# Additive value of Transarterial Embolization to systemic Sirolimus treatment in Kaposiform Hemangioendothelioma

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August 11, 2020

**Abstract**

Purpose: Kaposiform Hemangioendothelioma (KHE) is a rare vascular tumor in children, which can be accompanied by life-threatening thrombocytopenia, referred to as Kasabach-Merritt Phenomenon (KMP). The mTOR inhibitor sirolimus is emerging as targeted therapy in KHE. As the sirolimus effect on KHE occurs only after several weeks we aimed to evaluate if additional transarterial embolization is of benefit for children with KHE and KMP. Methods: 17 patients with KHE and KMP acquired from 11 hospitals in Germany were retrospectively divided into two cohorts. Children being treated with adjunct transarterial embolization and systemic sirolimus, and those being treated with sirolimus without additional embolization. Bleeding rate as defined by WHO was determined for all patients. Response of the primary tumor at 6 and 12 months assessed by Magnetic Resonance Imaging (MRI), time to response of KMP defined as thrombocyte increase >150 x 103/µl, as well as rebound rates of both after cessation of sirolimus were compared. Results: N= 8 patients had undergone additive embolization to systemic sirolimus therapy, sirolimus in this group was started after a mean of 6.5 ± 3 days following embolization. N=9 patients were identified who had received sirolimus without additional embolization. Adjunct embolization induced a more rapid resolution of KMP within a median of 7 days vs 3 months, however tumor response as well as rebound rates were similar between both

groups. Conclusion: Additive embolization may be of value for a more rapid rescue of consumptive coagulopathy in children with KHE and KMP compared to systemic sirolimus only.



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Conclusion: Additive embolization may be of value for a more rapid rescue of consumptive coagulopathy in children with KHE and KMP compared to systemic sirolimus only.

Introduction

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor affecting children with an incidence < 0.1:100.000 and most commonly occurs in neonates[1,2]. KHE frequently manifests as a rapidly growing mass, infiltrating adjacent tissue and organs. In up to 70% KHE is complicated by a life-threatening consumptive coagulopathy with severe thrombocytopenia referred to as Kasabach-Merritt Phenomenon (KMP)[1,3]. Different from disseminated intravascular coagulation (DIC), intratumoral platelet trapping through activated abnormal endothelium carrying a partial lymphatic phenotype results in severe thrombocytopenia and subsequent increase in D-dimers and consumption of fibrinogen[4]. This intratumoral coagulopathy may have a very fast onset and accounts for a high mortality in KHE of 10-30% in KHE patients[5]. As curative surgical resection of KHE is frequently not possible due to the infiltrative character of the tumor and is additionally associated with a high mortality[6], various systemic treatment options have been suggested including corticosteroids, antineoplastic agents such a vincristine[7,8], interferon-alpha[9] and platelet inhibition[10,11]. Of note, most studies report a combination therapy in KHE patients rather than monotherapy. In 2013 a consensus document recommended intravenous vincristine and either oral prednisolone or intravenous methylprednisolone as first line treatment of KHE associated with KMP[12], while two more recent meta-analyses have identified vincristine as safer and more effective in treatment of KHE compared to corticosteroids[8,13]. Image-guided embolization has been shown to induce a rapid decrease of the tumor mass but the effect is considered to be only temporary, if not combined with other therapies[12,14]. Besides the aforementioned approaches, the mammalian target of rapamycin (mTOR) inhibitor sirolimus is emerging as novel treatment option in KHE. As mTOR is highly overexpressed in KHE, targeting the PI3K-Akt-mTOR pathway seems a reasonable option[15,16]. Multiple reports have recently shown the efficiency of sirolimus in treating both KHE and the associated KMP[17]. In addition, sirolimus seems equally effective for initial therapy[18] and for steroid resistant KHE[19] showing low rates of recurrence[20], although relapse after cessation of sirolimus treatment has been observed[21]. Sirolimus treatment on the one hand initiates shrinkage and remission of the tumor and similarly it addresses KMP over time, leading to a normalization of thrombocyte counts within a period of approximately 20 days[18-20,22].

