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Hydroxyurea for the Treatment of Recurrence and Unresectable Meningiomas: A Systematic Review

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Abstract

BACKGROUND: Meningioma is mostly benign tumor (World Health Organization Grade 1) and surgery remains the best option in treating symptomatic or enlarging meningiomas where total removal of the tumor is the goal of surgery. Radiation therapy has shown to be effective to cease the growth of the tumor, but not in tumor regression. Adjuvant therapy may treat patients with recurrence or unresectable meningiomas yet the uses of hormone therapy, immunotherapy, or chemotherapy had many results and were not consistently effective. Hydroxyurea has promising results in patients with meningiomas.

AIM: This study analyzed the efficacy and safety of hydroxyurea for the treatments of recurrence or unresectable meningiomas.

MATERIALS AND METHODS: The study adapted PRISMA guidelines by searching electronic databases, PUBMED, Cochrane, and JNS in August 2020 and was full-text observational study or randomized control trial presented as PICO and assessed using the risk-of-bias assessment tool.

RESULTS: A total of six articles (157 patients with meningioma) were reviewed from the total of 425. Hydroxyurea was administered orally for 28 days continuously and repeated every 28 days or after recovery with various dosages in six studies.

DISCUSSION: Administration of hydroxyurea showed a varied stable disease rate ranging from 30 to 69% with a median progression-free survival med varying between 2 and 27.75 months. The studies performed oral hydroxyurea administration at a dose of 20–30 mg/kg body weight/day or 1000 mg/m2/day. However, the adverse events (AEs) that appear also, based on literature, are not much different from other chemotherapy administrations.

CONCLUSION: Patients with unresected and recurrent meningiomas have limited treatment options due to difficulty for surgical management. However, this study offers another perspective addressing the efficacy and safety results with the use of hydroxyurea. Overall, hydroxyurea showed good outcomes, particularly in low-grade meningioma, with relatively low AEs. Further combination treatment may be used as a multimodal therapy.

Introduction

Meningioma is the most common primary brain tumor, accounted for ±35%. It is estimated that 12 persons in a million have meningioma [1]. Meningioma is mostly benign (World Health Organization [WHO] Grade 1) and is often successfully treated with surgery [2], [3]. Surgery remains the best option in treating symptomatic or enlarging meningiomas where total removal of the tumor is the goal of surgery [4], [5]. However, in certain meningiomas due to its location, complete removal of the tumor is hard to achieve [6], [7]. Therefore, the degree of resection will increase the risk of post-surgical recurrence [8]. In some cases of patients with WHO Grade I meningioma where the tumor could not be totally resected, the tumor can transform to higher grade (atypical, WHO Grade II; anaplastic, WHO Grade III) ended with worse general outcomes and survival rate [3], [9].

Radiation therapy is now used as one of the treatment modalities in unresectable or recurrent meningiomas as well as in atypical or anaplastic meningiomas. Radiation therapy is shown to be effective to cease the growth of the tumor, but not in tumor regression [8]. An alternative treatment option as an adjuvant therapy for patients with recurrence or unresectable meningiomas is essential to improve the survival and clinical outcomes of these patients. Unfortunately, the uses of hormone therapy, immunotherapy, or chemotherapy had variable results and not consistently effective [8], [10]. Although only being reported in several small studies, hydroxyurea, a ribonucleotide reductase inhibitor, had promising results in patients with recurrence or unresectable meningiomas with radiographic response rates of 6% and med progression-free survival (PFS) of 44–176 weeks [10].

