Comparison of efficacy and safety of corticosteroid and vincristine in treating Kaposiform hemangioendothelioma and tufted angioma: A Multiicenter Prospective Randomized Controlled Clinical Trial

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Abstract

Purpose: To evaluate and compare the efficacy of corticosteroid and vincristine (VCR) in the treatment of kaposiform hemangioendothelioma (KHE) and tufted angioma (TA). Methods: This was a multicenter prospective randomized controlled study. All patients with KHE/TA who meet the diagnostic criteria were included. The patients were randomized to methylprednisolone (MP) group and VCR group. The primary outcome was the single main parameter effective rate (SMPE) and overall effective rate (OE) of corticosteroid and VCR over one month after treatment. The single main parameters included platelets, fibrinogen, tumor size, texture and appearance. Results: In single main parameters, VCR was superior to corticosteroid in the relief of platelet (80.0% vs 44.0, P = 0.019) and tumor texture (68.9% vs 30.8%, P = 0.007). Although the efficacy of VCR on fibrinogen (23.3% vs 20.7%, P=1.000), tumor size (23.3% vs 13.8%, P=0.273) and appearance (65.5% vs 46.2%, P=0.120) were higher than that of corticosteroid, there was no significant difference (P > 0.05). And the overall effective rate of VCR was higher than that of corticosteroid (31.0% and 56.7% vs 31.0%), but the differences were also not statistically significant. (P=0.067). Conclusions: Our prospective data show that the therapeutic effect of VCR was significantly greater than that of corticosteroid with regard to treating thrombocytopenia and improving tumor texture. So, we recommend that VCR could be an option for first-line treatment in KHE/TA patients.

Introduction

Kaposiform hemangioendothelioma (KHE) and tufted angioma (TA) are rare vascular tumors affecting predominantly infants and young children[1,2]. The lesion arises from the superficial or deep soft tissue of the extremities, head/neck, trunk, retroperitoneum or mediastinum. Although clinical and histopathological overlap in the same disease, KHE can be more susceptible to grow aggressively than TA leading to significant morbidity and mortality (up to 30%)[3,4]. The most common and severe complication of KHE/TA is the

life-threatening Kasabach–Merritt phenomenon (KMP) which result in profound thrombocytopenia and consumptive coagulopathy[5].

As KHE/TA could cause tumor progression and significant morbidity and mortality without treatment, early intervention is mandatory. Surgical resection is a curative modality but rarely used due to the infiltrative characteristics of the lesion[6]. The effective medical treatment options include corticosteroid[7,8], vincristine (VCR)[9,10], antiaggregant drugs and sirolimus[11,12], but the responses of different treatments are widely varied. Although corticosteroid was ever widely used as first-line therapy for KHE/TA, the response rates was up to about 11-66%[13-15]. Vincristine has also been widely used and the response rates was higher than that of corticosteroid[9,16,17]. But corticosteroid is still recommended as the first-line therapy for treating KHE/TA with or without KMP according to the Consensus-Derived Practice Standards Plan of 2013[18].

Due to the relative rarity of KHE/TA, no evidence-based treatment strategies or guidelines have yet been established, and its management is still a challenge. The purpose of this study is to assess and compare the efficacy and safety of corticosteroid and vincristine in the treatment of KHE/TA and to make optimal paradigm for the management of KHE.

Patients and methods

Study Design

In 9 tertiary clinical centers, this prospective randomized controlled clinical trial was carried out to evaluate and compare he short-term and mid-term efficacy and safety of corticosteroid and vincristine on KHE/TA between May 2016 and April 2018. The study was approved by the Research Ethics Boards both at the central coordinating center (approval #150 received November 11, 2015) and at each of the participating sites. Written informed consent from guardians of subjects have been obtained before they can be included in the study. The clinical trial was registered at the Chinese Clinical Trial Registry (www.chictr.org.cn) #ChiCTR-IOR-16008223.

Study Population

All KHE/TA patients admitted to the 9 participating clinical centers would be selected to participate in the study on the basis of the diagnostic criteria in the 2013 KHE/TA consensus statement[18]. The patients meeting any of the following criteria were excluded: older than 12 years; received any treatment including platelet transfusion before treatment; had a bacterial or viral infection or had immune deficiency. Investigators would conduct the study in accordance with Good Clinical Practices as outlined in the US Code of Federal Regulations, the Declaration of Helsinki (version 2013), and other applicable regulatory requirements.