Therapy of complicated KHE thus aims at 1) remission of the primary tumor, 2) rapid resolution of the life-threatening consumptive coagulopathy, and 3) prevention of recurrence of either one. As sirolimus is emerging as the most causal systemic approach to KHE with good results in tumor remission, and as embolization has the potential to rapidly resolve the severe intratumoral consumptive coagulopathy by excluding the abnormal endothelium from the systemic circulation, we thought to evaluate the added value of transarterial embolization to systemic sirolimus in children with KHE/KMP. We thus aimed to study the outcome after transarterial embolization followed by systemic sirolimus treatment compared to sirolimus without adjunct embolization in a retrospective multicenter cohort.

## Patients and Methods

### Study Design

The study was performed as a retrospective analysis. 17 patients with Kaposiform Hemangioendothelioma were recruited from 11 German tertiary care hospitals, covering a period from 2012-2020. Patients were divided into two groups: patients undergoing embolization as additive treatment to systemic sirolimus and patients receiving sirolimus without additional embolization. The study was approved by the local institutional review board (Protocol No. 2019-667-f-S). Informed consent for publication of patient's images has been obtained from the parents.

### Patients and Disease Manifestation

Demographic, clinical, laboratory and procedural data were retrieved from electronic patient records. Two of the patients reported have been previously published, including additional information about the cases[23,24]. Disease extent and therapy response were assessed from cross sectional imaging retrieved from the local Picture Archiving and Communication Systems.

Laboratory assessment in KMP was focused on thrombocyte counts, fibrinogen and D-dimers as markers of coagulopathy.

Bleeding grade associated with KHE was classified in four grades according to the World Health Organization (WHO) scheme[25].

### Treatment and Response Assessment

In patients receiving additive embolization the procedure was carried out under general anesthesia via a 4F groin access. Transarterial embolization was performed either using particles or liquid embolization material (ethylene vinyl alcohol copolymer). The procedure was considered technically successful if [?]80% of the tumor vasculature was occluded at the end of the intervention. Patients undergoing embolization underwent additional treatment with weight-adapted acetylsalicylate acid, weight-adapted, from 2-20mg/day for 6 months.

Systemic sirolimus was given at a dose of 0.1 to 1.8 mg/kg/m$^2$ to achieve serum levels of 4 to 15 ng/l.

Response to therapy was specifically assessed at 6 and 12 months after initiation of therapy, clinically as well as by MRI. Similarly, blood tests were performed at respective time points. Response to therapy was defined in two categories 1) response of the KMP, respectively normalization of coagulopathy, defined as platelet increase >150 x10$^3$/µl and 2) response of KHE itself (graded as complete response CR, partial response PR, stable disease SD and progressive disease PD) according the Response Evaluation Criteria in Solid Tumors, measured on MRI. Rebound of KHE and KMP after sirolimus discontinuation was defined as a switch to progressive disease either from SD, PR or CR after cessation of sirolimus treatment, defined either by an increase in tumor size or a decrease of platelet counts <150 x10$^3$/µl. Follow-up period was counted from beginning of sirolimus therapy ± embolization.

### Data analysis and statistics

Data are shown as mean ± standard error, median or as relative percentages. Group comparisons were performed between patients undergoing sirolimus with additive embolization of KHE and patients receiving

sirolimus without additional image-guided embolization. Comparison of demographic patient data was performed using Fisher's exact test for qualitative data or, depending on normality of data, either two-sample t-test or Mann-Whitney U test for quantitative data. Response to therapy was compared similarly with Fisher's exact test and Mann-Whitney U test. For comparison of response of KMP, median time of thrombocyte count normalization was compared between the two groups using Kaplan Maier analysis and log-rank test. A p-value $< .05$ was considered significant. Of note, due to the limited cohort size and heterogeneity of cases reported, statistics should be viewed in a descriptive manner only. Analysis was performed using Graph Pad Prism version 7 (GraphPad Software, San Diego, CA, USA) as well as SAS Version 9.4 for Windows (Copyright SAS Institute Inc, Cary, NC, USA).

