48; 95%CI: 0.34-0.67) but significantly shorter when high *EGFR* gene copy number was not accompanied by EGFR mutation (HR: 3.85; 95%CI: 2.09-7.09)[34]. Likewise, another multicenter phase Ⅲ trial demonstrated that patients with advanced-stage NSCLC containing EGFR mutations and treated with first-line gefitinib (compared with standard chemotherapy) had improved PFS[35]. Based on these results, the American Society of Clinical Oncology recommended EGFR mutation testing for patients with advanced NSCLC who are being considered for first-line therapy with an EGFR-TKI[12].

Two phase Ⅲ clinical trials suggested that gefitinib was more efficacious and less toxic than docetaxel as a second-line treatment in patients with previously-treated advanced NSCLC[36,37]. In the ISTANA trial, the primary endpoint of PFS was longer with gefitinib than

Table 1 Selected phase Ⅲ and randomized phase Ⅱ trials comparing epidermal growth factor receptor tyrosine kinase inhibitor and chemotherapy as first-line therapy in patients with advanced non-small cell lung cancer

Trial	*n*	Type of study	Study design	OS (mo) HR (95%CI)	*P* value	PFS (mo) HR (95%CI)	*P* value	ORR (%) HR (95%CI)	*P* value
Fukuoka *et al*[34]	261	Retrospective	Gefitinib *vs* PC	21.6 *vs* 21.9 1.00 (0.76-1.33)	0.99	9.6 *vs* 6.3 0.48 (0.36-0.64)	0.0001	71.2 *vs* 47.3 2.75 (1.65-4.6)	0.0001
Han *et al*[98]	42	Retrospective	Gefitinib *vs* Cis + G	27.2 *vs* 25.6 1.04 (0.49-2.18)	NA	8.0 *vs* 6.3 0.54 (0.26-1.1)	0.086	84.6 *vs* 37.5 9.16 (2.10-39.84)	0.002
Mitsudomi *et al*[99]	172	Prospective	Gefitinib *vs* Cis + D	35.5 *vs* 38.8 1.18 (0.76-1.8)	0.44	9.6 *vs* 6.6 0.52 (0.37-0.71)	0.001	62.1 *vs* 32.1 3.44 (1.60-7.37)	0.0001
Maemondo *et al*[35], Inoue *et al*[100]	228	Prospective	Gefitinib *vs* PC	27.7 *vs* 26.6 0.88 (0.63-1.24)	0.48	10.8 *vs* 5.4 0.32 (0.23-0.43)	0.001	73.7 *vs* 30.7 6.32 (3.55-11.25)	0.001
Chen *et al*[28]	154	Prospective	Erlotinib *vs* C + G	22.7 *vs* 28.85 1.04 (0.69-1.58)	0.69	13.7 *vs* 4.6 0.16 (0.10-0.26)	0.0001	83 *vs* 36 NA	0.0001
Rosell *et al*[29]	173	Prospective	Erlotinib *vs* platinum-based doublets	19.3 *vs* 19.5 1.04 (0.65-1.68)	0.87	9.7 *vs* 5.2 0.37 (0.25-0.54)	0.0001	58[1] *vs* 15[1] NA	NA
Yang *et al*[2][101]	345	Prospective	Afatinib *vs* Cis + P	NM		11.1[3] *vs* 6.9[3] 0.58 (0.43-0.78)	0.0004	56.1[3] *vs* 22.6[3] NA	0.001
Jänne *et al*[102]	345	Prospective	Erlotinib *vs* erlotinib + PC	24.6 *vs* 19.8 NA	NA	5.0 *vs* 6.6 NA	NA	35 *vs* 46 NA	NA

[1]Intention-to-treat population; [2]Only lung adenocarcinoma patients; [3]By independent review. PC: Paclitaxel and carboplatin; Cis: Cisplatin; C: Carboplatin; G: Gemcitabine; D: Docetaxel; P: Pemetrexed; OS: Overall survival; HR: Hazard ratio; NM: Not yet mature; NA: Not available; PFS: Progression-free survival; ORR: Objective response rate; *n*: Number of patients enrolled in the study.

docetaxel (HR: 0.729; 90%CI: 0.533-0.998; $P = 0.0441$), and the secondary endpoints showed superior ORR (28.1% *vs* 7.6%; $P = 0.0007$), good tolerability, and similar quality-of-life (QoL) improvement rates for gefitinib compared to docetaxel[37]. In the INTEREST trial, of 1433 patients analyzed (723 in gefitinib group and 710 in docetaxel group), non-inferiority of gefitinib compared with docetaxel was confirmed for OS (593 events *vs* 576 events; HR: 1.020, 95%CI: 0.905-1.150). Interestingly, superiority of gefitinib in patients with high *EGFR*-gene-copy number was not proven (72 *vs* 71 events; HR: 1.09, 95%CI: 0.78-1.51; $P = 0.62$; median survival 8.4 mo *vs* 7.5 mo)[36]. Table 1 summarizes the selected phase Ⅲ and randomized phase Ⅱ trials comparing EGFR-TKIs and chemotherapy as first-line therapy in patients with advanced NSCLC.

Vascular endothelial growth factor inhibition

Bevacizumab, a monoclonal antibody against circulating vascular endothelial growth factor (VEGF), was approved by Food and Drug Administration for the treatment of NSCLC in 2006. The combination of bevacizumab with carboplatin and paclitaxel was shown to prolong OS compared with chemotherapy alone (median OS, 12.3 *vs* 10.3 mo, respectively) in patients with nonsquamous advanced NSCLC[5]. Bevacizumab has also been combined with gemcitabine and cisplatin, with a modest benefit observed in PFS but no differences seen in OS[38]. Many other antiangiogenic agents have been under development.

Triple angiokinase inhibitors, which inhibit VEGF, platelet derived growth factor and/or fibroblast derived growth factor were thought to have the potential to improve the therapeutic outcomes for patients with NSCLC. Clinical trials have been ongoing involving several new antiangiogenic therapies, including ramucirumab, aflibercept, vandetanib, cediranib, nintedanib, sunitinib, pazopanib, brivanib, linifinib, axitinib, and motesanib (http://www.clinicaltrials.gov). To date, none of these agents in combination with chemotherapy have resulted in improvements in OS for patients with advanced NSCLC. Moreover, in a phase Ⅱ trial (ESCAPE), patients with squamous histology treated with chemotherapy plus sorafenib had a shorter OS than those receiving chemotherapy plus placebo (HR: 1.85; 95%CI: 1.22-2.81)[6]. A recent meta-analysis comparing the efficacy and toxicity of chemotherapy plus multitargeted antiangiogenic TKI with chemotherapy alone in patients with advanced NSCLC showed that chemotherapy plus a TKI significantly increased the ORR (HR: 1.71, 95%CI: 1.43-2.05) and PFS (HR: 0.83, 95%CI: 0.76-0.90], but not OS (HR: 0.93, 95%CI: 0.83-1.03). The toxicity was comparable between the two therapies[25]. Table 2 summarizes the phase Ⅲ clinical trials testing antiangiogenic TKIs in combination with chemotherapy in NSCLC.

There is evidence from the 3 phase Ⅱ clinical trials supporting the potential use of sorafenib as a monotherapy in chemotherapy refractory NSCLC[26,27]. Particularly, the BATTLE trial showed a promising response rate (8-wk disease control rate in 58% of patients) in heavily pretreated patients with single agent sorafenib. More impressively, in patients whose tumor harbored a KRAS mutation, sorafenib had a disease control rate of 79% while on a separate phase Ⅱ trial in NSCLC, the response rate to erlotinib was only 14% ($P = 0.016$)[28]. This indicates that the significant disease control rate in KRAS mutant NSCLC patients may be due to sorafenib's effects on KRAS downstream pathways such as Raf inhibition rather than its antiangiogenic effects. The randomized,

Table 2 Phase Ⅲ clinical trials testing antiangiogenic tyrosine kinase inhibitors in combination with chemotherapy in non-small cell lung cancer

Trial	*n*	Study design	PE	OS (mo)	PFS (mo)	ORR (%)
Vandetanib second-line						
ZEAL[103]	534	PV *vs* P	PFS	10.5 *vs* 9.2	17.6 wk *vs* 11.9 wk	19 *vs* 8
ZEST[104]	1240	EV *vs* E	PFS	6.9 *vs* 7.8	2.6 *vs* 2.0	12 *vs* 12
ZODIAC[105]	1391	DV *vs* D	PFS	10.6 *vs* 10.0	4.0 *vs* 3.2	NA
Vandetanib second or third-line						
ZEPHYR[106]	924	V *vs* placebo	OS	8.5 *vs* 7.8	NA	2.6 *vs* 0.7
Sorafenib first-line						
NEXUS[107]	904	G + Cis + S f/b S *vs* G + Cis f/b placebo	OS	376 d *vs* 379 d	183 d *vs* 168 d	28 *vs* 26
Motesanib first-line						
MONET[6]	1090	PC + M *vs* PC	OS	13.0 *vs* 11.0	5.6 *vs* 5.4	40 *vs* 26
Cediranib first-line						
BR29 (active, no longer recruiting, NCT00795340)	750	PC + Ced *vs* PC	OS	NA	NA	NA
Nintedanib second-line						
LUME-Lung 1 (active, no longer recruiting, NCT00805194)	1300	D + Nin *vs* D	PFS	NA	NA	NA
LUME-Lung 2 (active, no longer recruiting, NCT00806819)	1302	P + Nin *vs* P	PFS	NA	NA	NA

PC: Paclitaxel and carboplatin; P: Pemetrexed; E: Erlotinib; D: Docetaxel; V: Vandetanib; DV: Docetaxel-vandetanib; EV: Erlotinib-vandetanib; G: Gemcitabine; Cis: Cisplatin; S: Sorafenib; f/b: Followed by; M: Motesanib; Ced: Cediranib; Nin: Nintedanib; OS: Overall survival; PE: Primary endpoint; PFS: Progression-free survival; ORR: Objective response rate; NSCLC: Non-small cell lung cancer; NA: Not available.

placebo-controlled, multicenter international phase Ⅲ trial (NCT00863746 MISSION Trial) is currently underway to evaluate single agent sorafenib as third- or fourth-line therapy in patients with NSCLC. The enrollment for MISSION Trial has been concluded and data should be available later this year.