Study Interventions

Patients were randomly assigned to receive either methylprednisolone – the MP group- or vincristine – the VCR group. Participants in MP Group were first administered methylprednisolone 4mg/kg per day by intravenous. Once the treatment is effective, it was changed to methylprednisolone 4mg /kg QOD for oral administration. After maintaining 4-6 weeks, the dose of methylprednisolone was tapered. Participants in VCR Group were administered 0.05 mg/kg per dose weekly by intravenous for four times, followed by monthly for six times, and additional doses were added if necessary.

If one of the following conditions occurs after 1-2 weeks of treatment in MP Group or after 3 weeks of treatment in VCR Group, it is considered that the treatment is invalid and needs to be combined with other managements. After treatment, platelets did not improve, and the absolute value was less than 20×10^9/L; In the course of treatment, the ecchymosis, size or texture of the lesion was aggravated.

Randomization

Randomization was performed in a 1:1 ratio according to block randomization method developed by an independent research coordinator. There will be four strata per site. Concealed allocation will be achieved

via computer assignment of the treatment arm, and investigational site staff and study sponsor personnel will be unaware of the block size and randomization list.

Sample Size

As there was no study comparing corticosteroids and vincristine in the treatment of KHE/TA, treatment effectiveness of corticosteroids and vincristine in the results of meta-analysis was the basis for the initial sample calculation for the present study. Considering the different treatment effectiveness of corticosteroids and vincristine (35.8% Vs 79.5%), a total of 58 patients would be needed to detect a difference between groups, with a two-tailed α of 0.05 and a (1-β) of 0.80. The sample was increased by 5% to cover possible losses to follow-up, totaling 62 patients randomized into 31 patients per group.

Outcomes

The primary outcome was a composite outcome to evaluate and compare single main parameter effective rate (SMPE) and overall effective rate (OE) of corticosteroid and vincristine after 1 month. The secondary outcomes included not only SMPE and OE, but also the recurrence rate of corticosteroid and vincristine after 6 months.

Platelets and fibrinogen were the main hemostatic parameters to reflect the improvement of KMP. In addition to coagulation, the other three main parameters comprised tumor size, texture and appearance. Platelets and fibrinogen were assessed only in patients with KMP. The lesion texture and appearance were evaluated only in patients with superficial lesions of skin and soft tissue. The evaluation criteria of main parameters were listed in table1.

The SMPE were calculated based on the response of treatment, assessing the score changes of main parameters (table 2). So, the SMPE = (number of complete response cases + number of partial response cases) / total number of cases * 100%.

The OE was calculated based on the improvement rate of main parameters which summed the scores of the main parameters to compare the difference therapeutic effect of corticosteroid and vincristine. The improvement rate of main parameters = (sum of all major parameters scores pretreatment - sum of all major parameters scores posttreatment) / sum of all major parameters scores pretreatment *100%. And the criteria of therapeutic effect were listed in table 3. So, the OE= (number of complete effective cases + number of partial effective cases) / total cases * 100%.

The relapsed cases are defined as the main parameter score is increased by 2 points after effective treatment. The adverse reactions caused by corticosteroid and vincristine were recorded at any time during the treatment.

Statistical Analysis

Descriptive statistics will be used to summarize all subject baseline and outcome data collected during the study. A two-tailed statistical test was performed at the level of α=5% to evaluate the comparability between the two group. Continuous variables will be summarized by using means, standard deviations, medians, and ranges. Categorical variables will be summarized in frequency distributions. Statistical tests appropriate to the endpoint being examined will be used and identified. Parametric tests (e.g., Student's t tests) will be used if the distributional properties of the data are suitable. If parametric tests are not indicated, the associated non-parametric tests (e.g., Mann–Whitney tests and Fisher's exact tests) will be used. A two-sided P value of 0.05 or less for the primary endpoint will be considered evidence of statistical significance.

Results

Baseline data and clinical characteristics

A total of 73 patients were screened for eligibility and 62 patients met eligibility criteria and were randomized between May 2016 and April 2018. During the study, 3 patients withdrew from the clinical, and a total of 59 patients completed the clinical trial, including 29 in the MP group and 30 in the VCR group (Figure 1).

Baseline demographic and clinical characteristics were similar in both groups with no significant difference (Table 4).

