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ORIGINAL ARTICLE

Role of everolimus in the treatment of advanced neuroendocrine tumor: a meta-analysis of randomized trials

Ze-Guo Zhuo, Yun-Ke Zhu, Han-Yu Deng, Gang Li, Jun Luo, Gu-Ha Alai, Yi-Dan Lin

Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China.

Summary

Purpose: *There are two fundamentally groups of neuroendocrine neoplasms: neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs). Target therapy plays a quite important role in the treatment of NETs. However, whether everolimus (mTOR inhibitor) could improve the overall survival (OS) of NETs is contradictory and the efficacy of the agent in NETs from specific organ is lacking analysis. This meta-analysis enrolled the relevant published trials to see the results in a large sample size and further analyzed the efficacy of everolimus according to the tumor origin.*

Methods: *A systemic search was performed on four major medical databases and related studies were screened out of the result. All the works were done by two reviewers independently and then checked with each other.*

Results: *Finally, 5 articles and 4 conference abstracts from 3 trials were included. All of the trials indicated a statistically significant difference of progression free survival (PFS) in patients receiving everolimus. And the statistical differences remained significant when it came to the NETs from specific organ (overall HR=0.42, 95%CI 0.35, 0.51). As for OS, all the three trials showed no statistically significant difference between the experimental group (patients receiving everolimus) and control group (patients receiving placebo) and the pooled analysis also indicated no significant difference (HR=0.95, 95%CI 0.71,1.25, p=0.695).*

Conclusion: *Everolimus is effective in improving the PFS of NETs and the statistical difference remained significant when it came to the NETs from specific organs.*

Key words: *everolimus, mTOR inhibitor, meta-analysis, neuroendocrine tumor, NETs, target therapy*

Introduction

Neuroendocrine neoplasms are a heterogeneous group of malignancies originating from neuroendocrine cells in different organs [1,2]. They were first documented as a distinct class of neoplasms in 1907 [3]. Gastrointestinal tract, lung and pancreas are their predilection sites. Their management is a great challenge for clinicians because of their diverse clinical presentations and varying degree of aggressiveness. This may relate to an origin from different neuroendocrine progenitor cells [2]. Some of the neuroendocrine neoplasms are hormone-secreting which makes the disease even more challenging [4].

According to the differentiation grade, there are two fundamentally groups of neuroendocrine neoplasms (NEN). Well differentiated, low-proliferating NENs, called neuroendocrine tumors (NETs) or carcinoids, and poorly differentiated, highly proliferating NENs, called small-cell or large-cell neuroendocrine carcinomas (NECs) [5]. NECs are sensitive to platinum-based chemotherapies, but well-differentiated NETs have been shown to respond poorly [6]. So, target therapy plays a quite important role in the treatment of NETs. Everolimus and sunitinib have been approved by the US Food and Drug Administration (FDA) for the treat-

Correspondence to: Yi-Dan Lin, MD. Department of Thoracic Surgery, West China Hospital, Sichuan University, 37 Guoxue Alley, Chengdu 610041, China.
Tel: +86 18980602136, Fax: +86 28 2885422498, E-mail: linyidan.academy@foxmail.com
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ment of progressive, well-differentiated pancreatic NETs [7]. Everolimus is an mammalian target of rapamycin (mTOR) inhibitor. mTOR is an intracellular protein kinase that recognizes stress signals and regulates cell survival, proliferation and apoptosis [8,9]. The PI3K/AKT/mTOR pathway is constitutively activated in NETs [10]. The RANDANT trials [11-14] have firmly embedded everolimus in the management of patients with advanced NETs. However, whether everolimus could improve the overall survival (OS) is contradictory and the efficacy of the agent in NETs from specific organs is lacking analysis. Should the agent be recommended for NETs originating from lung or gastrointestinal tract? This meta-analysis enrolled the published trials to see the results in a large sample size and further analyzed the efficacy of everolimus according to the origin of tumor.

Methods

Search strategy

A systemic search was performed in the online databases PubMed, Medline, EMBASE and Cochrane library on 6th February 2018 using following terms: everolimus, mTOR inhibitor, RAD001, RAD SDZ, neuroendocrine tumor, NETs and carcinoid tumor. The last updating search was performed on 4th March 2018. We also screened the references of relevant articles to avoid missing any relevant studies that had not been included in these databases or could not be detected by our search strategy.