Hydroxyurea was previously known as a chemotherapy drug for chronic myelogenous leukemia and could be used for years with low or transient toxicity [8], [10]. Hydroxyurea is currently used in the treatment of myeloproliferative disorders, chronic

myelogenous leukemia, and polycythemia rubra vera in particular [11], Hydroxyurea plays a role as a cell cycle-specific urea analog that discourages the enzyme ribonucleotide diphosphate reductase and interferes with deoxyribonucleic acid (DNA) synthesis by minimizing the available pool of DNA [11], [12]. The cytotoxic effects of hydroxyurea correlate with the dose or concentration achieved, as well as with the duration of drug exposure [12]. Hydroxyurea also has a more global inhibitory effect on the replitase complex of tumor cells [12]. Some prospective studies had been done in investigating the efficacy of hydroxyurea with promise result in patients with recurrence or unresectable meningioma; however, the data are still indeterminate [8], [13], [14]. Therefore, this study is conducted to analyze the efficacy and safety of hydroxyurea for the treatments of patients with recurrence or unresectable meningiomas.

Materials and Methods

Information sources and search strategy

This systematic review was conducted based on PRISMA guidelines. Studies were obtained by searching electronic databases, PUBMED, Cochrane, and JNS in August 2020. Studies that were included ranged from 2000 - 2012. Only were articles in Bahasa and English included. Authors used the following keywords searching to find out all trial registers and databases: “hydroxyurea” or “meningioma” or “recurrent” or “recurrence” and “unresectable.” No ethical clearance was needed for this study.

Eligibility criteria

Study used was full-text observational study or randomized control trial (RCT) about hydroxyurea treatment in recurrent or unresectable meningioma. Reviews, unpublished articles, letter to editor, abstracts, and study not written in English or Bahasa were excluded from the study. Study characteristics are presented as PICO in Table 1.

Table 1: PICO of the study

Population	Adult aged 19–70, patient with recurrent or unresectable meningioma
Intervention	Hydroxyurea
Comparison	–
Outcome	PFS, safety

PFS: Progression-free survival.

Quality assessment

The methodological quality in each of these studies was assessed using the risk-of-bias assessment tool based on the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) by two reviewers.

Data collection and analysis

Selection of studies

The search results were excluded based on the relevancy of both the titles and the abstracts. Non-English/non-Bahasa publications were automatically excluded. Full-text articles were then assessed by all authors for potentially eligible RCTs. The reasons of exclusion were noted and reported. Included studies are represented in Table 2.

Results

Literature search

A flow diagram of study selection is shown in Figure 1. After initially identifying 425 articles, 212 were excluded and the full texts of 213 were reviewed. Subsequently, 207 studies were excluded, and 6 studies were included in the systematic review (Table 2).

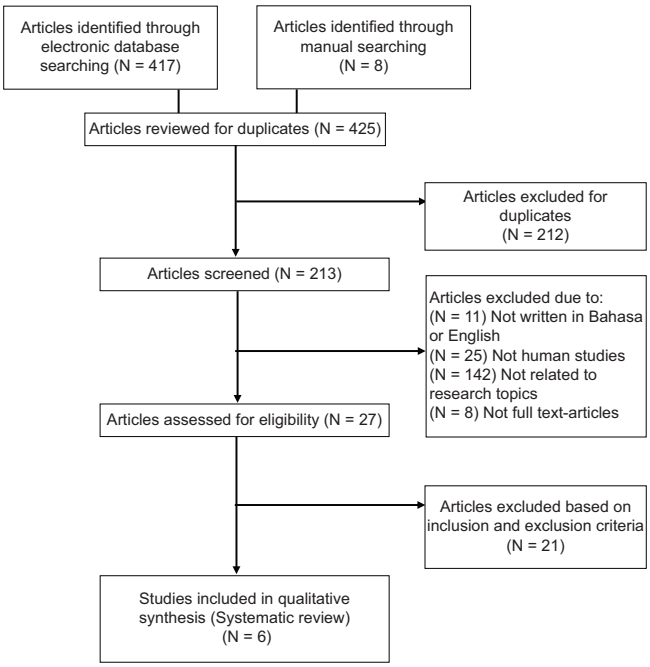

Figure 1: Study flowchart

Pre-treatments

There were six studies with total of 157 meningioma patients in this review. Among participants, 153 out of 157 patients (97.45%) had undergone surgery and 82 patients had undergone surgery more than once. In all, 117 patients (74.5%) had previously been treated with fractioned radiotherapy (total dose ranged from 50.4 to 61.2 Gy) and 91 patients (57.9%) were in addition treated with stereotactic radiotherapy (dose ranged from 12 to 18 Gy).

