·论著·

瑞派替尼加量治疗晚期胃肠道间质瘤临床效果的全国多中心研究

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【摘要】　目的　探讨瑞派替尼加量治疗晚期胃肠道间质瘤（GIST）的临床效果。**方法**　采用回顾性描述性研究方法。收集2020年1月至2022年10月中山大学附属第一医院等全国12家医学中心收治的14例晚期GIST患者的临床病理资料；男9例，女5例；年龄为63（40~73）岁。患者均行瑞派替尼加量治疗。观察指标：（1）患者临床特征情况。（2）瑞派替尼治疗效果。偏态分布的计量资料以*M*（范围）表示。计数资料以绝对数表示。采用Kaplan-Meier法绘制生存曲线并计算生存时间。**结果**（1）患者临床特征情况。14例患者中，肿瘤原发部位在小肠、胃、其他分别为8、4、2例，肿瘤转移部位在肝脏、腹膜、骨、肺分别为13、9、4、2例（每例患者可发生>1种转移），转移肿瘤数目1~5个、6~10个、>10个分别为2、8、4例，有手术史或转移灶局部消融治疗11例，既往治疗线数≤2线、≥3线分别为3、11例，既往治疗药物采用伊马替尼、舒尼替尼、瑞戈非尼、阿伐替尼分别为14、13、9、2例（每例患者治疗药物可>1种）。14例患者均进行基因检测，KIT外显子11合并外显子13基因突变5例，KIT外显子11合并外显子17基因突变4例，KIT外显子11合并外显子13和17基因突变2例，KIT外显子9合并外显子17基因突变、KIT外显子11突变和野生型各1例；其中继发基因突变12例。（2）瑞派替尼治疗效果。14例患者均获得随访，随访时间为17.3（4.4~30.0）个月。①瑞派替尼标准四线治疗：14例患者均行瑞派替尼标准四线治疗，治疗持续时间为6.0（2.0~17.0）个月，完全缓解、部分缓解、疾病稳定分别为1、2、11例，客观缓解占比为3/14，疾病控制占比为14/14；中位无进展生存时间为6.0个月。14例患者中，11例发生1~2级不良事件，均未发生3~4级不良事件。②瑞派替尼加量治疗：14例患者行瑞派替尼标准四线治疗后均发生疾病进展，均行瑞派替尼加量治疗，其中12例行150 mg 2次/d治疗，2例行200 mg 1次/d治疗。治疗持续时间为5.2（1.5~12.0）个月。12例患者可进行疗效评估，部分缓解、疾病稳定、疾病进展分别为1、10、1例，客观缓解占比为1/12，疾病控制占比为11/12；中位无进展生存时间为11.0个月，中位总生存时间为23.0个月。12例患者中，10例发生1~2级不良事件，1例发生3级不良事件为贫血。③瑞派替尼联合治疗：14例患者行瑞派替尼加量治疗后，7例发生疾病进展，其中3例行瑞派替尼联合其他药物治疗，分别为瑞派替尼100 mg 1次/d联合伊马替尼200 mg 1次/d、瑞派

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替尼标准四线治疗联合舒尼替尼 25 mg 1 次/d、瑞派替尼标准四线治疗联合阿帕替尼 250 mg 1 次/d，无进展生存时间分别为 7 个月、5 个月、尚未评估。**结论**　瑞派替尼加量治疗可为晚期 GIST 患者带来生存获益，安全性良好。

【关键词】　胃肠道间质瘤；　瑞派替尼；　加量治疗；　疗效；　安全性

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Clinical efficacy of ripretinib dose escalation for the treatment of advanced gastrointestinal stromal tumors: a nationwide and multicenter study