## Results

### Patient demographics

In total, 17 children with KHE and accompanying KMP were identified and included (11 male, 6 female) with no significant difference of sex distribution between the groups (p=0.131). Patients in the embolization group (n=8) were younger (11.3 ± 7 months versus 41.8 ± 19 months), however with no statistical difference (p=0.219). Histology was obtained in 15/17 (88%) of cases. In the remaining two patients the diagnosis was evident from the clinical picture and laboratory findings, thus histological assessment was omitted. Most KHEs were located along the extremities and the head and neck region. A short case description of each patient is presented in Table 1.

Bleeding grades were classified according to the World Health Organization (WHO) scale: No bleeding was reported in 1 patient, grade 1 was reported in 2 patients, grade 2 in 4 patients, and grade 3 in 10 patients. Grade 4 bleeding according to WHO was observed in neither of the patients. There was no significant difference between bleeding scores at baseline in patients with embolization (25% grade 1, 12.5% grade 2, and 62.5% grade 3) and patients without embolization (11.1% grade 1, 33.3% grade 2, and 55.6% grade 3; p=0.908). Median thrombocyte count at baseline was 38.5 x $10^3$/µl in group of patients with adjunct embolization vs 36.0 x $10^3$/µl in the group without additional embolization (p=0.408). Median fibrinogen levels at baseline were 132 mg/dl in group of patients with adjunct embolization vs 122.5 mg/dl in the group without additional embolization (p=0.798). Median D-dimer levels at baseline were 16.95 mg/l in group of patients with adjunct embolization vs 18.15 mg/l in the group without additional embolization (p=0.825).

### Treatment and Response

Embolization was performed in n=8/17 (47%) of the patients, while sirolimus without additional embolization was used in n=9/17 (53%) patients. Embolization with devascularization of >80% of tumor vasculature was technically successful in 100%, without major periprocedural complications. In 2/8 patients two subsequent embolization procedures were performed, while in 6/8 patients one treatment cycle was sufficient to complete the procedure. Sirolimus was applied with a mean dose of 0.46 ± 0.1 mg/kg/$m^2$ and was given for 278 ± 56 days in the embolization group, and with a mean dose of 0.58± 0.2 mg/kg/$m^2$ given for 434 ± 69 days in the group without embolization (p= 0.677 for dose, p=0.107 for time period differences). In the embolization group sirolimus was started 6.5 ± 3 days following the embolization procedure.

One patient had previously been treated by embolization only as systemic therapy was initially refused by the parents. Embolization only in this case initially led to a rapid regression of KHE and immediate release from KMP, however with complete relapse of KHE together with KMP after three months (Supplementary Figure 1).

Tumor response to therapy revealed no statistically significant differences between the two groups (Table 2). PR or CR was achieved in a majority of patients regardless of additive embolization (Figure 1).

Response of KMP differed between the two treatment regimens with respect to thrombocyte counts, while fibrinogen and D-dimers did not reveal marked differences (Figure 2 A-C) Embolization as additive treatment to sirolimus was associated with a more rapid recovery from KMP compared to sirolimus without embolization (Figure 3). Patients with additive embolization were faster to achieve a thrombocyte count of 150 x$10^3$/µl

than patients without embolization (HR=0.39, p-value logrank = 0.061). The median time to normalization occurred within the 7-14 days interval in patients treated with embolization plus sirolimus and at the 3 months in patients treated with sirolimus only. At 6 and 12 months KMP had resolved in patients with and without additive embolization. No major bleeding event was reported for either patients in both groups after initiation of therapy.