EML4-ALK inhibition

Rearrangements of the *ALK* gene are felt to be mutually exclusive of EGFR and KRAS mutations and occur in approximately 4% of NSCLC. The ALK mutations are more common in adenocarcinomas and in light smokers or non-smokers[39]. The phase I trial of the ALK-inhibitor crizotinib in advanced ALK-positive NSCLC revealed a response rate of 57% (95%CI: 46%-68%) and an estimated 6-mo PFS probability of 72% (95%CI: 61%-83%)[40]. A retrospective review of 82 ALK-positive patients (including patients who had received multiple lines of therapy) treated with crizotinib revealed an impressive 1-year survival of 74% (95%CI: 63%-82%) and 2-year survival of 54% (95%CI: 40%-66%)[41]. Crizotinib was approved in the United States in 2011, primarily based on response rates of 50% on the first 136 patients with *ALK*-rearranged NSCLC enrolled on PROFILE 1005[42] and secondarily on a response rate of 61% from the first 119 patients with *ALK*-rearranged NSCLC enrolled on PROFILE 1001[43]. Table 3 lists the major ongoing trials with crizotinib for advanced NSCLC.

New ALK inhibitors are under investigation, with phase I trials of LDK378 (not yet recruiting) and AP26113 (currently recruiting). NCT01449461, a phase I trial of AP26113, will be conducted in two parts, with the second part including expansion cohorts. The 4 cohorts include ALK mutations with no previous exposure to ALK inhibitors, ALK mutation with resistance to an ALK inhibitor, EGFR mutation with resistance to EGFR inhibitors, and non-lung malignancies with ALK mutations.

KRAS and BRAF mutations and MEK inhibition

Mutations in KRAS have been found in 15%-30% of patients with NSCLC and are considered to be one of the more frequent mutations in these tumors[44,45]. Approximately 97% of K-RAS mutations in NSCLC involve codons 12 or 13[46]. As with EGFR mutations, KRAS mutations are detected mainly in lung adenocarcinomas and are less frequently observed in squamous cell carcinomas of the lung[47,48]. In contrast with lung adenocarcinomas harboring EGFR mutations, tumors having KRAS mutations are seen at a higher frequency (20%-30%) in Caucasian patients than in East Asian patients (5%)[49]. Also, compared with EGFR mutations, KRAS mutations are more common in current or former smokers than in never-smokers[50].

Although the value of KRAS status as a prognostic and predictive biomarker for anti-EGFR therapy is less clear in NSCLC, several studies have demonstrated that KRAS mutations are a factor correlated with poor survival in patients with NSCLC[51-53]. A recent prospective biomarker-driven phase Ⅲ trial conducted in 889 patients comparing placebo with sequential erlotinib maintenance in unresectable NSCLC (SATURN, BO18192) showed that the presence of KRAS mutations was not predictive for erlotinib efficacy and was prognostic significantly associated with reduced PFS[54]. The predictive significance of KRAS mutation status is being further evaluated in BATTLE-2 clinical trial.

Table 3 Major ongoing clinical trials with crizotinib for advanced non-small cell lung cancer[1]

Trial number	Phase	Study design	Key entry criteria	PE
PROFILE 1007 (NCT00932893)	Ⅲ	Crizotinib *vs* Pem or Doc as second-line	ALK(+) and 1 prior platinum-based chemo	PFS
PROFILE 1014 (NCT01154140)	Ⅲ	Crizotinib + Pem + Cis/Carbo *vs* Pem + Cis/Carbo as first-line	ALK(+) and chemotherapy-naive	PFS
PROFILE 1005 (NCT00932451)	Ⅱ	Crizotinib *vs* placebo as third-line	ALK(+) and PD in arm B of study PROFILE 1007	RR
PROFILE 1001 (NCT00965731)	Ⅰ/Ⅱ	Crizotinib + erlotinib *vs* erlotinib as second or third-line	Adenocarcinoma NSCLC and 1-2 prior chemo	MTD
PROFILE 1001 (NCT01121575)	Ⅰ	Crizotinib + PF0299804	Acquired resistance to erlotinib or gefitinib	MTD

[1]Data available at URL: http://www.cancer.gov/clinicaltrials. chemo: Chemotherapy; Pem: Pemetrexed; Doc: Docetaxel; Cis: Cisplatin; Carbo: Carboplatin; PD: Progressive disease; NSCLC: Non-small cell lung cancer; ALK: Anaplastic lymphoma kinase; PFS: Progression-free survival; RR: Response rate; MTD: Maximum tolerated dose; PE: Primary endpoint.

BRAF encodes a non-receptor serine/threonine kinase that is a member of the Ras/MAPK signaling pathway downstream of Ras protein. Upon activation, BRAF directly phosphorylates MEK, which in turns phosphorylates ERK, thereby regulating cellular responses to growth signals[55]. BRAF mutations were first identified in melanoma cells, with 80% of mutations involving the Val600 residue in the kinase domain. By contrast, BRAF mutations account for only 1%-3% of NSCLC and they are mostly non-Val600Glu mutations including Gly468Ala and Leu596Val[56,57]. BRAF mutations were shown to be mutually exclusive with EGFR mutations within exons 18-21, KRAS codon 12 mutations, ERBB2 codon 20 mutations, and translocations in ALK[58]. Furthermore, V600E mutated NSCLCs showed a more aggressive tumor histology characterized by micropapillary features and were associated with poor prognosis[59].

A number of studies are currently examining the effect of MEK inhibitors on BRAF or KRAS-mutated solid tumors. As a downstream effector of the EGFR pathway that signals through K-RAS, MEK inhibition has also been suggested to play a role in patients who become resistant to EGFR inhibitors. A number of trials to examine MEK inhibitors alone or in combination with other targeted treatments are currently recruiting. The NCT00888134 phase Ⅱ trial is examining the effects of MEK inhibitor AZD6244 in patients with metastatic malignancy and a BRAF mutation. Dasatinib was shown to selectively induce senescence in NSCLC cells with inactivating BRAF mutations[60]. The NCT01514864 phase Ⅱ trial is now recruiting patients to examine the effect of dasatinib in patients with NSCLC or melanoma harboring a BRAF mutation (Clinicaltrials.gov).

GSK2118436 is a potent MEK inhibitor that has been shown to have preclinical activity in BRAF mutant NSCLC and melanoma. A phase Ⅱ trial (NCT01336634) is currently recruiting patients with previous exposure to platinum chemotherapy, and will examine GSK2118436 in advanced NSCLC patients with a BRAF mutation. The primary outcome will be ORR, and the trial is expected to be completed in late 2013. A phase Ⅰ trial (NCT01324258) of GSK1120212, another potent MEK inhibitor, in combination with gemcitabine is currently recruiting patients with solid tumors in Japan. An Open-Label, Phase Ⅰ / Ⅰb Dose Escalation Study to assess the safety and tolerability of GSK1120212 in combination with docetaxel, erlotinib, pemetrexed, pemetrexed + carboplatin, pemetrexed + cisplatin, or nab-paclitaxel in patients with advanced metastatic lung and/or pancreatic cancers is currently recruiting patients (NCT01192165). A number of phase Ⅰ trials are currently examining the combination of MEK162, a MEK1/2 inhibitor, with PI3K (BYL719) or Raf (Raf265) inhibitors in advanced solid tumors with documented KRAS or BRAF mutations (NCT01449058, and NCT01352273). Selumetinib (AZD6244, a potent MEK inhibitor) is being investigated in NSCLC patients with tumors harboring KRAS mutations[52]. Table 4 lists the ongoing clinical trials involving targeted agents for patients with advanced or metastatic NSCLC.

OVERCOMING ACQUIRED DRUG RESISTANCE TO EGFR TARGETED THERAPIES IN NSCLC

Despite the significant improvement in outcomes for these highly selected patients, treatment failures secondary to resistance have been described since 2005[61]. Known mechanisms of resistance include secondary EGFR mutations (T790M mutant) or persistent phosphorylation of EGFR that reduces the inhibitory ability of gefitinib or erlotinib, and MET amplification with subsequent activation of downstream pathways[61,62]. The discovery of resistance to the EGFR-TKIs has led to the development of second-generation EGFR-TKIs, or the use of combination of EGFR inhibitors with other targeted therapies. Moreover, a third generation of EGFR-TKIs is now entering clinical trials; these compounds bind covalently to the ATP-binding cleft of mutant EGFR and appear to have selective activity against the T790M mutant[63].

Second-generation EGFR-TKIs

Many trials have studied intensification of EGFR inhibition through use of second-generation TKIs such as neratinib, afatinib, and dacomitinib[64]. These inhibitors are different from erlotinib and gefitinib in 2 main ways: each forms a covalent, irreversible bond with the EGFR protein, and each also inhibits other members of the ERBB family of kinases[64].

Dacomitinib (PF0299804): PF0299804 is an oral irreversible inhibitor of the EGFR/HER1, HER2, and

Table 4 Ongoing phase Ⅱ/Ⅲ clinical trials involving targeted agents for patients with advanced or metastatic non-small cell lung cancer

Study design	Clinical trial ID	Phase	Status	Key entry criteria
EGFR inhibition				
Erlotinib *vs* docetaxel	NCT00637910	Ⅲ	Recruiting	WT EGFR, prior platinum chemo, no prior taxanes
Erlotinib *vs* pazopanib	NCT01027598	Ⅱ	Active, not recruiting	1 prior chemo
Erlotinib + OSI-906	NCT01221077	Ⅱ	Recruiting	EGFR mutation (+), chemotherapy-naive
Erlotinib + ARQ197	NCT01377376	Ⅲ	Recruiting	WT EGFR, prior platinum-based chemo
Erlotinib + ARQ197	NCT01244191	Ⅲ	Recruiting	2 prior lines of chemo
Erlotinib + PC + Bev	NCT00976677	Ⅱ	Active, not recruiting	Non-squamous, nonsmokers
Gefitinib (maintenance)	NCT01404260	Ⅲ	Active, not recruiting	Stable disease after chemo, EGFR unknown, never or light smokers
Gefitinib *vs* Pem	NCT00891579	Ⅱ	Recruiting	WT EGFR, prior platinum-based chemo
Afatinib	NCT00525148	Ⅱ	Active, not recruiting	EGFR mutation (+)
Afatinib	NCT00711594	Ⅱ	Active, not recruiting	Prior platinum-based chemo, progressed after erlotinib or gefitinib
PF00299804	NCT01000025	Ⅲ	Recruiting	1 prior chemo
PF00299804 *vs* erlotinib	NCT01360554	Ⅲ	Recruiting	1 prior chemo
BRAF inhibition				
AZD6244 + erlotinib	NCT01229150	Ⅱ	Recruiting	KRAS WT or KRAS mutant
Dasatinib	NCT01514864	Ⅱ	Recruiting	Tumors harboring DDR2 mutation or inactivating B-RAF mutation
AKT inhibition				
MK-2206 + erlotinib	NCT01294306	Ⅱ	Recruiting	Progressed after initial response to erlotinib
MEK inhibition				
GSK2118436	NCT01336634	Ⅱ	Recruiting	BRAF mutation (+)
HDAC inhibitor				
Vorinostat + gefitinib	NCT01027676	Ⅱ/Ⅲ	Recruiting	prior platinum-based chemo
Vorinostat + bortezomib	NCT00798720	Ⅱ	Completed recruiting	2 prior chemo
Belinostat + Bev + PC	NCT01090830	Ⅱ	Recruiting	Chemotherapy-naive
LBH589 + Pem	NCT00907179	Ⅱ	Recruiting	1 prior chemo
KRAS mutations				
AZD6244 + erlotinib	NCT01229150	Ⅱ	Recruiting	Prior platinum-based chemo
Erlotinib + ARQ197 *vs* single-agent chemo	NCT01395758	Ⅱ	Recruiting	KRAS mutation (+)
GSK1120212 *vs* docetaxel	NCT01362296	Ⅱ	Recruiting	KRAS mutation (+)