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【Abstract】　**Objective**　To investigate the clinical efficacy of ripretinib dose escalation for the treatment of advanced gastrointestinal stromal tumors (GIST). **Methods**　The retrospective and descriptive study was conducted. The clinicopathological data of 14 patients with advanced GIST who were admitted to 12 medical centers, including The First Affiliated Hospital of Sun Yat-sen University *et al*, from January 2020 to October 2022 were collected. There were 9 males and 5 females, aged 63 (range, 40−73)years. All patients underwent ripretinib dose escalation treatment. Observation indicators: (1) clinical characteristics of patients; (2) clinical efficacy of ripretinib treatment. Measurement data with skewed distribution were represented as *M*(range), and count data were described as absolute numbers. The Kaplan-Meier method was used to draw survival curve and calculate survival time. **Results**　(1) Clinical characteristics of patients. Of the 14 patients, cases with primary tumor located at small intestine, stomach and others were 8, 4, 2, respectively, and cases with tumor metastasis to liver, peritoneum, bone and lung were 13, 9, 4, 2, respectively (one patient may experience more than one type of metastasis). Cases with number of metastatic tumor as 1−5, 6−10 and >10 were 2, 8, 4, respectively. There were 11 patients with a history of surgery or local ablation treatment for metastatic lesions. Cases with previous treatment lines as ⩽2 and ⩾3 were 3 and 11, respectively. Cases with previous treatment drugs as imatinib, sunitinib, regofinib and atorvatinib were 14, 13, 9 and 2, respectively (one patient may have more than one type of medication). All 14 patients underwent genetic testing, including 5 cases of KIT exon 11 combined with exon 13 gene mutation, 4 cases of KIT exon 11 combined with exon 17 gene mutation, 2 cases of KIT exon 11 combined with exon 13 and 17 gene mutation, 1 case of KIT exon 9 combined with exon 17 gene mutation, 1 case of KIT exon 11 mutation and 1 case of wild-type gene type. There were 12 cases with secondary gene mutations. (2) Clinical efficacy of ripretinib treatment. All 14 patients were followed up for 17.3(range, 4.4−30.0)months. ① Standard fourth-line treatment with ripretinib. All 14 patients underwent standard fourth-line treatment with ripretinib, with a treatment duration of 6.0(range, 2.0−17.0)months. Cases achieved complete remission, partial remission and stable disease were 1, 2, 11, respectively. The objective response ratio and disease control ratio were 3/14 and 14/14. The median progression-free survival time was 6.0 months. Of the 14 patients, 11 cases experienced grade 1−2 adverse events. None of patients had grade 3−4 adverse events. ② Ripretinib dose escalation therapy. With disease progression after standard fourth-line treatment with ripretinib, all 14 patients underwent ripretinib dose escalation therapy, including 12 cases received escalated therapy of 2 times of ripretinib in 150 mg daily and 2 cases received escalated therapy of one time of

ripretinib in 200 mg daily. The treatment duration was 5.2(range, 1.5−12.0)months. Twelve patients were evaluable for efficacy, and cases achieved partial remission, stable disease and disease progression were 1, 10, 1 respectively. The objective response ratio and disease control ratio were 1/12 and 11/12. The median progression-free survival time and median overall survival time were 11.0 months and 23.0 months. Of the 12 patients, 10 cases experienced grade 1−2 adverse events and 1 case experienced grade 3 adverse event of anemia. ③ Ripretinib combined therapy. Seven of the 14 patients had disease progression after ripretinib dose escalation therapy, and 3 of them underwent ripretinib combined with other drug treatments, including 1 case of one time of ripretinib in 100 mg daily combined with one time of imatinib in 200 mg daily, 1 case of ripretinib standard fourth-line treatment combined with one time of sunitinib in 25 mg daily, 1 case of ripretinib standard fourth-line treatment combined with one time of apatinib in 250 mg daily. The progression-free survival time of the 3 patients were 7 months, 5 months and not yet evaluated, respectively. **Conclusion** Ripretinib dose escalation therapy can bring survival benefit for patients with advanced GIST and has good safety.

