Efficacy and Safety of Selumetinib Compared with Current Therapies for Advanced Cancer: a Meta-analysis

Chen-Tian Shen, Zhong-Ling Qiu, Quan-Yong Luo*

Abstract

**Background and Aim:** Selumetinib is a promising and interesting targeted therapy agent as it may reverse radiiodine uptake in patients with radiiodine-refractory differentiated thyroid cancer. We conduct this meta-analysis to compare the efficacy and safety of selumetinib with current therapies in patients with advanced cancer. **Methods:** An electronic search was conducted using PubMed/Medicine, EMBASE and Cochrane library databases. Statistical analyses were carried out using either random-effects or fixed-effects models according to the heterogeneity of eligible studies. **Results:** Six eligible trials involved 601 patients were identified. Compared with current therapies, treatment schedules with selumetinib did not improve progression free survival (hazard ratio, 0.91; 95% CI 0.70–1.17, P = 0.448), but did identify better clinical benefits (odds ratio, 1.24; 95% CI 0.69–2.24, P = 0.472) and less disease progression (hazard ratio, 0.72; 95% CI 0.51–1.00, P = 0.052) though its impact was not statistically significant. Sub-group analysis resulted in significantly improved progression free survival (hazard ratio, 0.61; 95% CI 0.49–0.75, P = 0.00), clinical benefits (odds ratio, 3.04; 95% CI 1.60–5.77, P = 0.001) and reduced disease progression (hazard ratio, 0.35; 95% CI 0.18–0.67, P = 0.001) in patients administrated selumetinib. Dermatitis aciform (risk ratio, 9.775; 95% CI 3.143–30.395, P = 0.00) and peripheral edema (risk ratio, 2.371; 95% CI 1.690–3.327, P = 0.00) are the most frequently observed adverse effects associated with selumetinib. **Conclusions:** Compared with current chemotherapy, selumetinib has modest clinical activity as monotherapy in patients with advanced cancer, but combinations of selumetinib with cytotoxic agents in patients with BRAF or KRAS mutations hold great promise for cancer treatment. Dermatitis aciform and peripheral edema are the most frequently observed adverse effects in patients with selumetinib.

**Keywords:** MEK1/2 inhibitor - selumetinib - advanced cancer - meta-analysis

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Introduction

The mitogen-activated protein kinases (MAPKs) are important signal transducing enzymes, evolutionarily conserved, which respond to various extracellular stimuli and play critical roles in a vast number of fundamental cellular processes including growth, proliferation, differentiation, motility, stress response, survival, apoptosis and angiogenesis via a series of phosphorylation events and protein-protein interactions (Shaull et al., 2007; Raman et al., 2007; Pimienta et al., 2007; Krishna et al., 2008). MAPK activity is regulated through three-tiered cascades composed of MAPK, MAPK kinase (MAPKK, MMK or MEK) and MAPKKK kinase or MEK kinase (MAPKKK or MEKK) (English et al., 1999). Four distinctly regulated groups of MAPKs have been identified and been named according to their MAPK module, namely extracellular signal-related kinases (ERK)-1/2, Jun amino-terminal kinases (JNK1/2/3), p38 proteins (p38α/b/g/d) and ERK5, all of which are activated by specific MAPKKs: MEK1/2 for ERK1/2, MKK3/6 for the p38 kinases, MKK4/7 (JNK1/2) for the JNKs, and MEK5 for ERK5 (Robinson et al., 1997; Schaeffer et al., 1999; Chang et al., 2001).