Table 2: Hydroxyurea study data

Author	Year	Type of study	Patients	History surgery TR/STR/Bio/No	Average Age/ Range	Grades I/II/ III/NS	Treatment dose	Outcomes	AEs
Newton *et al*. [13]	2000	PS	17	13 patients, NS; 6 patients more than 1	57.2 33–74	13/-/-/4	HU 20 mg/kg/d	14 out of 16 (88%) SD, PFS 5–36 mo, med PFS 20 mo Grd I 10 SD, PFS 2.5–36 mo; 1 ex NS 4 SD, PFS 14–36 mo	Hematological 11 (65%, grd III/IV 5) Uric acid 2 (12%) Fatigue 2 (12%)
Mason *et al*. [8]	2002	PS	20	All had surgery, NS; 14 patients more than 1	59 31–75	16/3/1/-	HU 20–30 mg/kg/d	65% SD, PFS 2–38 mo, med PFS 30,5 mo Grd I 12 SD 1 mPR, PFS 2–38 mo Grd II 1 SD PFS 3–11.25 mo Gr III 0 SD, PFS 1 mo	Hematological 8 (40%; grd III 3) Hepatic 1 (5%)
Loven *et al*. [14]	2004	PS	12	All had surgery, NS; 10 patients more than 1	56.9 41–77	8/4/-/-	HU 20 mg/kg/d	1 out of 10 (10%) SD-mPR, PFS 4 - 24 mo Grd I 1 SD-mPR, PFS 4–24 mo, 1 ex Grd II 0 SD, PFS 9–13 mo, 1 ex	Convulsion 1 (8.3%) Hematological 4 (33.3%; grd III/IV 4) Cutaneous 1 (8.3%) Hepatologic 1 (8.3%)
Chamberlain and Johnston [15]	2011	RS	60	20/31/9/- 29 patients more than 1	61.5 26–88	60/-/-/-	1000 mg/ m^2/d	35% SD; PFS 3–12 mo	Hematological 20 (33%) Fatigue 15 (25%) GIT 10 (16.7%) Infection 2 (3.3%) Thrombophlebitis 3 (5%)
Chamberlain [16]	2012	RS	35	17/13/5/- 21 patients more than 1	63 34–86	-/22/13/-	HU 1000 mg/m^2/d	43% SD, PFS 0.5–7 mo, med PFS 2 mo	Anemia 5 (14.28%, grd III 1) Fatigue 12 (34.28%, grd III 2) Neutropenia 3 (8.57%) Lymphopenia 5 (14.28%) GIT 8 (22.85%) Infection 2 (5.71%) Thrombophlebitis 2 (5.71%)
Kim [11]	2012	RS	13	All had surgery, NS; 2 patients more than 1 1/-/-/-	32–83	8/5/-/-	HU 1000 mg/m^2/d	Gr I/II 10 SD, PFS 8-128 mo, med PFS 72.4 mo	Persisting hematologic manifestation 1 (7.6%)

AEs: Adverse events; PS: Prospective study; RS: Retrospective study; NS: Not specified; HU: Hydroxyurea; Grd: Grade; PFS: Progression-free survival; SD: Stable disease; mPR Minor partial response; ex: Excluded due to adverse effect or died; mo: Month; yr: Year.

Hydroxyurea dosage

The schedule of hydroxyurea administration applied in the six studies was similar in which hydroxyurea was administered orally for 28 consecutive days (defined as a cycle of therapy) and repeated every 28 days or after the recovery from adverse events (AEs) acquired in previous cycle. The dosage of hydroxyurea was varied in six of studies. Hydroxyurea was administered at a dose of 20–30 mg/kg divided twice per day in three studies and 1000 mg/m^2 per day in two studies.