【 **Key words** 】 Gastrointestinal stromal tumor; Ripretinib; Dose escalation therapy; Efficacy; Safety

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酪氨酸激酶抑制剂(tyrosine kinase inhibitors,TKIs)是晚期胃肠道间质瘤(gastrointestinal stroma tumor,GIST)靶向治疗的首选方案[1-8]。瑞派替尼是一种新型开关控制 TKIs,用于既往接受过≥3 种 TKIs 治疗的晚期 GIST 成人患者[9-13]。目前,在瑞派替尼治疗疾病进展后尚无获批的有效治疗药物[14-18]。2023 年 NCCN 及中国临床肿瘤学会指南均推荐瑞派替尼 150 mg 1 次/d 治疗作为晚期 GIST 标准四线治疗方案,瑞派替尼 150 mg 2 次/d 可作为标准四线治疗后的选择之一[19-21]。目前国内瑞派替尼加量治疗的临床经验及报道较少[22-23]。本研究回顾性分析 2020 年 1 月至 2022 年 10 月全国 12 家医学中心收治的 14 例(中山大学附属第一医院、中国医学科学院肿瘤医院各 2 例,江苏省肿瘤医院、中山大学孙逸仙纪念医院、山东省立医院、天津医科大学肿瘤医院、复旦大学附属肿瘤医院、海南省肿瘤医院、河北医科大学第四医院、中国人民解放军联勤保障部队第九〇〇医院、北京大学肿瘤医院、福建医科大学附属协和医院各 1 例)晚期 GIST 患者的临床病理资料,探讨瑞派替尼加量治疗晚期 GIST 的临床效果。

资料与方法

一、一般资料

采用回顾性描述性研究方法。收集 14 例晚期 GIST 患者的临床病理资料;男 9 例,女 5 例;年龄为 63(40~73)岁。本研究通过福建医科大学附属协和医院医学伦理委员会审批,批号为 2023KY232。免除患者知情同意。

二、纳入标准和排除标准

纳入标准:(1)病理学证实为 CD117 或 DOG1 阳性的晚期 GIST。(2)经瑞派替尼标准四线治疗进展后接受瑞派替尼加量治疗≥28 d。

排除标准:无法行安全性和有效性评估。

三、治疗方法

瑞派替尼标准四线治疗:瑞派替尼 150 mg 1 次/d 治疗。

瑞派替尼加量治疗:瑞派替尼 150 mg 2 次/d 治疗。

四、观察指标和评价标准

观察指标:(1)患者临床特征情况。(2)瑞派替尼治疗效果。

评价标准:总生存时间为患者自接受瑞派替尼标准四线治疗之日起至死亡时间。治疗反应按 RECIST v1.0 评估。

五、随访

采用门诊、电话等方式进行随访,了解患者生存情况。随访时间截至 2022 年 12 月 31 日或患者死亡。

六、统计学分析

应用 SPSS 27.0 统计软件进行分析。偏态分布的计量资料以 M(范围)表示。计数资料以绝对数表示。采用 Kaplan-Meier 法绘制生存曲线并计算生存时间。

结　果

一、患者临床特征情况

14 例患者中，肿瘤原发部位在小肠、胃、其他分别为 8、4、2 例，肿瘤转移部位在肝脏、腹膜、骨、肺分别为 13、9、4、2 例（每例患者可发生>1 种转移），转移肿瘤数目 1~5 个、6~10 个、>10 个分别为 2、8、4 例，有手术史或转移灶局部消融治疗 11 例，既往治疗线数≤2 线、≥3 线分别为 3、11 例，既往治疗药物采用伊马替尼、舒尼替尼、瑞戈非尼、阿伐替尼分别为 14、13、9、2 例（每例患者治疗药物可>1 种）。

14 例患者均进行基因检测，KIT 外显子 11 合并外显子 13 基因突变 5 例，KIT 外显子 11 合并外显子 17 基因突变 4 例，KIT 外显子 11 合并外显子 13 和 17 基因突变 2 例，KIT 外显子 9 合并外显子 17 基因突变、KIT 外显子 11 突变和野生型各 1 例；其中继发基因突变 12 例。