Included were 37 males and 22 females, with a male-to-female ratio of 1.68:1. The mean age of the participants was 89.51(±97.64) days and age distribution was showed in table 5. The tumor was located on the extremities (n=21), trunk (n=15) and head and neck (n= 14); in 5 cases it extended to adjacent regions; in 4 patients presented with retroperitoneal lesion. Among 59 children, 20 patients (33.9%) were diagnosed by pathology after biopsy, of which 19 cases were KHE, and only 1 case was TA.

KMP was found in 50 of all patients (84.7% of 59) and the clinical characteristics were compared between KMP and non-KMP patients (Table 6). The results showed that the patients with KMP were significantly younger than the patients without KMP (P=0.003). And the hematologic parameters, tumor size and tumor appearance in patients with KMP are more serious than those patients without KMP (Table 6). Among all KMP cases, 2 patients (4.0%) did not have KMP at the initial stage of onset, but gradually developed KMP 6 weeks and 4 weeks after the diagnosis.

Primary outcomes

After one month of treatment, SMPE was compared between MP group and VCR group. The results showed that VCR was superior to MP in the relief of thrombocytopenia (80.0% vs 44.0, P = 0.019) and tumor texture (68.9% vs 30.8%, P = 0.007). Although the efficacy of VCR on fibrinogen, tumor size and appearance were higher than that of corticosteroid, there was no significant difference (P > 0.05) (Table 7).

The overall effective rate of all enrolled cases was 44.1%, of which the overall effective rate of the MP group was 31.0%, and the overall effective rate of the VCR group was 56.7%. There was no statistically significant difference between the two groups (P=0.067) (Table 8).

Secondary outcomes

After 6 months of treatment, SMPE comparison results showed that VCR were superior to MP in the efficacy of platelet and fibrinogen (P=0.022, P=0.038), but there was no significant difference in tumor size, appearance and texture (P>0.05) (Table 9).

The overall effective rate of all enrolled cases was 47.5%, of which the overall effective rate of the MP group was34.5%, and the overall effective rate of the VCR group was 60.0%. There was no statistically significant difference between the two groups (P=0.069) (Table 10).

There were 11 cases of recurrence after treatment, of which 2 cases occurred within 1 month after treatment, and the other 9 cases occurred after 1 month of treatment. The average recurrence time was 65.55+-48.92 days. Among the recurring symptoms, there were 6 cases with decreased platelets and changes in tumor appearance, and 5 cases with simple tumor appearance changes. There were 4 recurrences in the MP group and 7 recurrences in the VCR group. The average recurrence time in MP group and in VCR group were 65.00+-67.21 days and 65.86+-41.60 days, respectively. There was no significant difference in the recurrence time between the two groups (P=0.979). The overall recurrence rate was 18.6%, of which the recurrence rate in the MP group was 13.8% (4/29), and the recurrence rate in the VCR group was 23.3% (7/30). There was also no significant difference in the recurrence rate between the two groups (P=0.506).

Other results

In the MP group, the average response time was 4.31+-2.02 days (range 2-8 days), while in the VCR group, the average response time was 15.25+-10.34 days (range 3 days to 45 days).

Side effects

After corticosteroids treatment, 21 cases had Cushing-like facial appearance, of which 8 cases had mild changes, 10 cases were moderate, and 3 cases were severe; 19 cases had changes in mental and behavior, mainly manifested as easy crying, noisy, and fright; 1 case had upper gastrointestinal bleeding; 1 case had severe lung infection and 1 case had growth retardation.

After VCR treatment, there were 6 cases of neutropenia; 2 cases of constipation; 1 case of abdominal pain and 1 case of peripheral nerve paresthesia.

Discussion

Both corticosteroid and VCR were effective medicine ever used for the treatment for KHE/TA and it was reported in the literature that the efficacy of VCR was better than corticosteroid, especially for refractory cases[9,19,20]. However, due to the relative rarity of KHE/TA, these findings were based on case report or relatively small sample sizes research. So, the purpose of this study was to compare the efficacy of corticosteroids and VCR in the treatment of KHE/TA and to confirm whether the response rate of VCR was really better than corticosteroid. To the best of our knowledge, this is the first randomized controlled trial on KHE/TA therapy.