Histopathology grading

It is essential to consider the grades of the tumor in evaluating the tumor responses to hydroxyurea, its effect might be different for different grade of the tumor. In a study reported by Newton *et al*., the histological feature of tumor from 17 patients was 13 (76.47%) with Grade I meningioma and 4 (23.53%) with no histopathological confirmation (not operated). In another study reported by Mason et al., a prospective study, histological features reported from 20 patients include 16 (80%) subjects with Grade I meningioma, 3 (15%) with Grade II meningioma, and 1 (5%) with Grade III meningioma. Other prospective studies had been conducted to determine the effect of hydroxyurea in different grades of the tumors. Loven *et al*. included 12 patients: 8 (66.67%) had Grade I meningioma and 4 (33.33%) had Grade 2 meningioma. Meanwhile, other two different retrospective studies including larger number of meningioma patients had been reported by Chamberlain and Chamberlain–Johnston with total of 95 patients: 60 (63.15%) had Grade I meningioma, 22 (23.16%) had Grade II meningioma, and 13 (13,69%) had Grade III meningioma.

Effectiveness of hydroxyurea

This study included total 105 cases of Grade I meningioma, 48 cases of Grades II and III, and 4 cases with no histopathological confirmation. PFS was used to determine the effectiveness of hydroxyurea in different grades of the tumors. PFS was defined as the time from the 1st day of treatment with hydroxyurea until initial disease progression. Patient with Grade I meningioma which as many as 54 out of 105 (51%) had stable disease (SD) with the shortest PFS of 2 months and the longest PFS of 128 months. For high-grade meningioma (Grades II and III) with total of 48 patients, the PFS ranged from 0,5 - 13 months. Meanwhile, four patients without histopathological confirmation, all of 8 patients had SD (100%) with PFS ranging from 10 to 36 months.

Dose and outcome

According to the treatment doses compared to the outcomes, it is implied that the intervention using hydroxyurea 20–30 mg/kg/d was associated with prolonged PFS (2-38 months) in Grade I compared to Grade II with shorter PFS (3-11.25 months). Besides, there were 12 SDs represented in Grade I, surpassing SD alone observed in Grade II. Another study used 20

mg/kg/d only for both Grades I and II group. The result was surprisingly consistent with the previous one in which there was prolonged PFS (4–24 months) in Grade I group and shorter PFS (9–13 months) in Grade II group. The SD number did not show any differences among both groups. Thus, hydroxyurea administration with dose ranging from 20 to 30 mg/kg/d was considered as the suitable dose and more effectively for Grade I class.

Adverse effect

Overall, the majority of patients tolerated the dosage of hydroxyurea used in these series with minimal complications. Hematological AE was the most common AE with frequency range 33–65% followed by other AEs. Fatigue was in the second place with frequency range 12–34.28%. Meanwhile, there were also certain AEs with lesser frequency range (5–33.33%) such as GIT, hepatic, lymphopenia, and cutaneous manifestation. One severe manifestation was a convulsion (8.3%) reported by Loven *et al*. [14] Most studies had limitation and did not explain whether the adverse effect occurred in the same subject or not.

Discussion

In general, administration of hydroxyurea to the patients in the six studies above showed sufficiently good results. The result presented a varied SD rate, ranging from 30 to 69% (>60% in three studies) with a med PFS varying between 2 and 27.75 months. The level of safety and tolerance is also rather advanced in which all studies found only two major pathological responses to hydroxyurea administration. In addition, the most common side effects are hematological disorders (anemia, thrombocytopenia, and leukopenia) which range from 20 to 65% [8], [9], [13], [14], [15], [16].