MEK1 and MEK2, closely related, are dual specificity enzymes that phosphorylate threonine and tyrosine residues (in the activation sequence Thr-Glu-Tyr of ERK1/2) within the activation loop of their MAP kinase substrates (Pearson et al., 2001). Their key position within the Ras/Raf/MEK/ERK signal cascades (Wortzel et al., 2011), which is one of the most frequently disregulated pathways involved in the process of human tumorigenesis (Peyssonnaux et al., 2001), provides a strong rationale for the development of small molecule inhibitors of MEK1/2 in the treatment modality of human cancer. Several MEK1/2 inhibitors have been identified, studied and have progressed to clinical trials since the first MEK inhibitor (PD098059) was described in the literature in 1995 (Dudley et al., 1995). MEK1/2 inhibitors have shown clinical benefits in the treatment of many types of malignancy and trametinib has been approved for use in patients with metastatic melanoma by the United States Food and Drug Administration (Wright and McCormack, 2013). Currently, thirteen MEK inhibitors (trametinib, selumetinib, PD-0325901, MEK162, among others.) have been tested clinically (Akinleye et al., 2013). Among them,
the MEK1/2 inhibitor, selumetinib is the most frequently studied drug that has demonstrated activity in preclinical models in a variety of tumors and recently a study (Ho et al., 2013) published in the New England Journal of Medicine made the authors interested in the new agent. Selumetinib (AZD6244, ARRY-142886, initially developed by Array BioPharma, Boulder, CO) is an orally available, potent, selective, allosteric, ATP-uncompetitive (they do not directly compete for the ATP–binding site) inhibitor of MEK1/2 (Yeh et al., 2007) and several randomized clinical trials have been conducted to evaluate the effectiveness and adverse effects of selumetinib in patients with advanced cancer. Most of these trials are characterized by a small sample size, with inadequate statistical power to exclude potentially clinically relevant differences in efficacy, and as a result, whether selumetinib should be the treatment of choice for patients with advanced cancer is still unknown. To our knowledge, to date there has been no meta-analysis with a greater statistical power conducted to compare treatment agents and detect differences.

In the current meta-analysis we attempted to analyze and combine the results of all eligible randomized trials to increase statistical power and investigate whether selumetinib is more effective than current chemotherapy in the treatment of patients with advanced cancer.

Materials and Methods

Literature search to identify related studies

A search for human trials without language restrictions in the bibliographic databases PubMed/MEDLINE and EMBASE was conducted using the terms “selumetinib”, “AZD6244”, “ARRY-142886”, “clinical trials” and “cancers” as well as text terms such as “efficacy” and “safety” to identify relevant information. We also carried out independent searches using the Cochrane library databases to ensure that no clinical trials were overlooked. The list of articles was supplemented through extensive crosschecking of the reference lists of all retrieved articles. Unpublished data and conference proceedings were not included.

Study selection

Two reviewers (ZL Qiu and CT Shen) independently assessed the eligibility of each article. After screening all titles and reading the abstracts, the full text of the selected articles was reviewed to determine their eligibility for inclusion in the study and any discrepancy between the reviewers was resolved by consensus. The criteria for inclusion of the clinical trials were: (1) phase II and III randomized controlled trials (RCTs); (2) random assignment of participants to selumetinib or control treatments (placebo or concurrent therapy using a chemotherapeutic or biological agent); (3) trials that recorded necessary data about therapy efficacy and safety and (4) patients with a diagnosis of advanced cancer. Exclusion criteria were: (1) pharmaceuticals used were not MEK1/2 inhibitors, (2) studies used animal or cell cultures and (3) letters, abstracts, reviews, case reports, editorials and comments. The quality of each clinical trial was assessed and calculated using the Jadad scale including randomization (0–2 scores), blinding method (0–2 scores), withdrawals and dropouts (0–1 scores) (Moher et al., 1998).

Data extraction

Data extraction was conducted independently by two investigators (CT Shen and ZL Qiu) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). For each relevant study, collected data included the following: (1) basic information of each eligible study such as year of publication, journal name, and author name; (2) characteristics of patients such as median age, gender composition, tumor type; (3) information of study designation such as number of enrolled subjects, group sample size, and treatment regimen; (4) results of treatment such as complete response (CR), partial response (PR), stable disease (SD), overall survival (OS), disease progression, and median progression-free survival (PFS). To resolve disagreements between reviewers, a third reviewer (QY Luo) assessed all discrepant items and the majority opinion was used to choose studies for analysis. To evaluate the toxicity of selumetinib, the authors also calculated the number of the following adverse effects (AEs) reported in the safety profile section of each study: dermatitis aciform, peripheral edema, diarrhea, nausea, vomiting and fatigue. When available, all-grade (1–4) and high-grade (3–4) events provided in the studies were included in the analysis.