PC: Paclitaxel and carboplatin; Bev: Bevacizumab; Pem: Pemetrexed; NSCLC: Non-small cell lung cancer; chemo: Chemotherapy; WT: Wild-type; EGFR: Epidermal growth factor receptor; HDAC: Histone deacetylase inhibitor.

HER4 tyrosine kinases. Preclinical data showed activity for PF0299804 against EGFR mutations and T790M[61,65]. Two phase Ⅱ studies highlighted the agent's clinical antitumor effect, both in first-line therapy and in treatment-refractory settings. In the first of the studies, PF0299804 was compared with erlotinib[66]. That trial enrolled a range of molecular subgroups, including a group of patients with wild-type KRAS. In all subgroups, PF0299804 showed a PFS advantage (12.4 wk *vs* 8.3 wk; HR: 0.704; $P = 0.030$). In the second phase Ⅱ trial, dacomitinib demonstrated significantly improved PFS over erlotinib (2.86 mo for patients treated with dacomitinib and 1.91 mo for patients treated with erlotinib, HR: 0.66; 95%CI: 0.47-0.91; $P = 0.012$), with an acceptable toxicity. PFS benefit was observed in most clinical and molecular subsets, notably KRAS wild-type/EGFR any status, KRAS wild-type/EGFR wild-type, and EGFR mutants[67].

Afatinib: Afatinib has been shown to suppress the kinase activity of wild-type and activated EGFR, including erlotinib-resistant isoforms with the T790M mutation. The phase Ⅱb/Ⅲ LUX-Lung 1 randomized, double-blind trial examined best supportive care plus afatinib or placebo in patients in whom chemotherapy and a reversible EGFR inhibitor had failed. No difference in OS was observed; however, PFS was significantly improved with afatinib (3.3 mo *vs* 1.1 mo; HR: 0.38; 95%CI: 0.306-0.475; $P < 0.001$), as were tumor-related symptoms and QoL[68]. The most exciting clinical trial of afatinib in the acquired-resistance setting was a phase I b study in the United States and Netherlands. Patients who had progressed on erlotinib or gefitinib were given afatinib and cetuximab. Approximately 94% of patients, regardless of T790M mutation status, had a partial response or stable disease[69].

A number of phase Ⅱ trials continue to examine the safety and efficacy of afatinib as a second-line therapy. LUX-Lung 2 phase Ⅱ trial (NCT00525148) has completed enrollment of patients with activating EGFR mutations in whom first-line chemotherapy has failed. Similarly, LUX-Lung 4 phase Ⅰ/Ⅱ Japanese trial (NCT00711594) has completed accrual; results are awaited from this group of patients with first generation EGFR-TKI-resistant advanced NSCLC.

The phase Ⅲ LUX-Lung 3 trial reported the efficacy and safety data of first-line afatinib *vs* cisplatin and pemetrexed (PC) in patients with EGFR mutation-positive tumors. Treatment with afatinib led to a significantly prolonged PFS *vs* PC (median 11.1 mo *vs* 6.9 mo; HR: 0.58; 95%CI: 0.43-0.78; $P = 0.0004$). In 308 patients with common mutations (Del19/L858R), median PFS was 13.6 *vs* 6.9 mo, respectively (HR: 0.47; 95%CI: 0.34-0.65; $P < 0.0001$). ORR was significantly higher with afatinib (56%

vs 23%; $P < 0.0001$). Significant delay in time to deterioration of cancer-related symptoms of cough (HR: 0.60, $P = 0.0072$) and dyspnea (HR: 0.68, $P = 0.0145$) was seen with afatinib *vs* PC. Drug-related adverse events led to discontinuation in 8% (afatinib; 1% due to diarrhea) and 12% of patients (PC). Given the promising results of this pivotal trial, afatinib is now being compared with gefitinib as first-line treatment in patients with stage ⅢB/Ⅳ lung adenocarcinoma with EGFR activating mutations (LUX-Lung 7; NCT01466660).

Dual inhibitors

Increasing evidence has suggested that solid tumors have multiple salvage and resistance pathways that allow them to circumvent inhibition of a single signaling pathway[70]. In fact, EGFR is known to regulate the production of VEGF and other proangiogenic factors[71], and increased VEGF expression has been associated with resistance to EGFR inhibition in a human tumor xenograft model of NSCLC[72]. Thus, it is likely that blocking only one of these pathways will be insufficient for providing any meaningful therapeutic outcomes. Based on the logical strategy for improving anti-tumor efficacy by inhibition of multiple signaling pathways, a number of clinical trials are currently dual-inhibition strategies [*e.g.* mTOR, c-MET, PIK3CA, insulin-like growth factor 1 receptor (IGF-1R) or histone deacetylase (HDAC) inhibitor plus EGFR inhibitor].

Combination of EGFR and VEGF inhibitors: There have been promising results from combination of sorafenib with erlotinib. The combination has shown encouraging disease stabilizing effects with tolerable toxicity profiles[73-75]. In a randomized, double-blind, placebo controlled, phase Ⅱ trial in 168 patients with previously treated advanced NSCLC, sorafenib plus erlotinib was compared with erlotinib plus placebo. Overall, there were no significant differences in OS, PFS, or ORR between these two groups. However, in 67 patients with tumors bearing wild-type EGFR, sorafenib/erlotinib group showed a superior median PFS (3.38 mo in sorafenib/erlotinib group *vs* 1.77 mo in placebo/erlotinib group; $P = 0.018$) and a superior mean OS (8 mo for sorafenib/erlotinib *vs* 4.5 mo for placebo/erlotinib; $P = 0.019$)[74]. Another phase Ⅱ study evaluated sorafenib in combination with gemcitabine or erlotinib in 60 elderly patients with previously untreated advanced NSCLC[52]. ORR and median OS were 6.5% and 6.5 mo with sorafenib plus gemcitabine, and 10.3% and 12.6 mo with sorafenib plus erlotinib[75]. Similarly designed randomized phase Ⅱ/Ⅲ trials failed to show any improvement in OS from the addition of sunitinib to erlotinib (9.0 mo *vs* 8.5 mo with placebo plus erlotinib; HR: 0.922; 95%CI: 0.797-1.067)[74]. In a phase Ⅲ trial, the addition of bevacizumab to erlotinib suggested a non-significant OS benefit with the combined inhibition therapy in patients with EGFR-mutant tumors (median OS: 18 mo for bevacizumab plus erlotinib *vs* 12 mo for erlotinib; HR: 0.44; 95%CI: 0.11-1.67)[76].

A recent meta-analysis[77] evaluated the safety and efficacy of the combined inhibition of the VEGFR and EGFR signaling pathways with single-targeted therapy. Patients receiving combined inhibition therapy had a significant longer PFS than the group with single-targeted therapy (HR: 0.80; 95%CI: 0.67-0.95; $P = 0.011$). The combined therapy was associated with a non-significant 3% improvement in OS (HR: 0.97; 95%CI: 0.89-1.05; $P = 0.472$) confirming the previous studies. Also, no difference in the ORR between the study groups were detected (HR: 1.44; 95%CI: 0.95-2.18; $P = 0.085$). Subgroup analysis revealed that combined inhibition therapy using combination regimens was associated with statistically significant improvement in both ORR and PFS in the expense of increased toxicity in combined inhibition therapy. Currently, there is no evidence to support the use of combined inhibition of the VEGFR and EGFR signaling pathways in unselected patients with advanced NSCLC. Nonetheless, combined inhibition therapy may have a potential advantage in the treatment of advanced NSCLC compared with single inhibition therapy if the subsets of patients who may benefit from this treatment are well identified.

MET inhibitors: Investigation of resistance to current EGFR inhibitors has highlighted the role of the c MET/ALK pathway. MET amplification leads to EGFR-independent activation of the PI3K/Akt pathway through the activation of erbB3-dependent signaling and thereby could lead to EGFR inhibitor resistance[78,79]. Thus, combinations of EGFR and c-MET/ALK inhibitors hold potential for overcoming resistance[80].

The addition of c-MET inhibitor to erlotinib has demonstrated promising clinical activity in phase Ⅱ studies[81,82] when compared with erlotinib alone, particularly among patients with MET overexpression and non-squamous histology. The subset analyses of the trial by Spigel *et al*[82] suggested that METMab plus erlotinib was associated with increased PFS and OS as compared with erlotinib alone in patients with MET overexpression. In the study[81] comparing ARQ 197-209 (c-MET inhibitor) plus erlotinib *vs* erlotinib alone, a statistically significant improvement in OS was also found in non-squamous patients favoring ARQ 197-209 and erlotinib combination. In another randomized phase Ⅱ study[83] investigating second-line erlotinib with or without ARQ-197 in patients with advanced NSCLC, primary objective of the trial (PFS) was met in 167 patients (HR: 0.68, 95%CI: 0.47 to 0.98; $P < 0.05$) and the phase Ⅲ trial is ongoing[84]. Furthermore, albeit in a small subgroup of patients, that trial showed an advantage in terms of PFS for the combination of erlotinib and ARQ-197 in K-RAS-mutated, EGFR wild-type and c-MET amplified subjects.