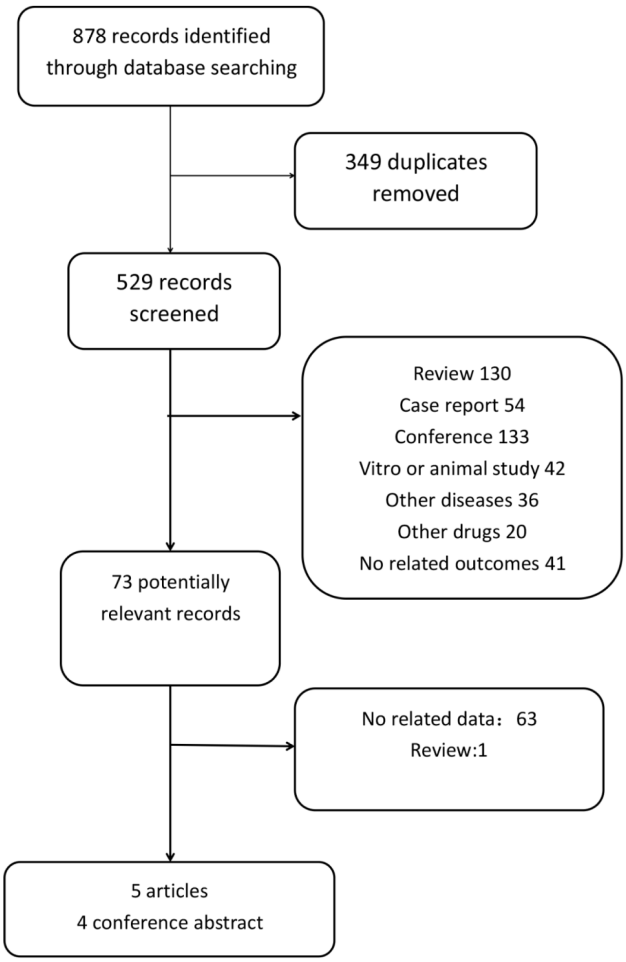

Figure 1. Flow chart showing the process of article selection.

Inclusion and exclusion criteria

Inclusion criteria: a) Studies focused on patients with neuroendocrine tumors; b) Everolimus was used as the major systemic treatment agent; c) Studies provided original data of related outcomes.

Exclusion criteria: a) The following types of articles were excluded: review, meta-analysis, case report, letter and reply; b) Not neuroendocrine tumor; c) Not everolimus-based treatment; e) The relevant data was unavailable.

The included studies should meet all of the inclusion criteria, and any study meeting any one of the exclusion criteria was excluded.

Article screening and quality assessment

The potential relevant studies were screened out of the searching result through reading titles and abstracts. Then, we read the full-texts and extracted the relevant data to finally confirm the studies included in the meta-analysis. All the work was done by two reviewers independently and then checked with each other. The disagreements were resolved by discussing with the third reviewer. The Jadad 5-item scale [15] was used to assess the quality of included trials.

Major outcomes

The major outcomes were progression free survival (PFS) and overall survival (OS). Other information such as study design, histologic type, treatments and tumor location were also collected.

Statistics

Data analysis was performed by STATA Version 12.0 software (Stata Corporation, College Station, TX, USA). Hazard ratio (HR) was used to compare the difference of PFS and OS between the experimental and control group. We used I^2 as the indicator of heterogeneity. $I^2<25\%$, $25\%\leq I^2<50\%$ and $I^2\geq 50\%$ indicated low, moderate and high heterogeneity. When high heterogeneity was detected, a random effects model was adopted. In the analysis of HR, Begg's and Egger's tests were used to detect publication bias. $P<0.05$ was considered to be statistically significant.

Results

Finally, 5 studies [12,13,16-18] from the initial 804 studies were included in the analysis. They were all from the RADIANT trials. The RADIANT-2 trial didn't focus on NETs from specific organ while the RADIANT-3 aimed at pancreatic NETs, and the

RADIANT-4 focused on NETs from gastrointestinal tract or lung. To make the best use of the limited trials, the data from related conferences [14,19-21] were also extracted. The studies screening procedures are presented in Figure 1. The baseline characteristics of the trials are shown in Table 1. These trials enrolled 1141 patients in total (628 in the experimental group, 513 in the control group). Fortunately, PFS and OS of the three trials were all obtained.

Survival data

All the three trials showed improvement on the PFS in the experimental group. The pooled analysis also indicated a statistically significant difference of everolimus in improving PFS (HR=0.51, 95%CI 0.31, 0.82, p=0.000). In the organ-specific analysis, a statistically significant difference between experimental and control group was also observed in NETs from specific organs (overall HR=0.42, 95%CI 0.35, 0.51, p=0.000, Figure 2). As for OS, all three trials showed no statistically significant difference between the experimental and control group and the pooled analysis also indicated no significant difference (HR=0.95, 95%CI 0.71,1.25, p=0.695). Unfortunately, the OS of specific organs was unavailable. So, the effect of everolimus in the OS of NETs from specific organ was impossible to analyze.