Statistical analysis

For each trial, the hazard ratio (HR) for PFS and disease progression, odds ratio (OR) for clinical benefits (the total of CR, PR and SD), and risk ratio (RR) for AEs were analyzed from the extracted data and 95% confidence intervals were derived. Heterogeneity analysis was performed by calculating the I² index, which was interpreted as low (25%), moderate (50%) and high heterogeneity (75%) (Higgins et al. 2003). It is reported that the I² index is an assessment not only of heterogeneity in a meta-analysis but also the extent of that heterogeneity, and as such it is considered a more appropriate procedure than Dixon’s Q test in assessing whether there is true heterogeneity among studies in a meta-analysis (Berlin, 1995; Huedo-Medina et al., 2006). For the meta-analysis, both fixed-effects (weighted with inverse variance) and random-effects models were considered. A random-effects model was chosen when heterogeneity was > 50%, while a fixed-effects model was chosen when heterogeneity was < 50% (DerSimonian and Laird, 1986). In addition, if any eligible study reported zero events in the treatment or control arm, continuity corrections with 0.5 were adopted to calculate the incidence and the OR (Robins et al., 1986). Publication bias was assessed using a standard funnel plot, and funnel plot asymmetry was further tested using Begg’s and Egger’s regression method (Copas and Shi, 2000). Forest plots were sorted according to first author’s name and year of publication to illustrate the HR, OR and RR. All statistical analyses were performed using Stata Version 12.0 software (Stata Corporation, College Station, TX).
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Table 1. Baseline Characteristics of Each Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Tumor type</th>
<th>Phase Enrolled</th>
<th>Patients per arm/n</th>
<th>Regimens</th>
<th>Median age/years</th>
<th>M/F</th>
<th>mPFS/d</th>
<th>OS/m</th>
<th>DP/n</th>
<th>SD/n</th>
<th>PR/n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennouna et al.</td>
<td>2010</td>
<td>CRC</td>
<td>II</td>
<td>69</td>
<td>34 selumetinib 100 mg</td>
<td>61.5</td>
<td>22/12</td>
<td>81</td>
<td>21</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35 capecitabine 1250 mg/m²</td>
<td>60</td>
<td>17/18</td>
<td>88</td>
<td>18</td>
<td>15</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40 selumetinib 100 mg</td>
<td>61.5</td>
<td>26/14</td>
<td>67</td>
<td>18</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>44 pemetrexed 500 mg/m²</td>
<td>63.5</td>
<td>27/17</td>
<td>90</td>
<td>18</td>
<td>21</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hainsworth et al.</td>
<td>2010</td>
<td>NSCLC</td>
<td>II</td>
<td>84</td>
<td>40 selumetinib 100 mg</td>
<td>57.1</td>
<td>55/49</td>
<td>-</td>
<td>40</td>
<td>48</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46 temozolomide 200 mg/m²</td>
<td>57</td>
<td>65/31</td>
<td>-</td>
<td>43</td>
<td>36</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Kirkwood et al.</td>
<td>2011</td>
<td>Melanoma</td>
<td>II</td>
<td>200</td>
<td>104 selumetinib 100 mg</td>
<td>57.1</td>
<td>55/49</td>
<td>-</td>
<td>40</td>
<td>48</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Bodoky et al.</td>
<td>2012</td>
<td>PC</td>
<td>II</td>
<td>70</td>
<td>38 selumetinib 100 mg</td>
<td>65</td>
<td>24/14</td>
<td>63</td>
<td>32</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32 capecitabine 1250 mg/m²</td>
<td>62</td>
<td>11/21</td>
<td>68</td>
<td>28</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Jänne et al.</td>
<td>2013</td>
<td>NSCLC*</td>
<td>II</td>
<td>87</td>
<td>44 selumetinib 75 mg+docetaxel</td>
<td>59.5</td>
<td>21/23</td>
<td>5.3m</td>
<td>9.4</td>
<td>8</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43 placebo+docetaxel</td>
<td>59</td>
<td>20/23</td>
<td>2.1m</td>
<td>5.2</td>
<td>18</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Robert et al.</td>
<td>2013</td>
<td>Melanoma#</td>
<td>II</td>
<td>91</td>
<td>45 selumetinib 75 mg+dacarbazine</td>
<td>57</td>
<td>22/23</td>
<td>5.6m</td>
<td>13.9</td>
<td>14</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46 placebo+dacarbazine</td>
<td>52</td>
<td>28/18</td>
<td>3m</td>
<td>10.5</td>
<td>24</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; NSCLC, non-small-cell lung cancer; PC, pancreatic cancer; d, day; m, month; M, male; F, female; mPFS, median progression-free survival; OS, overall survival; DP, disease progression; SD, stable disease; PR, partial response; *indicates NSCLC with KRAS mutation; #indicates melanoma with BRAF mutation; "_" indicates a parameter that was not reported in the trial.