HDAC inhibitors: The HDACs act to tighten the bond between histones and DNA, thus inhibiting gene transcription by blocking binding sites on promoters[55]. Inhibition of HDAC leads to induction of apoptosis in ma-

lignant cells[56]. Vorinostat is currently the furthest along in the development. A phase I trial (NCT00702572) with carboplatin, paclitaxel, bevacizumab and vorinostat for patients with advanced NSCLC is recruiting patients. A number of other phase I clinical trials to examine the effect of vorinostat with other targeted treatments including inhibitors of EGFR, mTOR, and a proteasome inhibitor, NP10052 are ongoing.

PI3K-AKT-mTOR inhibitors: One downstream mutation that has been described in lung cancers with acquired resistance to TKIs is in PIK3CA, a gene encoding a protein in the PI3K/AKT/mTOR pathway[85]. The PI3K/AKT pathway up-regulates mTOR in response to stimulation by growth factors[86]. Loss of inactivating mutations of phosphatase and tensin homolog (PTEN) results in a gain in function of the *PI3KCA* gene[87]. Phosphorylated AKT overexpression and loss of PTEN expression in NSCLC was shown to confer poor prognosis[88]. Phase Ⅱ study of everolimus (an oral mTOR inhibitor) plus erlotinib in previously treated patients with advanced NSCLC yielded a 11% difference in disease-control rate at 3 mo favoring the combination but did not meet the prespecified threshold to support a phase Ⅲ study[89]. Preclinical trials of PI3K inhibitors have shown efficacy, and research is ongoing[90,91]. A phase Ib trial is going to evaluate the combination of BYL719 (a selective inhibitor of PI3Kα) and the MEK inhibitor (MEK162). This international multicenter trial is not recruiting patients yet, but is expected to be completed by 2014 (NCT01449058).

IGF-1R inhibitors: Activation of the IGF-1R pathway has been noted as a consequence of EGFR inhibition in a variety of NSCLC cell lines, leading to cellular proliferation and evasion of apoptosis[92]. Studies have also documented heterodimerization of EGFR and IGF-1R in response to stimulation with either EGF or IGF-1, the ligands for the two receptors[91]. In a preclinical study, coinhibition of EGFR and IGF-1R resulted in synergistic growth inhibition of H1299NSCLCxenografts *in vivo* compared with treatment with erlotinib alone[93].

Unfortunately, the clinical studies have not been promising. A randomized phase Ⅱ study of erlotinib in combination with R1507 (a recombinant monoclonal antibody against IGF-1R) did not provide PFS or survival advantage over erlotinib alone in an unselected group of patients with advanced NSCLC[94]. The absence of therapeutic benefit with EGFR inhibitor in combination with an IGF-1R-targeted agent was further substantiated by other phase Ⅲ clinical trials[95,96]. The study evaluating the use of OSI-906 (IGF-1R TKI) in combination with erlotinib in patients with advanced NSCLC with activating mutations of the EGFR is ongoing but not actively recruiting patients (NCT01221077).

CONCLUSION

Recent research in NSCLC has focused on understanding the molecular abnormalities associated with NSCLC cell growth and proliferation and their impact on response to treatment and survival. In addition to histology, testing EGFR mutation and ALK rearrangement has now become the standard of care for treatment selection in NSCLC patients. However, only 20% of Western NSCLC patients have an activating EGFR mutation or ALK translocation[97]. Targetable molecular abnormalities have not yet been identified in approximately 80% of NSCLC patients. Multiple targeted agents, including monoclonal antibodies and receptor TKIs, are at various stages of development and hold promise. The results from ongoing trials will determine if the newer targeted agents will be incorporated into clinical practice.

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P- Reviewers Cadena MP, Vetvicka V
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World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
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doi:10.5306/wjco.v4.i2.43

World J Clin Oncol 2013 May 10; 4(2): 43-46
ISSN 2218-4333 (online)

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Statin a day keeps cancer at bay

Siddharth Singh, Preet Paul Singh

Siddharth Singh, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, United States
Preet Paul Singh, Department of Medical Oncology, Mayo Clinic, Rochester, MN 55905, United States
Author contributions: Both authors contributed equally to drafting the manuscript and approved the final version of the manuscript.
Correspondence to: Siddharth Singh, MD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States. singh.siddharth2@mayo.edu
Telephone: +1-507-5381231 Fax: +1-507-2840538
Received: February 20, 2013 Revised: March 28, 2013
Accepted: April 28, 2013
Published online: May 10, 2013

Abstract

In addition to cholesterol reduction, statins, currently the most commonly prescribed drug in the world, have been shown to have anti-neoplastic and immunomodulatory effects. Several observational studies and meta-analyses have shown reduction in risk of multiple cancers. More recently there has been an increasing interest in the potential role of statins as adjuvant therapy after cancer diagnosis and in modifying cancer mortality. Although post-hoc analyses of randomized controlled trials of statins for cardiovascular outcomes have not shown reduction in the risk of cancer mortality with statin use, these studies lack sufficient power to detect a significant difference in cancer outcomes. Recently, in a Danish nationwide population-based cohort study, Nielsen *et al* showed a 15% reduction in all-cause and cancer-specific mortality in statin users as compared to non-users. Improved survival with statin exposure was seen in 13/27 cancer subtypes, including the 4 most common cancers - lung, prostate, colorectal and breast. In this commentary, we examine this important study, review its implications and limitations, and briefly discuss impact of other drugs like metformin and aspirin that also exhibit anti-neoplastic effects.

Key words: Statins; Cancer; Mortality; Chemoprevention; Metformin

Core tip: With increasing economic burden of cancer care, cost-effective, preventive strategies are in focus. Commonly used drugs like statins, metformin and aspirin have been shown to have anti-neoplastic effects and are attractive candidates for cancer chemoprevention and reducing cancer-related mortality. Recently, in a Danish nationwide population-based cohort study, statin users had 15% reduction in all-cause and cancer-specific mortality as compared to non-users. These results are encouraging and show that statin use may be associated with reduced cancer mortality across different subgroups and cancer sites. However, several confounding variables remain, which merit further evaluation before this can change clinical practice.

Singh S, Singh PP. Statin a day keeps cancer at bay. *World J Clin Oncol* 2013; 4(2): 43-46 Available from: URL: http://www.wjgnet.com/2218-4333/full/v4/i2/43.htm DOI: http://dx.doi.org/10.5306/wjco.v4.i2.43

STATINS AND CANCER MORTALITY

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been used for primary and secondary prevention of cardiovascular diseases and currently are among the most commonly prescribed medications in the world. Besides cholesterol reduction, pre-clinical studies have shown that statins may exert anti-neoplastic effects, through both HMG-CoA reductase-dependent and HMG-CoA reductase-independent pathways. By competitive inhibition of HMG-CoA reductase, statins prevent post-translational prenylation of the Ras/Rho superfamily, which are important mediators of cell growth, differentiation and survival[1]. In addition, statins exert proapoptotic, antiangiogenic, and immunomodulatory

effects, which may prevent cancer growth[1,2]. Indeed, several observational studies and meta-analyses have shown that statin use may be associated with reduced risk of prostate cancer[3], hepatocellular cancer[4], gastric cancer[5] and esophageal cancer[6] but not others[7,8]. More recently, there has been greater interest in the potential role of statins in modifying cancer outcomes and mortality. Early data from post-hoc individual patient data meta-analysis of randomized controlled trials (RCTs) of statins for cardiovascular outcomes has not shown reduction in the risk of cancer mortality with statin use, but these studies are limited by short follow-up and insufficient power to detect a significant difference in cancer outcomes between placebo and statin group[9].

In the November issue of the *New England Journal of Medicine*, Nielsen *et al*[10] studied the relationship between statin use (prior to cancer diagnosis) and cancer-related mortality in the entire Danish population from 1995-2009 in adults > 40 years of age. Through record linkage between the Danish Registry of Medicinal Products Statistics (which records information on all drugs dispensed from Danish pharmacies), the Danish Cancer Registry (which tracks data on 98% of all incident cancers in Denmark) and the Danish Register of Causes of Death, in 1072503 person-years of follow-up on 295925 patients with incident cancer, they observed 195594 deaths, of which 162067 were cancer-related. As compared to statin non-users, patients using statins prior to cancer diagnosis were 15% less likely to die from any cause [adjusted hazard ratio (HR): 0.85; 95%CI: 0.83-0.87] or cancer specifically (adjusted HR: 0.85; 95%CI: 0.82-0.87). On evaluating risk of death from 27 individual cancers comparing 18721 statin users and 277204 statin non-users, they observed improved survival with statin exposure for 13 cancers, including the 4 most common cancers - lung (adjusted HR: 0.87; 95%CI: 0.83-0.92), colorectal (adjusted HR: 0.79; 95%CI: 0.75-0.85), prostate (adjusted HR: 0.81; 95%CI: 0.75-0.88) and breast (adjusted HR: 0.88; 95%CI: 0.80-0.99). The hazard ratios for cancer death in statin users ranged from 0.64 (95%CI: 0.46-0.88) for cervical cancer to 0.89 (95%CI: 0.81-0.98) for pancreatic cancer. These results were stable across a nested 1:3 matched case-control study of statin users *vs* statin non-users with matching for sex, age at cancer diagnosis, cancer type and year of diagnosis to adjust for the evolving cancer treatments and increasing use of statins over the follow up period. Their robust study design adjusted for multiple confounding factors including age at diagnosis, sex, level of education, residential area, cancer stage, presence of cardiovascular disease or diabetes before cancer diagnosis and whether they received chemotherapy and/or radiotherapy. They also accounted for probability of prescribing statins through propensity score analysis.

Despite the comprehensive nature of the analysis and well thought out adjustments for confounding factors, several important limitations remain. Firstly, no data was available on smoking that affects cancer incidence and related mortality. Conceivably patients may stop smoking after starting statin for a recent acute myocardial infarction, which may favorably modify the relationship between statin use and mortality from smoking-related cancers. Secondly, the healthy user effect and the healthy adherer effect needs to be considered while interpreting the results of this study. Studies[11] have shown that doctors may selectively under-prescribe lipid-lowering agents to smokers or obese patients, because of their unhealthy lifestyle, both of which are associated with increased all-cause and cancer mortality[12,13]. Statin users are more likely to be health-conscious and be more compliant with cancer screening leading to early cancer detection and treatment, translating into improved survival. This may partially be addressed by the study adjusting for cancer stage (tumor size and spread to the lymphatic system), but as nearly one-third of the patients in the statin use group and three-quarters of the no-statin use group had missing data pertaining to tumor size and lymphatic spread, residual confounding cannot be completely excluded. Also, no data is provided in terms of incident cancers or mode of cancer diagnosis - it is plausible that more cancers in the statin users were detected on screening exams in asymptomatic individuals. Besides early diagnosis, statin use prior to cancer diagnosis may also reduce the risk of cancer metastases. *In vitro* studies have shown that lipophilic statin use may reduce the formation and spread of metastatic prostate colonies[14]. This reduction in the risk of cancer metastases has also been observed with aspirin use, and has been implicated in the early reduction in cancer deaths observed in trials of daily aspirin *vs* control[15].