Rebound of KHE together with KMP after discontinuation of sirolimus occurred in 0/8 patients in the embolization group and in 3/9 patients in the group without embolization (p=0.200).

Overall, 2/8 patients in the embolization group died within 12 months, one child due to metastatic disease, one child due to congestive heart failure attributed at least partially to the high arteriovenous shunting of the KHE together with a patent ductus arteriosus. Mean follow up was 667 ± 151 days in patients with embolization and 1501 ± 361 days in patients without additional embolization (p=0.060).

Discussion

Kaposiform Hemangioendothelioma is a very rare vascular tumor in infants associated with a potentially life-threatening severe thrombocytopenia[1-3]. In KMP intratumoral dysplastic and pathologically activated endothelium causes local platelet and fibrinogen sequestration leading to severe thrombocytopenia, with or without lowered fibrinogen and altered D-dimers levels[4,26]. Heterogeneous treatment approaches have been reported, including vasoactive substances (propranolol), thrombocyte inhibitors (acetylsalicylate acid, ticlopidin), corticosteroids, interferon, chemotherapy (vincristine, cyclophosphamide), mTOR inhibitors, imaged-guided embolization and surgery. In 2013 a consensus document recommended intravenous vincristine together with oral prednisolone as the treatment of choice in KHE presenting with KMP[12], with the positive effect of vincristine confirmed in a large meta-analysis[8]. In recent years, especially sirolimus has emerged as a potent agent in KHE, as it targets the specific overexpression and -activation in the PI3K-Akt-mTOR signaling pathway. Retrospective multicenter studies recommend sirolimus as a potential first-line treatment alone or as part of a multimodal approach[17,27]. Clinical multicenter trials investigating the use of sirolimus in KHE in a prospective design are currently ongoing. Sirolimus has been shown to provide recovery from life-threatening KMP after a period of three weeks of oral application[18-20,22]. With respect to this period of severe coagulopathy our aim was to evaluate whether transarterial embolization in adjunct to sirolimus treatment provides a more rapid resolution of KMP and has a potential effect on tumor outcome.

Our results suggest that KMP resolution, measured as thrombocyte increase >150 x$10^3$/µl, occurs more rapidly after embolization plus sirolimus, however, tumor response was similar between both treatment regiments. Interestingly in the cohort of children receiving sirolimus without embolization 3/9 patients suffered rebound of KHE/KMP within a one-year period, whereas in the combined treatment group no rebound was observed.

Transarterial embolization has been used in the past to treat KHE and KMP, however most reports similarly use embolization only in combination with systemic chemotherapy, mostly vincristine[14,28]. Embolization alone seems to be associated with a high relapse rate of KHE. Of note, one patient in our cohort had initially been treated by embolization alone leading initially to a rapid regression of KHE and immediate release from KMP. However complete relapse of KHE together with KMP occurred after three months. Thus, embolization alone should not be considered an adequate therapeutic approach for KHE. In our cohort, embolization was technically successful in all patients and with exception of two patients, only a single treatment cycle was required to rapidly rescue children from KMP. Embolization may therefore be a promising option to bridge the gap between occurrence of life-threatening KMP and the effect of systemic treatment. In our study embolization was regularly combined with platelet inhibition by ASA, which may exert two different effects in this scenario. On the one hand, platelet inhibition may reduce intralesional platelet sequestration. On the other hand, children with consumptive coagulopathy appear to have a hyperplastic bone marrow, as evidenced by the rapid endogenous increase of thrombocytes within a few days after embolization. Thrombocytopenia may thereby potentially switch into thrombophilia following embolization and ASA can potentially counteract this effect and serve as protection of potentially thrombotic

events. Several reports have demonstrated beneficial effects of platelet inhibition in KHE in combination therapies[10,11], however with no prove of causality in this special scenario.