二、瑞派替尼治疗效果

14 例患者均获得随访，随访时间为 17.3（4.4~30.0）个月。

（一）瑞派替尼标准四线治疗

14 例患者均行瑞派替尼标准四线治疗，治疗持续时间为 6.0（2.0~17.0）个月，完全缓解、部分缓解、疾病稳定分别为 1、2、11 例，客观缓解占比为 3/14，疾病控制占比为 14/14；中位无进展生存时间为 6.0 个月（图 1）。

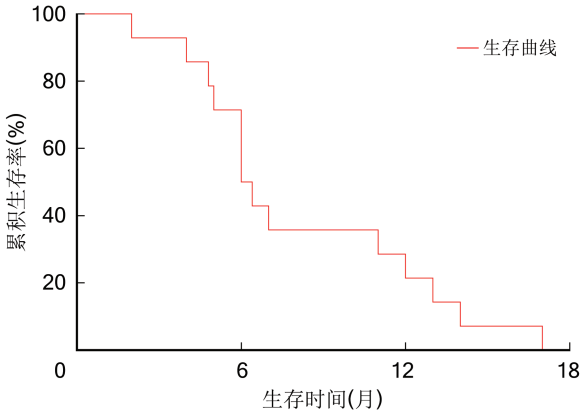

图 1　14 例行瑞派替尼标准四线治疗胃肠道间质瘤患者无进展生存曲线

Figure 1　Progression-free survival curve of 14 patients with gastrointestinal stromal tumors who underwent standard fourth-line treatment of ripretinib

14 例患者中，11 例发生 1~2 级不良事件，其中脱发、手足综合征、肌痛、乏力分别为 6、4、2、1 例（同 1 例患者可合并>1 种不良事件）；均未发生 3~4 级不良事件。

（二）瑞派替尼加量治疗

14 例患者行瑞派替尼标准四线治疗后均发生疾病进展，均行瑞派替尼加量治疗，其中 12 例行 150 mg 2 次/d 治疗，2 例行 200 mg 1 次/d 治疗。治疗持续时间为 5.2（1.5~12.0）个月。12 例患者可进行疗效评估，部分缓解、疾病稳定、疾病进展分别为 1、10、1 例，客观缓解占比为 1/12，疾病控制占比为 11/12；中位无进展生存时间为 11.0 个月（图 2），中位总生存时间为 23.0 个月（图 3）。

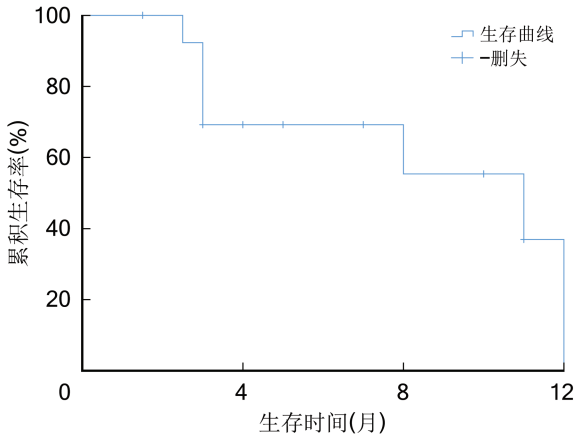

图 2　14 例行瑞派替尼加量治疗胃肠道间质瘤患者无进展生存曲线

Figure 2　Progression-free survival curve of 14 patients with gastrointestinal stromal tumors who underwent ripretinib dose escalation therapy

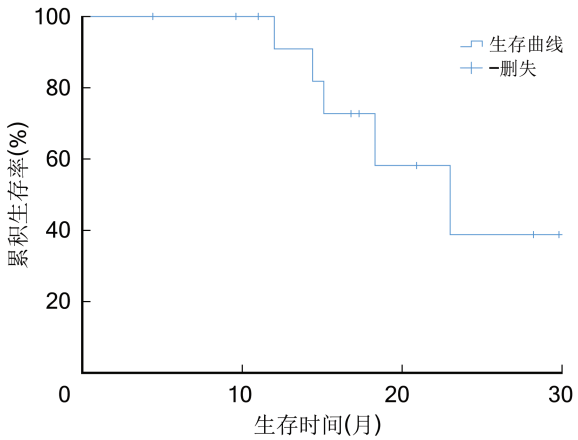

图 3　14 例行瑞派替尼加量治疗胃肠道间质瘤患者总生存曲线

Figure 3　Overall survival curve of 14 patients with gastrointestinal stromal tumors who underwent ripretinib dose escalation therapy