Figure 1. Flow Chart Showing the Process of Study Selection

Results

Study characteristics

The current meta-analysis was carried out in accordance with the guidelines of PRISMA. The literature search identified 176 potentially relevant articles. After screening titles and abstracts, 157 irrelevant articles were excluded because they involved other treatment agents, duplicates, review articles, case reports, abstracts presented at meetings, letters or commentaries. Following a more detailed review, eleven articles were excluded because they are not RCTs. After reading the full text of the remaining eight studies, two papers were excluded as their purpose was to assess the tolerability, pharmacokinetics and pharmacodynamics of selumetinib. Finally six clinical trials (Hainsworth et al., 2010; Bennouna et al., 2011; Kirkwood et al., 2012; Bodoky et al., 2012; Jänne et al., 2013; Robert et al., 2013) involving 601 patients matched our inclusion criteria. The process of study selection is shown in a flow chart (Figure 1).

The baseline characteristics of each trial are shown in Table 1. These six RCTs were published between 2010 and 2013 and all of them were phase II clinical trials. In all, there were 601 patients (median age: 52–65 years) with a male to female ratio of 338 to 263 who were diagnosed with cancer at four sites, namely colorectal cancer (CRC), non-small-cell lung cancer (NSCLC), melanoma, and pancreatic cancer (PC). Most of the subjects were considered to require treatment but had failed to respond to previous chemotherapeutic regimens. The quality of the six included trials was high: two of them achieved Jadad scores of 5 and the others scored 3.

Publication bias

Several strategies were used in the study design to minimize the potential for publication bias. These were the extension of search strategy, strict inclusion criteria and the careful design of the analytic method (when analyzing the HR for PFS and disease progression, and the OR for clinical benefits, the eligible studies were divided into two sub-groups according to the particular mutation of the tumors). Publication bias was not found according to the funnel plot (Begg’s test, P = 0.707; Egger test, P = 0.997).

Efficacy

Progression-free survival: All of the eligible trials...
Table 2. Meta-analysis of All Grade AEs Comparing Selumetinib with Current Chemotherapies in Patients with Advanced Cancer

<table>
<thead>
<tr>
<th>Toxicity/all grade</th>
<th>Trials/n</th>
<th>Selumetinib</th>
<th>Current chemotherapy</th>
<th>Heterogeneity</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis acneiform</td>
<td>5</td>
<td>135/261 14/257</td>
<td>0.006 72.6</td>
<td>9.775 (3.143-30.395)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5</td>
<td>98/258 19/248</td>
<td>4.920 (2.926-8.274)</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Diarrhea</td>
<td>6</td>
<td>152/298 62/289</td>
<td>0.261 23.0</td>
<td>2.371 (1.690-3.327)</td>
<td>0.00</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>121/298 128/289</td>
<td>0.708 0.0</td>
<td>0.913 (0.676-1.234)</td>
<td>0.554</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>92/298 85/289</td>
<td>0.27 21.7</td>
<td>1.044 (0.743-1.467)</td>
<td>0.805</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>70/298 93/289</td>
<td>0.696 0.0</td>
<td>0.731 (0.513-1.041)</td>
<td>0.082</td>
<td></td>
</tr>
</tbody>
</table>

RR, risk ratio; CI, confidence interval

Discussion

The MAP kinase signaling pathway has been one of the most studied signaling pathways in human solid tumors with the molecular rationale that the RAF/MEK/ERK1/2 signaling pathway plays an essential role in cell proliferation and survival. It has been hypothesized that inhibition of this pathway leads to tumor growth inhibition and regression (Alnogueria et al., 1988; Smit et al., 1988; Messersmith et al., 2006; Wang et al., 2007), so until now plenty of small molecule compounds that may inhibit this pathway have been studied in vitro and in vivo (Frémin and Meloche, 2010).