Heterogeneity and publication bias

Pooled analysis of PFS and OS showed a high heterogeneity (I^2 of PFS=88.8%, I^2 of OS=61.2%), so a random effect model was adopted. The organ-specific analysis of PFS according to the tumor origin greatly decreased the heterogeneity (I^2=32.8%).

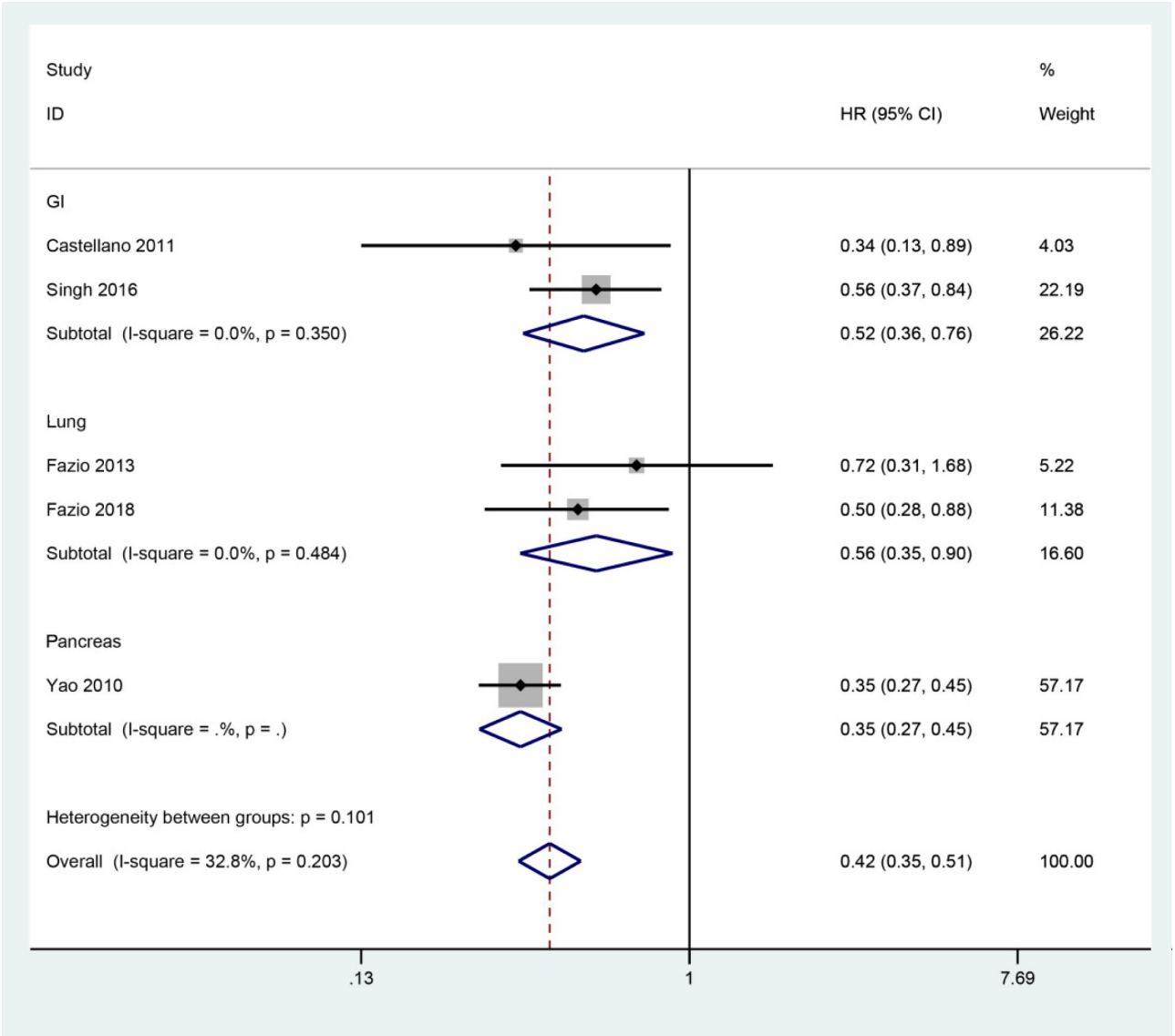

Figure 2. Site-specific analysis of everolimus in improving progression-free survival.
Overall I^2=32.8%. Overall HR=0.42 (95% CI 0.35, 0.51) favoring everolimus