Thirdly, the study does not take into account the potential for concomitant use of other drugs with known anti-proliferative activity and anti-neoplastic potential. Statin users in the study had a significantly higher proportion of patients with cardiovascular disease (70% *vs* 21%, $P < 0.001$) and diabetes mellitus (18% *vs* 3%, $P < 0.001$) and conceivably would have a disproportionately higher use of aspirin or metformin that could have led to significant confounding. The authors do report that a sensitivity analysis excluding patients with cardiovascular disease (which is the only indication for aspirin use with statins in Denmark) produced results similar to the main finding, which adjusts for the impact of aspirin use. Aspirin as well as anti-diabetic medications like metformin use has been associated with reduced cancer-related mortality[15-18] and cancer risk[19-21]. In a post-hoc individual patient data meta-analysis of 51 RCTs, aspirin users were 15% less likely to die from cancer (OR = 0.85; 95%CI: 0.76-0.96), with a more profound effect seen with > 5 years of aspirin use (OR = 0.63; 95%CI: 0.49-0.82)[22]. Aspirin may inhibit cancer cell proliferation and promote apoptosis through cyclo-oxygenase 2 (COX2) mediated and COX2 independent effects[23]. Likewise, metformin use may improve colorectal cancer mortality in observational studies[17], with its anti-neoplastic effects being mediated by activation of adenosine monophosphate-activated protein kinase and consequent inhibition of the

mammalian target of rapamycin pathway, a downstream effector of growth factor signaling which is frequently activated in malignant cells[24]. In addition, metformin may also inhibit cell growth and promote cell senescence by inhibiting cyclin D1 expression and pRb phosphorylation[25].

Additionally, while Nielsen *et al* identified a consistent reduction in mortality across various cancer types and various sub-groups of patients, there was no clear dose-response relationship with statin use. The reduction in all-cause mortality was similar in patients with defined daily dose of statins of 0.01-0.75 (HR: 0.82; 95%CI: 0.81-0.85), 0.76-1.50 (HR: 0.87; 95%CI: 0.83-0.89) and > 1.50 (HR: 0.87; 95%CI: 0.81-0.91). This partially could be accounted for by the increased cardiovascular mortality of patients who were on higher defined daily dose of statins, however, there was similar lack of gradient even for cancer-related mortality. This could be secondary to a threshold effect but based on Hill's criteria for causality, presence of a biological gradient or dose-response effect helps to strengthen a causal association. Moreover, they have not explored the potential effects of statins as adjuvant therapy after cancer diagnosis and this merits further evaluation. Lastly, as 97% of their study population was comprised of white persons of Danish descent, their results are not generalizable to other ethnic populations, especially in United States.

In conclusion, statins are gaining traction for multiple non-cardiac indications including cancer. The results of this large nationwide observational study are encouraging and show that statin use may be associated with reduced cancer mortality across different subgroups and cancer sites. However, there are several confounding variables which merit further evaluation and it still is a long way from changing clinical practice. Although cancer risk and mortality have been studied in secondary analyses of many RCTs to assess the efficacy of statins for cardiovascular indications[9,26,27], clinical trials evaluating cancer as primary outcome are lacking. Well-designed, prospective, randomized trials of statins with cancer incidence or mortality as the primary endpoint are needed to confirm or refute these findings. These must take into account various other factors that tend to cluster in statin users and may independently modify cancer risk. Certainly, focusing on high risk populations or patients with pre-existing cancer may be a first step towards the right direction. Nonetheless, as we await data from ongoing RCTs where statins are being investigated for primary cancer prevention (NCT01500577), preventing recurrent cancer (NCT01011478) or reduced cancer mortality when combined with conventional chemotherapy for different cancers (NCT00433498 and NCT01238094), Nielsen *et al*' notable data moves us probably another step closer to broadening recommendations for statin use. Statins as well as other commonly used and safe drugs like metformin and aspirin may cause a paradigm shift in how we approach cancer prevention and treatment in the years to come.

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P- Reviewer Vetvicka V **S- Editor** Wen LL
L- Editor A **E- Editor** Xiong L

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
wjco@wjgnet.com
doi:10.5306/wjco.v4.i2.47

World J Clin Oncol 2013 May 10; 4(2): 47-51
ISSN 2218-4333 (online)

BRIEF ARTICLE

Combined chemo-radiotherapy in locally advanced nasopharyngeal carcinomas

Francesco Perri, Giuseppina Della Vittoria Scarpati, Carlo Buonerba, Giuseppe Di Lorenzo, Francesco Longo, Paolo Muto, Concetta Schiavone, Fabio Sandomenico, Francesco Caponigro

Francesco Perri, Francesco Caponigro, Head and Neck Medical Oncology Unit, National Tumor Institute of Naples, 80131 Naples, Italy
Giuseppina Della Vittoria Scarpati, Medical Oncology Unit, Hospital of Salerno, 84090 Salerno, Italy
Carlo Buonerba, Giuseppe Di Lorenzo, Medical Oncology Unit, University Federico II of Naples, 80131 Naples, Italy
Francesco Longo, Otolaryngology Unit, National Tumor Institute of Naples, 80131 Naples, Italy
Paolo Muto, Concetta Schiavone, Fabio Sandomenico, Radiotherapy Unit, National Tumor Institute of Naples, 80131 Naples, Italy
Author contributions: Perri F, Della Vittoria Scarpati G and Buonerba C designed the research; Perri F, Della Vittoria Scarpati G, Buonerba C, Di Lorenzo G, Longo F, Muto P, Schiavone C, Sandomenico F and Caponigro F contributed to the acquisition of data; Perri F and Buonerba C contributed to the analysis of data, drafting and revising the article; all authors approved the final version of the paper.
Correspondence to: Francesco Perri, MD, Head and Neck Medical Oncology Unit, National Tumor Institute of Naples, Via Mariano Semmola 80131 Naples, Italy. francesco.perri80@alice.it
Telephone: +39-815-903362 Fax: +39-815-903822
Received: February 14, 2013 Revised: March 30, 2013
Accepted: April 13, 2013
Published online: May 10, 2013

Abstract

AIM: To provide efficacy and safety data about the combined use of radiotherapy and chemo-radiotherapy in nasopharyngeal carcinoma (NPC).

METHODS: We reviewed data of 40 patients with locally advanced NPC treated with induction chemotherapy followed by concomitant chemo-radiotherapy (CCRT) (22/40 patients) or CCRT alone (18/40) from March 2006 to March 2012. Patients underwent fiberoscopy with biopsy of the primitive tumor, and computed tomography scan of head, neck, chest and abdomen with and without contrast. Cisplatin was used both as induction and as concomitant chemotherapy, while 3D conformal radiation therapy was delivered to the nasopharynx and relevant anatomic regions (total dose, 70 Gy). The treatment was performed using 6 MV photons of the linear accelerator administered in 2 Gy daily fraction for five days weekly. This retrospective analysis was approved by the review boards of the participating institutions. Patients gave their consent to treatment and to anonymous analysis of clinical data.

RESULTS: Thirty-three patients were males and 7 were females. Median follow-up time was 58 mo (range, 1-92 mo). In the sub-group of twenty patients with a follow-up time longer than 36 mo, the 3-year survival and disease free survival rates were 85% and 75%, respectively. Overall response rate both in patients treated with induction chemotherapy followed by CCRT and in those treated with CCRT alone was 100%. Grade 3 neutropenia was the most frequent acute side-effect and it occurred in 20 patients. Grade 2 mucositis was seen in 29 patients, while grade 2 xerostomia was seen in 30 patients. Overall toxicity was manageable and it did not cause any significant treatment delay. In the whole sample population, long term toxicity included grade 2 xerostomia in 22 patients, grade 1 dysgeusia in 17 patients and grade 1 subcutaneous fibrosis in 30 patients.

CONCLUSION: Both CCRT and induction chemotherapy followed by CCRT showed excellent activity in locally advanced NPC. The role of adjuvant chemotherapy remains to be defined.

Key words: Nasopharyngeal carcinoma; Induction chemotherapy; Concurrent chemoradiotherapy; Adjuvant chemotherapy; Locally advanced disease

Core tip: Clinical data of 40 patients (33 males, 7 females) with locally advanced nasopharyngeal carcinoma (NPC) treated at two participating institutions from March 2006 to March 2012 were reviewed. Patients received either induction chemotherapy followed by concomitant chemo-radiotherapy (CCRT) (22/40 patients) or CCRT alone (18/40). Patients underwent fiberoscopy with biopsy of the primitive tumor, and a computed tomography scan of the head, neck, chest and abdomen with and without contrast. Cisplatin was used both as induction and as concomitant chemotherapy, while 3D conformal radiation therapy was delivered to the nasopharynx and node areas (total dose, 70 Gy). A complete response rate of approximately 95% was achieved both in patients treated with induction chemotherapy followed by CCRT and in those treated with CCRT alone. In the sub-group of twenty patients with a follow-up time longer than 36 mo, the 3-year survival and disease free survival rates were 85% and 75%, respectively. These results showed that both CCRT and induction chemotherapy followed by CCRT have excellent activity in locally advanced NPC. The role of adjuvant chemotherapy remains to be defined.