12 例患者中，10 例发生 1~2 级不良事件，其中脱发、肌痛、疲乏分别为 4、3、3 例；1 例发生 3 级不良事件为贫血。

（三）瑞派替尼联合治疗

14 例患者行瑞派替尼加量治疗后，7 例发生疾病进展，其中 3 例行瑞派替尼联合其他药物治疗，分别为瑞派替尼 100 mg 1 次/d 联合伊马替尼 200 mg 1 次/d、瑞派替尼标准四线治疗联合舒尼替尼 25 mg 1 次/d、瑞派替尼标准四线治疗联合阿帕替尼 250 mg 1 次/d，无进展生存时间分别为 7 个月、5 个月、尚未评估。

讨　论

国内外 GIST 诊断与治疗指南均推荐瑞派替尼加量治疗可作为晚期 GIST 标准四线治疗进展后的选择之一。本研究纳入 14 例行瑞派替尼标准四线治疗进展后再行瑞派替尼加量治疗的晚期 GIST 患者，是国内首次对真实世界中瑞派替尼加量治疗临床效果的分析。瑞派替尼标准四线治疗阶段的中位无进展生存时间为 6.0 个月，与既往研究数据相似[11-13]。而疾病进展后的加量治疗阶段，其中位无进展生存时间长达 11.0 个月，中位总生存时间为 23.0 个月，均优于既往报道的数据[23-27]。

较好的药物安全性与耐受性是患者接受瑞派替尼加量治疗的关键。本研究中，瑞派替尼标准四线治疗常见不良事件包括脱发、手足综合征、肌痛、疲乏，以 1~2 级为主；瑞派替尼加量治疗阶段，1 例患者发生 3 级不良事件为贫血。瑞派替尼标准四线治疗和加量治疗不良事件均临床可控。

FIH Ⅰ期研究和 INVICTUS Ⅲ期研究结果显示：行瑞派替尼加量治疗患者的中位无进展生存时间分别为 4.6 个月和 3.7 个月[19-20]。英国 1 项真实世界研究结果显示：瑞派替尼加量治疗患者中位无进展生存时间为 5.9 个月[26]。INVICTUS 国内桥接试验中，患者经瑞派替尼标准四线治疗发生疾病进展后，可行加量治疗，但加量治疗的临床结局尚未发布。本研究中，受经济因素的影响，部分患者未能接受足量治疗（2 例患者仅行 200 mg 1 次/d 治疗）。

瑞派替尼加量治疗进展后，联合其他 TKIs 治疗晚期耐药 GIST 的方案初见效果，可能为后线 GIST 患者提供新的治疗选择[28-29]。有研究结果显示：瑞派替尼单药治疗失败后的 10 例患者中，6 例行瑞派替尼联合其他 TKIs 治疗，获得 4.7 个月的无进展生存时间[30]。本研究中瑞派替尼加量治疗进展后，3 例患者进一步接受以瑞派替尼为基础的联合治疗方案，无进展生存时间约为 5 个月。这提示瑞派替尼联合其他 TKIs 治疗可延长晚期 GIST 患者的生存时间。

本研究的局限性：（1）未行瑞派替尼加量治疗效果的相关因素分析。（2）未探索可从瑞派替尼加量治疗中获益的患者特征。（3）瑞派替尼加量治疗进展后的后续治疗方案选择等问题。（4）样本量小。期待未来大样本量研究进一步探索其临床疗效。

综上，瑞派替尼加量治疗可为晚期 GIST 患者带来获益，安全性良好。

利益冲突　所有作者均声明不存在利益冲突

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