Table 1. Characteristics of included trials

Characteristics	*RADIANT-2*	*RADIANT-3*	*RADIANT-4*
Design	RCT, double blind	RCT, double blind	RCT, double blind
Pathologic type	Well or moderately differentiated NETs	Low or intermediate grade pancreatic NETs	Well-differentiated, nonfunctional lung/GI NETs
Tumor stage	Metastatic or unresectable	Metastatic or unresectable	Metastatic or unresectable
Number of patients receiving everolimus (experimental group)	216	207	205
Number of patients receiving placebo (control group)	213	203	97
Treatment of experimental group	Everolimus + Octreotide LAR	Everolimus + Best supportive care	Everolimus + Best supportive care
Treatment of control group	Placebo + Octreotide LAR	Placebo + Best supportive care	Placebo + Best supportive care
PFS	HR=0.77 95%CI (0.59,1)	HR=0.35 95%CI (0.27,0.45)	HR=0.48 95%CI (0.35,0.67)
OS	HR=1.17 95%CI (0.92,1.49)	HR=0.94 95%CI (0.73,1.20)	HR=0.64 95%CI (0.40,1.05)
Jaded score	5	5	5

RCT: randomized controlled trial; PFS: progression free survival; OS: overall survival, HR: hazard ratio

This change came from the loss of data of some patients. Most of them were diagnosed with small intestine NETs (115 in the experimental group, 113 in the control group). What's more, the heterogeneity within a specific organ was extremely low. This strongly indicated the heterogeneity coming from the tumor location. No publication bias was detected.

Discussion

Despite the similarities of NETs, there are striking organ specific features of the disease [1]. NETs originate from different organs and are different from each other both in biological behavior and treatment sensitivity. Pancreatic NETs have a better response to target therapy than other non-pancreatic NETs [22]. The survival rates also vary greatly by tumor origin [23]. Our analysis also indicated that the heterogeneity was closely related to the origin of tumor. The I^2 of organ-specific analysis declined to 32.8% and the heterogeneity within the same organ was extremely low. It is reasonable and scientific to treat the tumor from different organs differently.

Due to the limited efficacy of traditional chemotherapy on NETs, target agents are widely applied in the treatment of this special disease. Except for everolimus, applied are also sunitinib, bevacizumab, pazopanib and sorafenib in the treatment of NETs [24]. Roviello et al. [22] collected related trials and summarized the role of target agents in the treatment of NETs. Their pooled analysis indicated improvements of PFS and OS in patients receiving target therapy. However, neither the single agent nor the tumors from specific organ were further analyzed.

Our study focused on everolimus and further analyzed the effects of the agent on tumors from specific organs independently. Differ from the mixing analysis of different agents, our results showed no improvement of OS in patients received everolimus. So we checked the efficacy of every single target agent in improving the OS to locate the source of the difference. It seemed that the trial of sunitinib [25] had a strong effect in improving the OS. When it was mixed with other studies, it covered the real effect of other agents.

All the three trials included in our analysis proved the efficacy of everolimus in improving the PFS of NET patients independently. What's more, the statistical difference remained significant in the analysis of NETs from different organs. So everolimus was effective in improving the PFS of NETs originating from lung and gastrointestinal tract besides pancreas. As for the OS, the conclusions of the trials were also identical. All of them showed everolimus could not improve OS. Although OS is regarded as the most important index of outcome for randomized trial in oncology [22], the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting consensus report recommended PFS as a primary endpoint for clinical studies in NETs [26]. The use of OS as the primary

endpoint is particularly challenging because of extended post-progression survival, use of a range of salvage therapies after progression, and the crossover study design [27,28]. Considering this, although everolimus failed to improve OS, its great value in improving PFS should be emphasized. Unfortunately, the data of OS for NETs from specific sites was unavailable. So further organ-specific analysis was impossible to perform.

Conclusion

Everolimus is effective in improving the PFS of NETs, and the statistical difference remained significant when it came to the NETs from specific organs. Although in our analysis we did our best to extract the data according to the tumor location, the sample size of NETs from specific organs was still too small. What's more, no study provided OS data of specific NETs. So we are unaware whether the efficacy of everolimus in OS differs from each other in NETs from different organs. Excluding patients with small intestine NETs in organ-specific analysis, the heterogeneity declined sharply. NETs originating from small intestine may be quite different from other NETs. More studies focusing on NETs from specific sites are in great need, especially concerning the data on the OS and the data about small intestine independently.

Author's contribution

Ze-Guo Zhuo and Yun-Ke Zhu collected data and drafted the manuscript. Gang Li and Jun Luo analyzed the data under the guidance of Han-Yu Deng. Gu-ha Alai found the full-texts of relevant studies. Yi-Dan Lin designed the study and revised the manuscript. All authors read and approved the final manuscript. We sincerely thank all the authors of the original articles for their efforts in this area.

Conflict of interests

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Conflict of interests

The authors declare no conflict of interests.

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