KHE/TA is more common in infants, especially in patients before one month of age. Among the 107 cases in the Boston Children's Hospital between 1991 and 2009, KHE manifested before one month of age in 60% of cases and during infancy in 93% of cases[2]. From our data, we found that KHE/TA was present in 96.6% of infants which is similar to the literature. But newborns only accounted for 25.4% of the total, which was lower than the results reported in the literature. The reason for this difference may be that the proportion of patients who can be diagnosed at the onset is relatively low, so that the children who have symptoms in the neonatal period are often delayed to infancy to confirm the diagnosis.

KHE/TA most frequently involved an extremity, followed by torso, then the cervicofacial region[2,21]. Deep lesions, including intrathoracic cavity and retroperitoneum are frequently described in the literature because of their severity. And tumor can involve more than one anatomical region, accounting for about 22%-26%[16,22]. In our study, about 2/3 of the tumors were located either in the extremities (38%) or in the trunk (24%) and about 23% in the area of the head and neck, which is consistent with the characteristics reported in the literature. Retroperitoneal tumors were found only in 4 patients, a lower proportion than previously published[2,23].

KHE/TA can develop a life-threatening thrombocytopenia and consumptive coagulopathy, known as KMP. Some studies have confirmed that infants and toddlers have a higher risk of developing a KMP as compared to older children[2,21]. Our study found that the incidence of KHE/TA with KMP was 84.7%, and the average age of onset of KMP with and without KMP was 73.76 days and 177.00 days, respectively. It also indicated that the younger the patients were, the more likely they were to develop KMP. Most studies demonstrated the correlation between the size of the tumor and the incidence of KMP[21,24]. In our analysis, tumor median size of patients without KMP (36.70 +- 34.41cm^3) was significantly smaller than that of children with KMP (77.63 +- 54.00cm^3), which was similar to the results reported in the literature. There are special tumor locations, which are also associated with a higher incidence of KMP[2,23]. Croteau et al showed that retroperitoneal and intrathoracic KHE had a KMP in 85 and 100% of cases, respectively[2]. From our data, all patients had KMP when KHE/TA lesions are located in retroperitoneum or involve multiple anatomical sites.

KHE/TA is a rare and complex disease, so the management of these tumors in infants and children remains controversial and problematic. Corticosteroid was used as first-line treatment over the past few decades, but its low success rate and varied response rate had been demonstrated in majority of studies[13-15]. VCR is now utilized for approximately 18 years in KHE/TA, and it had relatively high response rate, especial for steroid-resistant patients in case reports or limited retrospective series[9,16,19]. In the meta-analysis of Liu et al, the data of 344 patients collected from 13 studies were analyzed, the response rate of corticosteroid and VCR were 24% and 66%, respectively[7]. The results showed that VCR was relatively more effective than systemic corticosteroids. In our study, the difference between two groups was not statistically significant across the treatment period of 1 and 6 month, but the overall response rate of VCR (56.7%, 60.0%) is superior to that of corticosteroids (30.0%, 34.5%). In addition, the overall response rate of corticosteroid is similar to the literature, but the overall response rate of VCR is slightly lower than the results reported in the literature. We consider this may be related to the usage of 5 parameters to evaluate the therapeutic

effect. If only the single parameter of platelet is used in the VCR group in this study, its response rate can reach 80%, which is similar to the literature.

In this study, we included not only common parameters such as platelets, fibrinogen, and tumor size, but also the parameters of tumor appearance and texture for the first time, so as to further comprehensively evaluate the therapeutic effect of the disease. The results show that the response rate of VCR is better than that of corticosteroids in all individual parameters, and the difference between platelet and tumor texture is statistically significant. After further analysis of each individual parameters, we found that whether corticosteroid or VCR is used, the effective rate of platelet, tumor appearance and texture in this treatment group is higher than that of tumor size and fibrinogen. The result means that in addition to platelets, changes in tumor appearance and texture are also important indicators for evaluating the therapeutic effect of KHE/TA. Compared with platelets, tumor appearance and texture do not require additional inspection and can be observed at any time.

According to literature reports, corticosteroid therapy for KHE/TA usually takes effect within 3 to 10 days[8,25], while VCR has a relatively slow onset of effect, which usually takes about 4 to 5 weeks[9,16]. The results of this study showed that the response time of MP was faster than that of VCR, which is similar to the literature. However, we also found that the average response time of VCR in this study was about 2 weeks, which was also faster than the reported in the literature. This may be due to the large sample size of our study on the one hand, and on the other hand, all patients were treated with VCR initially, unlike most of the patients received VCR were refractory to other therapy in the literature.