Perri F, Della Vittoria Scarpati G, Buonerba C, Di Lorenzo G, Longo F, Muto P, Schiavone C, Sandomenico F, Caponigro F. Combined chemo-radiotherapy in locally advanced nasopharyngeal carcinomas. *World J Clin Oncol* 2013; 4(2): 47-51 Available from: URL: http://www.wjgnet.com/2218-4333/full/v4/i2/47.htm DOI: http://dx.doi.org/10.5306/wjco.v4.i2.47

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a rare malignancy that arises from the epithelium of the nasopharynx. It is particularly frequent in Southeast Asia and can be classified into three histological types, namely nonkeratinizing squamous cell carcinoma, keratinizing squamous cell carcinoma and undifferentiated carcinoma[1,2]. NPC presents several features that differentiate it from other head and neck carcinomas, such as its prognosis and its association with the Epstein-Barr virus (EBV)[3]. While radiotherapy alone is associated with a 5-year disease free survival (DFS) of 95/100% in patients with early stage disease (T1,2aN0M0), locally advanced disease requires combined use of chemotherapy and radiotherapy[4-6]. Two large meta-analysis studies showed superiority of concurrent chemo-radiotherapy (CCRT) compared to radiotherapy alone[7,8]. The role of adjuvant chemotherapy remains controversial. A significant survival advantage was reported for CCRT followed by adjuvant chemotherapy with respect to radiotherapy alone in some trials[9,10], but it was not confirmed by others[11]. Neoadjuvant chemotherapy also appears to be a feasible option, since it may control subclinical metastatic foci, especially patients with locally advanced disease (T4b and/or N2/3). Although several phase Ⅱ and Ⅲ trials of induction chemotherapy followed by radiotherapy have been carried out, no conclusive evidence in favor of its efficacy is presently available[12-15].

In this retrospective analysis, we reviewed data of 40 patients with locally advanced NPC treated with induction chemotherapy followed by CCRT or CCRT alone .

MATERIALS AND METHODS

Patients selection

Data regarding patients with a histologically confirmed diagnosis of locally advanced NPC (T2bN0M0-T4bN3M0) and treated with chemotherapy and radiotherapy from March 2006 to March 2012 at the participating Institutions, were retrieved from reviewed charts. Patients underwent fiberoscopy with biopsy of the primitive tumor, and computed tomography (CT) scan of head, neck, chest and abdomen with and without contrast. A 18-fluoro-2-deoxy-*D*-glucose positron emission tomography (FDG-PET) scan was performed in selected patients according to the physician's judgment.

Treatment plan

Patients were treated with the either induction chemotherapy followed by CCRT (22 patients) or with CCRT alone (18 patients). Several cisplatin-based regimens were used for induction chemotherapy (Table 1). After induction chemotherapy, a CT scan of head, neck, chest and abdomen and a fiberoscopy were performed for re-staging. Patients receiving CCRT were treated with cisplatin (100 mg/m^2 on days 1, 22 and 43) and 3D conformal radiation therapy, which was administered concurrently in cycle 1.

The nasopharynx and other relevant anatomic regions were included in the treatment plan. Gross tumor volume (GTV), clinical target volumes (CTVs), planning target volume and planning organ at risk volumes were defined for each patient according to the reports 50 and 62 of the International Committee on Radiation Units and Measurements. The CTV-T included the GTV-T, the posterior third of the nasal cavity, the maxillary sinuses, the inferior sphenoidal body, the clivus and the pterygoid fossae. CTV-N was defined as the volume encompassing GTV-N (if macroscopic nodal metastases were present) and bilateral cervical lymph node stations (levels Ib-V), the medial supraclavicular fossae and retro/parapharyngeal spaces. In order to account for set-up errors and patient movements, two sets of planning target volumes were also defined by adding a 5 mm margin to each corresponding CTV. A total dose of 70 Gy was planned. The treatment was performed using 6 MV photons of the linear accelerator administered in 2 Gy daily fraction for five days weekly. In all patients, an electron beam boost (8-10 MeV) was administered to limit the dose to spinal cord. Late toxicity was graduated according to the Radiation Therapy Oncology Group guidelines for toxicity.

Response assessment

Patients underwent a fiberoscopy and a FDG-PET scan 60-90 d after radiotherapy, while a CT scan of head,

Table 1 Patients characteristics

Characteristic	Patients
Total	40
Male	33
Female	7
Age, yr, median (range)	60 (24-82)
Stage	
Ⅱb	3
Ⅲ	18
Ⅳa	15
Ⅳb	4
ECOG performance status	
0	36
1	4
2	0
Treatment performed induction CT followed by	
CCRT[1]	22
CCRT[2]	18
Total	40
Induction chemotherapy scheme	
PF[3]	9
TPF[4]	3
TP[5]	9
BMC[6]	1
Total	22
Total radiation dose delivered	
70 Gy	36
68 Gy	3
66 Gy	1
Histology squamous cell	
G1	1
G2	2
G3	4
Undifferentiated	33

[1]Induction chemotherapy followed by concomitant chemo-radiotherapy; [2]Concurrent chemoradiotherapy; [3]Cisplatin (100 mg/m^2 every 3 wk) and 5-fluorouracil (5-FU) (1000 mg/m^2 per day, 4-d continuous infusion every 3 wk); [4]Docetaxel (75 mg/m^2 every 3 wk), cisplatin (75 mg/m^2 every 3 wk) and 5-FU (750 mg/m^2 per day, 4-d continuous infusion every 3 wk); [5]Docetaxel (75 mg/m^2 every 3 wk) and cisplatin (75 mg/m^2 every 3 wk); [6]Bleomycin (25 mg/m^2 on days 1 and 8 of a 21-d cycle), methotrexate (35 mg/m^2 weekly) and cisplatin (80 mg/m^2 every 3 wk). ECOG: Eastern Cooperative Oncology Group; CT: Computed tomography.

neck, chest and abdomen with and without contrast was performed 45-50 d after completion of radiotherapy. The response evaluation criteria in solid tumors criteria were used to define response.

This retrospective analysis was approved by the review boards of the participating institutions. Patients gave their consent to treatment and to anonymous analysis of clinical data.

RESULTS

Patients characteristics

Forty patients (33 males and 7 females) were included in this analysis. Median age was 60 years (range, 24-82 years). The majority of patients had an undifferentiated carcinoma (33 patients, 82.5%) and a stage Ⅲ-Ⅳ disease (37 patients, 92.5%). Patients' characteristics are detailed in Table 1.

Table 2 Results *n* (%)

Treatment performed	Results
ORR	40 (100)
Total (all group)	
Induction chemotherapy followed by	
CCRT[1] group	22 (100)
CCRT[2] group	22 (100)
CR rate	
Induction chemotherapy followed by	38 (95)
CCRT[1] group	21 (95.5)
CCRT[2] group	17 (94.4)
3-yr OS	
Total (all group)	17 (85)
3-yr DFS	
Total (all group)	15 (75)

[1]Induction chemotherapy followed by concomitant chemoradiotherapy; [2]Concurrent chemoradiotherapy. ORR: Overal response rate; CR: Complete response; OS: Overall survival; DFS: Disease free survival.

Response rate

All patients were evaluable for response after completion of the planned treatment. In patients receiving induction chemotherapy followed by CCRT, overall response rate (ORR) to induction chemotherapy was 90.9% (20/22), with a complete response (CR) rate of 36.4% (8/22). In this sub-group, after completion of chemoradiotherapy, ORR was 100% with a CR rate of 95.5% (21/22). In the CCRT only group, an ORR of 100% was obtained, with a CR rate of 94.4% (17/18).

Survival

Median follow-up time was 58 mo (range, 1-92 mo). At the time of the analysis, no patient had been lost to follow-up, six had died for the disease, twenty-eight were disease free, and the remaining six patients were alive with recurrent/persistent disease.

In the sub-group of 20 patients with a follow-up period > 3 years (12 treated with induction chemotherapy followed by CCRT, 8 treated with CCRT only), the 3 year overall survival and DFS rate were respectively 85% (17/20) and 75% (15/20). These results are detailed n Table 2.

Toxicity

Grade 3 neutropenia was the most frequent acute side-effect and it occurred in 20 patients. Grade 2 mucositis was seen in 29 patients, while grade 2 xerostomia was seen in 30 patients. Overall toxicity was manageable and it did not cause any significant treatment delay. In the whole sample population, long term toxicity included grade 2 xerostomia in 22 patients, grade 1 dysgeusia in 17 patients and grade 1 subcutaneous fibrosis in 30 patients.

DISCUSSION

NPC is highly chemo and radiosensitive, and an excellent disease control can be achieved using combined modal-

ity chemoradiation even in patients with locally advanced disease[1,2]. Presently, the benefit of adding neoadjuvant/adjuvant chemotherapy remains to be defined. Three large phase Ⅲ trials confirmed the superiority of CCRT followed by adjuvant cisplatin and 5fluorouracil *vs* radiotherapy alone[9-11]. Interestingly, a combined analysis of two large studies (NPC-9901 and the NPC-9902) revealed that the dose of cisplatin during the CCRT had a significant impact on locoregional control[16,17]. Despite patients included in this retrospective study did not receive adjuvant chemotherapy, a CR rate of approximately 95% a 3-year DFS rate of approximately 75% were obtained. These results are in line with published data and highlight the need of further phase Ⅲ trials to assess the role of adjuvant therapy.

One possible way to select better patients suitable for an adjuvant approach may be assessment of plasma EBV DNA levels. In fact, several data showed that EBV DNA levels correlated significantly with tumor load, recurrence rate and survival[18,19]. An early post-CCRT detection of high EBV DNA levels may be an indication to administer adjuvant chemotherapy.

One strategy to further improve the efficacy of chemotherapy is to use induction chemotherapy followed by radiation therapy alone or CCRT. Induction chemotherapy is generally better tolerated than adjuvant chemotherapy and might provide early eradication of distant micro-metastases[3], especially in patients with locally advanced disease (T4 and/or N2/3). In addition, induction chemotherapy could shrink the primary tumor to give wider margins for irradiation. In several phase Ⅱ clinical trials, induction cisplatin-taxane containing chemotherapy followed by radiotherapy or chemo- radiotherapy has been employed, with a median ORR of 94% and a 3-year DFS of 81%[20-22]. These results are in line with those reported here. One interesting strategy may include selection of NPC patients who are more likely to benefit from chemotherapy. Human papilloma virus positivity, high Ki-67 value, absence of p53 mutation are strongly related to chemo and radiosensitivity in head and neck squamous cell carcinomas[23,24]. These factors should be explored in NPC also.

Patients included in this retrospective analysis received 3D conformal radiation therapy. Of note, intensity-modulated radiation therapy (IMRT) can improve dose conformity for complex tumor targets and is able to obtain a better protection of adjacent organs[25,26]. It is likely that IMRT will become the standard technique employed for head and neck malignant tumors.

In conclusion, our study confirms that concurrent chemoradiotherapy represents the standard treatment for patients with locally advanced NPC. The role of adjuvant chemotherapy following CCRT is not well defined and requires to be investigated in phase Ⅲ trials. Assessment of EBV DNA titers in patients treated with CCRT may be helpful to select patients requiring adjuvant chemotherapy.