While initially vincristine was considered the chemotherapeutic agent of choice for KHE, the beneficial effects of sirolimus are becoming increasingly evident. First studies recently reported long-term follow up after KHE treatment with sirolimus. Wang et al report a follow-up period of 28 months with only mild side effects and no report of recurrence[20]. While previously dosing was calculated to achieve target sirolimus levels of 10 to 15ng/l, our cohort applied significantly lower sirolimus dosing. Similarly, other reports suggest that levels around 5ng/l may be sufficient for successful treatment of KHE[29,30]. Thus, decreased dose regimens may explain the low rate of systemic side effects of sirolimus reported in the vascular anomalies literature compared to its use in transplantation medicine.

While chemotherapeutic agents such as vincristine exert unspecific effects on KHE, somatic or mosaic mutations of the PI3KCA gene provide a molecular rationale for sirolimus treatment in KHE. As such, sirolimus seems to exert both antiproliferative and antiangiogenic/lymphangiogenic effects by inhibiting the mTOR, a serine-threonine kinase which is regulated by PI3K. While currently sirolimus is the dominating agent to interfere with the PI3K-Akt-mTOR pathway other specific agents such alpelisib might similarly become an alternative[31] and further investigations into the molecular pathogenesis of KHE might lead to more targeted therapies[32].

Our study is limited by the small cohort size and the retrospective study design. Moreover, the patient cohort reported is heterogenous with regard to age and more importantly with respect to previous and concomitant systemic treatments, which may all have impact on the long-term outcome and similarly on the recurrence rates of the disease. Thereby, this study is limited in evidence but can serve as a hypothesis generating work. Further studies are therefore requested to answer these questions with more robust evidence. Those studies have to be realized via a prospective registry, as randomized controlled trials are not likely to succeed in the field of orphan diseases.

In summary, our study suggests that transarterial embolization adds to systemic sirolimus in the treatment of Kaposiform Hemangioendothelioma and provides are more rapid resolution of potentially life-threatening Kasabach-Merritt phenomenon. However, in this cohort no differences in resolution of KHE itself were observed. Severely affected patients might benefit from additional embolization to achieve a normalized coagulation.

Conflict of interest: The authors declare no conflict of interest.

Original data are available upon request.

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Figure Legends

**FIGURE 1** Tumor Response of Kaposiform Hemangioendothelioma

Tumor Response Assessment is shown for both groups sirolimus +- embolization, with no statistically significant differences between children receiving adjunct embolization to systemic sirolimus (n=8) compared to patients receiving sirolimus without additive embolization (n=9).

**FIGURE 2** Response of Kasabach-Merrit phenomenon

Laboratory course of thrombocyte counts (A), fibrinogen (B) and D-dimers (C) is shown for children receiving adjunct embolization to systemic sirolimus (n=8, right panels) compared to patients receiving sirolimus without additive embolization (n=9, left panels).

**FIGURE 3** Kaplan - Meier Analysis of thrombocyte course after initiation of therapy

To compare response of consumptive coagulopathy time periods where compared between start of therapy until patients exceeded a thrombocyte count >150 x$10^3$/µl. Hazard Ratio of children receiving sirolimus without additive embolization was 0.39 compared to children undergoing additive embolization (p-value log-rank 0.061).

Table Legends

**TABLE 1** Patient Characteristics

Detailed patient characteristics of children undergoing additive embolization with systemic sirolimus treatment compared to children being treated with systemic sirolimus without additional embolization.

**TABLE 2** Tumor Response of Kaposiform Hemangioendothelioma

Tumor response of KHE to systemic sirolimus ± embolization was compared with respect to progressive disease (PD), stable disease (SD), partial response (PR) and complete response (CR), without revealing statistically significant differences between the two cohorts.

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### Hosted file

`Table 2_KHE_1.5.docx` available at https://authorea.com/users/350091/articles/475032-additive-value-of-transarterial-embolization-to-systemic-sirolimus-treatment-in-kaposiform-hemangioendothelioma