Sorafenib was one of the first compounds aimed at targeting the RAF/MEK/ERK1/2 pathway, but its results were not as promising as expected (Flaherty et al., 2008; Flaherty et al., 2013). While MEK1/2 inhibitors have shown clinical benefits in the treatment of many types of malignancy, currently thirteen MEK inhibitors (trametinib, selumetinib, PD-0325901, and MEK162, among others) have been tested clinically and of these (Akinleye et al., 2013), selumetinib, which is a selective, non-ATP-competitive agent that blocks the MAP kinase-signaling cascade, is the most frequently studied drug. In addition to the cancer sites in the studies we analyzed in the current meta-analysis, there have been many other clinical studies estimating the clinical benefits of selumetinib in other types of malignancy including thyroid carcinoma (Ho et al.,...
Efficacy and Safety of Selumetinib Compared with Current Therapies for Advanced Cancer: a Meta-analysis

In conclusion, our meta-analysis demonstrated that compared with current chemotherapy, selumetinib, a MEK1/2 inhibitor, has modest clinical activity as monotherapy in patients with advanced cancer (patients in whom the specific mutations were not identified), but combinations of selumetinib with cytotoxic agents in patients with the BRAF or KRAS mutation can significantly improve PFS, clinical benefits and reduce disease progression. Dermatitis acniform and peripheral edema, both reversible and manageable, are the most frequently observed AEs in patients treated with selumetinib. Based on the findings in the current meta-analysis, the authors suggest that molecular testing (to identify the status of BRAF and RAS) can play a significant role in the selection of patients for treatment with selumetinib, and that combinations of selumetinib with cytotoxic or other biological agents show promise for the treatment of patients with advanced cancer.

Acknowledgements

The author(s) declare that they have no competing interests.

References


Bodoky G, Timcheva C, Spigel DR, et al (2012). A phase II open-label randomized study to assess the efficacy and power and improve estimates of any effects. However, several limitations had to be considered in the current meta-analysis. Firstly, four of the eligible trials lacked blinding, which might have resulted in an overestimate of the effects, although these trials were well randomized. Secondly, the differences in treatment schedules and malignancies lead to increased clinical heterogeneity, but it might improve generalizability due to the observed heterogeneity. Thirdly, the current meta-analysis was not based on individual patient data, another possible cause of an overestimate of the treatment effects. However, individual patient data-based analyses might include fewer studies if the authors did not agree to submit their full databases to the analyzing group. Finally, we performed subgroup-analysis according to specific mutations (BRAF and KRAS), but the limited data would potentially limit detection of the therapeutic effects.

In conclusion, our meta-analysis demonstrated that compared with current chemotherapy, selumetinib, a MEK1/2 inhibitor, has modest clinical activity as monotherapy in patients with advanced cancer (patients in whom the specific mutations were not identified), but combinations of selumetinib with cytotoxic agents in patients with the BRAF or KRAS mutation can significantly improve PFS, clinical benefits and reduce disease progression. Dermatitis acniform and peripheral edema, both reversible and manageable, are the most frequently observed AEs in patients treated with selumetinib. Based on the findings in the current meta-analysis, the authors suggest that molecular testing (to identify the status of BRAF and RAS) can play a significant role in the selection of patients for treatment with selumetinib, and that combinations of selumetinib with cytotoxic or other biological agents show promise for the treatment of patients with advanced cancer.

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safety of selumetinib (AZD6244 [ARRY-142886]) versus capcitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy. Invest New Drugs, 30, 1216-23.