COMMENTS

Background

Nasopharyngeal carcinoma (NPC) is a rare malignancy that has several distinct features with respect to other head and neck tumors. While radiotherapy alone is associated with a 5-year disease free survival of 95/100% in patients with early stage disease (T1, 2aN0M0), locally advanced disease requires combined use of chemotherapy and radiotherapy.

Research frontiers

Adjuvant and neoadjuvant chemotherapy may have a role for the treatment of locally advanced NPC.

Innovations and breakthroughs

Three large phase Ⅲ trials confirmed the superiority of concurrent chemotherapy and radiotherapy followed by adjuvant chemotherapy *vs* radiotherapy alone in NPC.

Applications

Results obtained in this retrospective review confirm the effectiveness of combined use of chemotherapy and radiotherapy in locally advanced NPC. The role of adjuvant chemotherapy remains to be ascertained.

Terminology

Epstein-Barr virus is a virus of the herpes family that is best known as the cause of infectious mononucleosis, but it is also associated with human malignancies, such as NPC and lymphomas. Intensity-modulated radiation therapy is an advanced type of radiation therapy that uses multiple small radiation beams of varying intensities to radiate a tumor in a precise way. It is considered to be more accurate than 3D conformal radiation therapy.

Peer review

The article is a retrospective study about the efficacy of induction chemotherapy in the context of chemoradiotherapy for locally advanced NPC and serves to confirm what has been published in several large studies and in some meta-analysis.

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P- Reviewer Araújo AM **S- Editor** Gou SX
L- Editor A **E- Editor** Xiong L

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
wjco@wjgnet.com
doi:10.5306/wjco.v4.i2.52

World J Clin Oncol 2013 May 10; 4(2): 52-57
ISSN 2218-4333 (online)

BRIEF ARTICLE

Non-AIDS-related Kaposi's sarcoma: A single-institution experience

Pasquale Rescigno, Rossella Di Trolio, Carlo Buonerba, Gaia De Fata, Piera Federico, Davide Bosso, Antonella Virtuoso, Michela Izzo, Tania Policastro, Luca Vaccaro, Gianfranco Cimmino, Francesco Perri, Elide Matano, Mario Delfino, Sabino De Placido, Giovannella Palmieri, Giuseppe Di Lorenzo

Pasquale Rescigno, Rossella Di Trolio, Carlo Buonerba, Piera Federico, Davide Bosso, Antonella Virtuoso, Michela Izzo, Tania Policastro, Luca Vaccaro, Francesco Perri, Elide Matano, Sabino De Placido, Giovannella Palmieri, Giuseppe Di Lorenzo, Genitourinary Cancer Section and Rare-Cancer Center, Medical Oncology Division, University Federico II, 80131 Napoli, Italy

Gaia De Fata, Gianfranco Cimmino, Mario Delfino, Department of Dermatology, University Federico II of Naples, 80131 Napoli, Italy

Author contributions: Rescigno P, Di Trolio R and Di Lorenzo G contributed to the conception and design; Di Trolio R, Buonerba C, De Fata G, Federico P, Bosso D, Virtuoso A, Izzo M, Policastro T, Vaccaro L, Cimmino G, Perri F, Matano E, Delfino M and Palmieri G contributed to the acquisition of data; Buonerba C performed the statistical analysis; Rescigno P, Buonerba C, De Placido S and Di Lorenzo G contributed to drafting and revising the article; all authors approved the final version for publication.

Correspondence to: Giuseppe Di Lorenzo, MD, PhD, Genitourinary Cancer Section and Rare-Cancer Center, Medical Oncology Division, University Federico II, Via S. Pansini 5, 80131 Napoli, Italy. giuseppedilorenzoncol@hotmail.com
Telephone: +39-81-7463660 Fax: +39-81-7463660

Received: February 21, 2013 Revised: March 29, 2013
Accepted: April 9, 2013
Published online: May 10, 2013

Abstract

AIM: To evaluate the outcomes and potential prognostic factors in patients with non-acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma (KS).

METHODS: Patients with histologically proven non-AIDS-related KS treated with systemic chemotherapy were included in this retrospective analysis. In some cases, the human herpes virus 8 status was assessed by immunohistochemistry. The patients were staged according to the Mediterranean KS staging system. A multivariable model was constructed using a forward stepwise selection procedure. A P value < 0.05 was considered statistically significant, and all tests were two-sided.

RESULTS: Thirty-two cases were included in this analysis. The average age at diagnosis was 70 years, with a male/female ratio of approximately 2:1. Eighty-four percent of the cases had classic KS. All patients received systemic chemotherapy containing one of the following agents: vinca alkaloid, taxane, and pegylated liposomal doxorubicin. Ten patients (31.5%) experienced a partial response, and a complete response was achieved in four patients (12.4%) and stable disease in sixteen cases (50%). Two patients (6.2%) were refractory to the systemic treatment. The median progression-free survival (PFS) was 11.7 mo, whereas the median overall survival was 28.5 mo. At multivariate analysis, the presence of nodular lesions (*vs* macular lesions only) was significantly related to a lower PFS (hazard ratio: 3.09; 95%CI: 1.18-8.13, P = 0.0133).

CONCLUSION: Non-AIDS-related KS appears mostly limited to the skin and is well-responsive to systemic therapies. Our data show that nodular lesions may be associated with a shorter PFS in patients receiving chemotherapy.

Key words: Kaposi's sarcoma; Human herpes virus 8; Paclitaxel; Pegylated liposomal doxorubicin; Vinblastine

Core tip: Non-acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma (KS) is usually relatively benign, with an indolent disease course. It appears to be highly responsive to a wide variety of chemotherapy agents, including pegylated liposomal doxorubicin, vinca-alkaloids, etoposide and taxanes. However, fac-

tors predictive of progression-free survival are lacking. In our series of 32 patients with non-AIDS-related KS, we showed that presence of nodular lesions (*vs* macular lesions only) was associated with a 3-fold increased risk of progression. If confirmed by further studies, such a finding may be useful to improve the therapeutic strategy for this disease at the individual level.

Rescigno P, Di Trolio R, Buonerba C, De Fata G, Federico P, Bosso D, Virtuoso A, Izzo M, Policastro T, Vaccaro L, Cimmino G, Perri F, Matano E, Delfino M, De Placido S, Palmieri G, Di Lorenzo G. Non-AIDS-related Kaposi's sarcoma: A single-institution experience. *World J Clin Oncol* 2013; 4(2): 52-57 Available from: URL: http://www.wjgnet.com/2218-4333/full/v4/i2/52.htm DOI: http://dx.doi.org/10.5306/wjco.v4.i2.52

INTRODUCTION

Kaposi's sarcoma (KS) is a multifocal angioproliferative disorder of the vascular endothelium that usually presents itself with multiple vascular, cutaneous and mucosal nodules[1].

The four described clinical variants, *i.e.*, classic, endemic, iatrogenic and epidemic KS, show a distinct natural history and prognosis[2], but all share a causal relationship with human herpes virus 8 (HHV-8)[3]. Infection with this virus is a necessary condition, but it is not sufficient alone to cause KS, highlighting how genetic and angiogenic factors and the production of several inflammatory cytokines play a role in the multistep pathogenesis of KS[4].

As KS can be considered to be an opportunistic tumour, the restoration of immune competence is associated with remission in organ transplant recipients[5] and in acquired immune deficiency syndrome (AIDS)-related KS[6]. In classic KS, the cause of the underlying immunodeficiency is more difficult to identify and therefore to target by treatment.

Classic KS is a rare and mild form of the disease, primarily affecting men over 50 years old in endemic areas[7]. Lesions present themselves as purplish-red pigmented nodules on the legs and arms and tend to spread to more proximal sites[8]. The reported male-to-female ratio is 17:1[9]. Patients with classic KS have a greater risk to develop solid or haematopoietic neoplasms[10].

Iatrogenic KS is associated with the use of corticosteroids and other immunosuppressive agents[11]. The duration of immunosuppressive therapy does not seem to affect the risk of KS[12]. Iatrogenic KS more frequently involves the lymph nodes and viscera compared with classic KS[1,2].

The definition of the therapeutic strategy for KS depends on a number of factors, which include the location and variant of the KS, the pace of disease progression, the presence and severity of the symptoms (*e.g.*, pain and oedema), the number of lesions, the degree of host immune competence and comorbidities[2,7,13].

We present data about the treatment, response and outcome of 32 patients with non-AIDS-related KS treated with chemotherapy at our institution from January 2008 to December 2012.

MATERIALS AND METHODS

A retrospective review study of patients who received systemic treatment for classic or iatrogenic KS from January 2008 to December 2012 at the Division of Dermatology and Oncology of University Hospital Federico Ⅱ, Naples was performed. Informed consent for the anonymous publication of the data was obtained for all patients.

Patients who had histologically proven KS lesions of the skin and were negative for human immunodeficiency virus (HIV)-1/2 by macro enzyme immunoassay were included in this study. The histologic diagnosis required the presence of proliferative miniature vessels and tumour-like fascicles composed of spindle cells and a vascular network[1,2]. The HHV-8 status was assessed by immunohistochemistry using a monoclonal antibody against the latent nuclear antigen 1. Positivity for HHV-8 confirmed but was not strictly necessary for the diagnosis.

The tumour staging was performed with an ultrasound of the abdomen and the superficial lymph nodes, a chest X-ray and/or a whole body computed tomography scan. An esophagogastroduodenoscopy and rectosygmoidoscopy were performed in fit patients. Demographic features, such as origin, age at onset and gender, of the patients were retrieved. Data regarding the type, response and duration of the first systemic treatment delivered at our Institution and its related progression-free survival (PFS), overall survival (OS), comorbidities, number and extent of lesions and the presence of complications, such as lymphoedema, haemorrhage, pain, functional impairment and ulcerations, were also extracted from a review of the charts. The staging was performed according to criteria by Brambilla *et al*[14].

Five levels of the response to treatment were defined according to the revised World Health Organization criteria[15]: complete response, major response, minor response, stable disease and progression. All levels were based on the number of lesions: complete response, 100% resolution of the lesions; major response, > 50% to < 100% decrease; minor response, > 25% to < 50% decrease; stable disease, < 25% decrease to < 25% increase; and progression, > 25% increase in the number of lesions or worsening of the tumour-associated pain/oedema. Cox proportional hazards regression was used to investigate the prognostic factors of PFS and OS. A multivariable model was constructed using a forward stepwise selection procedure. A P value < 0.05 was considered statistically significant, and all tests were two-sided. All results are considered hypothesis-generating and require independent validation.