The most common reasons for the failure of KHE/TA treatment are recurrence. The recurrence rate of corticosteroid is about 15%-50%[7,18], there are few literatures about the recurrence of VCR[7,26]. We conducted a meta-analysis and systematic review on the treatment of corticosteroids and vincristine and concluded that the recurrence rate of VCR treatment was 11.1% and 22.2%, respectively, which was lower than corticosteroids (50.0% and 36.0%)[13]. However,it showed that the recurrence rate of VCR was higher than that of corticosteroid in this study, which was different from the results of meta-analysis and systematic review. We consider that VCR is often used in combination with other drugs to treat refractory cases in meta-analysis, but it is only used alone in this study, which may be the possible reason for the difference. In addition, the average recurrence time of corticosteroid and VCR was about 2 months. This may be related to the fact that the dose of corticosteroid is in the tapered phase, while VCR is in the prolonging phase of the drug use cycle, which leads to the similar recurrence time.

Generally, KHE/TA patients are well tolerated to corticosteroid therapy. However, adverse effects, such as temporary growth retardation, hypertension, metabolic disorders, osteoporosis and infection are commonly reported[27,28]. Although VCR is a chemotherapeutic drug, it rarely causes serious adverse reactions such as vomiting and bone marrow suppression, and its main side effect is transient neurotoxicity, including loss of deep tendon reflexes, peripheral paresthesias, abdominal pain and constipation[9,10]. In our study, due to the short course of corticosteroid therapy for KHE/TA, the side effects were relatively mild, the most important being Cushion's face and mental changes. We also found that although the side effects of VCR are rare and mild, there may be obvious agranulocytosis when using VCR in the neonatal period, which needs more attention.

This study had some limitations, such as no blinding and the small sample size. Due to the rarity of the disease, we can't set up another group to both corticosteroid and VCR at the same time, which will increase the bias of the study.

Conclusions

This is the first multicenter randomized controlled trial to compare the therapeutic effects of corticosteroid and VCR and to determine if VCR used alone as first-line treatment is possible. Our prospective data show that the therapeutic effect of VCR was significantly greater than that of corticosteroid with regard to treating thrombocytopenia and improving tumor texture. And VCR was also well-tolerated without serious adverse reactions. So, we recommend that VCR could be an option for first-line treatment in KHE/TA patients.

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Figure Legends:

Figure 1 Diagram of KHE/TA patients included in this study

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`Table 1 Scoring system of single main parameters before and after treatment.pdf` available at https://authorea.com/users/367015/articles/487592-comparison-of-efficacy-and-safety-of-corticosteroid-and-vincristine-in-treating-kaposiform-hemangioendothelioma-and-tufted-angioma-a-multiicenter-prospective-randomized-controlled-clinical-trial

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`Table 4 Baseline characteristics of eligible patients with KHW.pdf` available at https://authorea.com/users/367015/articles/487592-comparison-of-efficacy-and-safety-of-corticosteroid-and-vincristine-in-treating-kaposiform-hemangioendothelioma-and-tufted-angioma-a-multiicenter-prospective-randomized-controlled-clinical-trial

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Table 6 Comparison of clinical characteristics of patients with and without KMP.pdf available at https://authorea.com/users/367015/articles/487592-comparison-of-efficacy-and-safety-of-corticosteroid-and-vincristine-in-treating-kaposiform-hemangioendothelioma-and-tufted-angioma-a-multiicenter-prospective-randomized-controlled-clinical-trial

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Table 8 Overall treatment effect after 1 month of treatment.pdf available at https://authorea.com/users/367015/articles/487592-comparison-of-efficacy-and-safety-of-corticosteroid-and-vincristine-in-treating-kaposiform-hemangioendothelioma-and-tufted-angioma-a-multiicenter-prospective-randomized-controlled-clinical-trial

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Table 10 Overall treatment effect after 6 months of treatment.pdf available at https://authorea.com/users/367015/articles/487592-comparison-of-efficacy-and-safety-of-corticosteroid-and-vincristine-in-treating-kaposiform-hemangioendothelioma-and-tufted-angioma-a-multiicenter-prospective-randomized-controlled-clinical-trial