Table 1 Patient characteristics *n* (%)

	Patients number
Sex	
Male	21 (65.6)
Female	11 (34.4)
Comorbidities	
Diabetes	6 (18.7)
Alzheimer's	2 (6.3)
Hypertension	15 (46.9)
Kaposi variant	
Classic	27 (84.3)
Iatrogenic	5 (15.6)
Anatomic site	
Limbs	24 (75)
Limbs and trunk	5 (15.6)
Scrotum	1 (3.1)
Glans	1 (3.1)
Lymph node involvement	1 (3.1)
Number of lesions	
1	0
2	0
3	0
> 3	32 (100)
Stage	
Stage Ⅱb	18 (56.2)
Stage Ⅲ-Ⅳ	14 (43.7)

Table 2 Chemotherapy agents employed in the sample population *n* (%)

	Patients number
Sytemic treatment[1]	
Vinblastine	17 (53.1)
Pegylated liposomal doxorubicin	8 (25)
Paclitaxel	5 (15.6)
Gemcitabine	1 (3.1)
Vinorelbine	1 (3.1)
Overall number of lines of systemic treatment received by the patient	
1 line	26 (81.2)
> 1 line	6 (18.8)

[1]The first systemic treatment delivered at our institution is reported.

Table 3 Response to treatment *n* (%)

Response	
Complete response	4 (12.4)
Partial response	10 (31.5)
Stable disease	16 (50)
Progressive disease	2 (6.2)
Progression-free survival, mo (range)	11.7 (3-48)
Overall survival, mo (range)	28.5 (12-48)

Disease control rate is 93.7%.

RESULTS

Thirty-two cases of non-AIDS-related KS were included in this study. The mean age at diagnosis was 70 years. Twenty-one patients (65.6%) were male, and 11 (34.4%) were female, with an approximate male:female ratio of 2:1. All patients were Italian. With respect to the clinical subtype, 27 (84.3%) cases of classic KS and five cases (15.6%) of iatrogenic KS were included in this analysis. Of note, two patients with classic KS suffered from tumour-induced immunosuppression: one had B-cell lymphoma, and the other presented with Good's syndrome associated with a thymic epithelial tumour[16].

In particular, three patients were on immunosuppressive therapy due to an autoimmune disease (rheumatoid arthritis or systemic lupus erythematosus). The medication used included systemic corticosteroids and cyclosporin A. Two patients were on systemic corticosteroids due to severe chronic obstructive pulmonary disease. All 25 cases tested for HHV-8 were positive.

In 90.6% (n = 29) of the cases, the KS was limited to the skin. One patient (3.1%) presented mucosal lesions of the glans, and another case had axillary lymph node invasion. The KS lesions were multiple (> 3) in all patients (n = 32). The patient characteristics are detailed in Table 1.

All patients received systemic chemotherapy. The most frequently used drugs were vinblastine, pegylated liposomal doxorubicin (PLD) and paclitaxel. One patient (3.1%) affected by thymoma and KS received gemcitabine, capecitabine and immunoglobulins. The treatments that were administered are detailed in Table 2.

We obtained a disease control rate (93.8%), as shown in Table 3. The median PFS was 11.7 mo (range, 3-48 mo) (Figure 1), and the median OS was 28.5 mo (range, 12-48 mo) (Table 3).

Of note, the presence of nodular lesions was related to a lower PFS compared with macular lesions in both the univariate and multivariate analyses. The results of the Cox proportional hazard analysis are detailed in Table 4.

No death was directly related to KS. One patient, affected by Good's syndrome, died as a result of an opportunistic infection.

DISCUSSION

Classic KS is a rare disease. Its incidence is affected by factors such as sex, age and immune status. Interestingly, the geographic origin may affect the female to male ratio, as shown by the male to female ratio reported in our case series (2:1) and in a case series of 874 classic KS patients from 15 Italian Cancer Registries (3:2)[17], which appear to be markedly different from that reported in other studies conducted in distinct geographic areas[9,10].

Different routes of transmission have been hypothesised for HHV-8[17]. In addition to sexual transmission, a number of studies support a role for saliva as an infection route. The copy numbers of HHV-8 were higher in the saliva then in the semen in patients with and without KS, and these differences were independent of the HIV status. Oropharyngeal epithelial cells may harbour HHV-8 and facilitate its replication[18]. A potential role in HHV-8 transmission could be played by haematophagous insects (*e.g.*, malaria vector Anopheles, black flies, sand flies, biting midges and mosquitoes), which could explain

Table 4 Cox proportional hazard regression for progression-free survival

Characteristic	Hazard ratio (95%CI)	*P* value
Univariable		
Stage (Ⅱ *vs* Ⅲ/Ⅳ)	1.63 (0.74-3.57)	0.22
Cutaneous lesion (macules *vs* nodules)	3.09 (1.18-8.13)	0.01
Extent (lower limb only *vs* other parts of the body)	1.61 (0.72-3.59)	0.24
Symptoms (no *vs* yes)	0.72 (0.32-1.62)	0.44
Age	0.97 (0.93-1.01)	0.16
Sex (female *vs* male)	0.73 (0.32-1.69)	0.47
Multivariable		
Cutaneous lesion (nodular/papular/macules *vs* macules only)	3.09 (1.18-8.13)	0.013

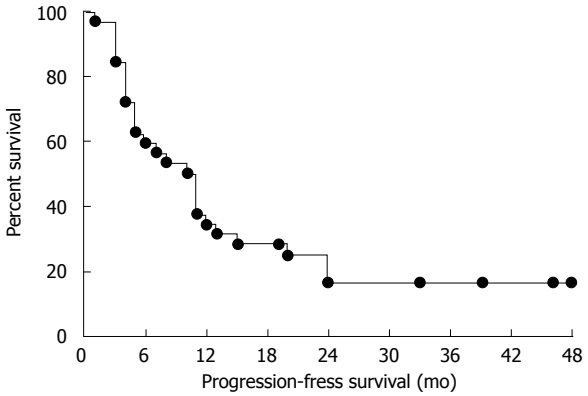

Figure 1 Kaplan-Meier plot of progression-free survival associated with the first line of systemic treatment delivered at our institution.

the high incidence in Italian areas where wetlands and swamps are widespread (*e.g.*, the Po delta and part of Sardinia) and malaria is epidemic[17]. Notably, the majority of our patients are elderly people from Campania, an area that used to be covered by wetlands.

Classic and iatrogenic KS mostly present themselves as multiple bilateral cutaneous lesions of the lower limbs[10]. We found that the lesions were multiple in 100% of the cases, as expected in a series of patients undergoing systemic treatment, and that the lesions involved the limbs in 75% of the cases. Only one patient with lymph-nodal disease was identified in our series.

One finding of interest was that the patients with nodular lesions appeared to display a more aggressive course of the disease, with an increased risk of progression compared with the patients with macular lesions in the multivariate analysis (hazard ratio: 3.09; 95%CI: 1.18-8.13; $P = 0.0133$). These data have not been reported previously in the literature.

A number of cytotoxic agents proved to be effective for the systemic treatment of recurrent, visceral, aggressive and widespread disease. These agents have not been tested in large, randomised-controlled trials[19]. The response rates (> 50% decrease in lesions) associated with the chemotherapy agents in classic KS ranged between 71% and 100% for PLD[20-22], 58% and 90% for vinca-alkaloids[23-25], 74% and 76% for etoposide[26], and 93% and 100% for taxanes[27,28]. Gemcitabine showed a response in 100% of the patients[29], and the combination of vinblastine and bleomycin was associated with a response rate of 97%[30].

All of these agents were employed in our patient population (PLD, vinca alkaloids, taxanes, and gemcitabine), with a remarkable overall disease control rate of 93.7%, which is in line with the literature data. At the time of the analysis, no patient had died as a direct consequence of KS, which confirmed the relatively benign behaviour of classic KS[31].

We performed immunohistochemical tests for HHV-8 staining on tissue samples of 25 patients (78.1%). All 25 patients (100%) were positive for infection.

These data suggest the high sensitivity of immunohistochemistry to detect HHV-8 infection, as previously reported in the literature[32].

In summary, in this study, KS nodular lesions appeared to be significantly associated with a decreased PFS in patients receiving chemotherapy. In sharp contrast to AIDS-related KS, classic and iatrogenic KS appear to have a more indolent course, being mostly limited to the skin and highly responsive to systemic therapeutic strategies.

The retrospective nature of this study and the small sample size mandate confirmation of our findings in further prospective trials.

ACKNOWLEDGMENTS

We thanks American Journal Experts for editing service.

COMMENTS

Background

Non-acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma (KS) usually displays an indolent course, with a relatively benign behaviour of the disease. It is generally highly responsive to chemotherapy agents, including pegylated liposomal doxorubicin, vinca-alkaloids, etoposide and taxanes. However, some patients show a more aggressive course of the disease.

Research frontiers

Factors predictive of progression-free survival associated with chemotherapy are lacking and are required in this rare disease.

Innovations and breakthroughs

The multivariate analysis performed in our series of 32 patients with non-AIDS-related KS showed that the presence of nodular lesions (*vs* macular lesions only) is associated with a 3-fold increased risk of progression.

Applications

If confirmed by further studies, the presence of nodular lesions may be incorporated into the clinical decision-making process for the definition of the therapeutic strategy for this disease on an individual level.

Terminology

Juman herpes virus 8 stands for human herpes virus 8, a large double-stranded DNA virus that is the causative agent of KS.

Peer review

The paper by Rescigno *et al* evaluates outcomes and potential prognostic factors in patients with classic and iatrogenic KS. In this study the authors retro-

spectively reviewed all cases of non-AIDS related KS treated at their institution from January 2008 to December 2012. One finding of interest was that patients with nodular lesions appeared to display a more aggressive course of the disease, with an increased risk of progression compared to patients with macular lesions at multivariate analysis (HR: 3.09; 95%CI: 1.18-8.13; $P = 0.0133$). These data were not reported before in literature. The paper is well written and of interest for readers.

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World J Clin Oncol 2013 May 10; 4(2): I-V
ISSN 2218-4333 (online)

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World Journal of Clinical Oncology

ISSN

ISSN 2218-4333 (online)

Launch date

November 10, 2010

Frequency

Quarterly

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Acknowledgments

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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