The mechanism of hydroxyurea therapy administration to patients in the six studies above was not much different. All studies performed oral hydroxyurea administration at a dose of 20–30 mg/kg body weight/day or 1000 mg/m2/day [8], [13], [14], [15], [16]. Based on the experience of the study by Grabenbauer *et al*. in 2002, glioblastoma patients were given infusion topotecan and accelerated hyper fractionated 3d-conformal radiation [17]. However, the results of this different regimen were not different from other studies, where in this study the SD rate was around 66% and med PFS ranged from 13 months (Grade II/III meningioma) to 20 months (Grade I meningioma). Similarly, the AEs rate was not much different from other studies [8], [9], [13], [14], [15], [16]. Mason *et al*. [8] revealed that there was about 75% SD in Grade I (12 of 16 patients) while Grade II/III had higher percentage (25% SD in 1 of 4 patients). Similar results were presented by Newton et al., discovering 76% SD in Grade I. In other studies, the SD rates between Grade I and Grade II/III meningiomas in each study were not different. This is consistent with the previous studies which show that the use of hydroxyurea is more intended to prevent the progression of high-grade meningioma, not to achieve a complete or partial response [18], [19].

However, med PFS in the above studies showed some differences. The response rate to hydroxyurea in all studies was very low, with only two patients from all studies showing minimal response, and the rest showing SD or PD [8], [9], [13], [14], [15], [16]. A recent study by Chamberlain *et al*., 2011 and 2012, showed that the med PFS in all patients with Grade II/III was only 2 months [15], [16]. Whereas in another study, there was a difference in med PFS between patients with Grade I and Grade II/III meningiomas with med PFS ranging from 13 to 22.77 months for Grade I meningiomas and 1–27.75 months for Grade II/III meningiomas. This is most likely due to different follow-up methods in the more stringent Chamberlain study in which a complete neurological examination was performed every 4 weeks and an magnetic resonance imaging (MRI) examination every 8 weeks. Meanwhile, other studies only performed follow-up MRI/computed tomography scans and complete neurological examinations every 12–16 weeks. This may also be due to the improvement of MRI imaging technologies, considering that the time distance between Chamberlain's study and other studies was 6–12 years and the Chamberlain study performed follow-up imaging with MRI alone in all patients [8], [9], [13], [14], [15], [16], [20], [21].

The progressive rate in the six studies can be seen from the SD rate where the SD rate ranged from 30 to 69% but the average study found that the SD rate is above 60% (three studies) [8], [9], [13], [15], [16]. Another difference between the SD rate of Grade I and Grade II/III meningiomas can be seen in the Chamberlain study where in 60 patients with Grade I meningiomas, the SD rate is 35% while in 35 patients with Grade II/III meningiomas, the SD rate is 43% [15], [16].

Patient tolerance to hydroxyurea was high in that in all studies there were only two major pathological responses (both in Grade 1 meningioma). AEs that appear also, based on literature, are not much different from other chemotherapy administration in which in this study, the most frequent AEs were hematological AE with hematological Grade AE I and II [8], [9], [13], [14], [15], [16], [19].

Concurrently, if AEs appeared in Grade III patients, the samples were excluded except those emerged in Grade II patients. This was due to the shorter PFS observed in Grade III patient which presented meaningless outcome [8]. In addition, although hydroxyurea has some advantages particularly related to safety effects, it is considered that the treatment for Grade III may not able to be administered for favorable outcomes.

Overall, the use of hydroxyurea showed good outcomes, regardless of achieving partial or complete responses. Further investigation studies of hydroxyurea in combination with other modality treatments, such as radiation and bevacizumab, are essential to explore the use of hydroxyurea in treating meningioma. Bevacizumab is also well-tolerated and active against recurrent malignant gliomas [22], [23]. In addition, important advantages of bevacizumab are its ability to decrease peritumoral edema and function as a corticosteroid-sparing agent [22]. Moreover, study from Hahn *et al*. [9] using both hydroxyurea and radiotherapy demonstrated an increasing PFS among 21 patients with meningioma, compared to those who were given radiotherapy only. Thus, it is needed to consider the combination therapy with either bevacizumab or radiotherapy which also offered encouraging efficacy and safety results in managing patients with meningioma [24], [25].

Conclusion

Patients with unresected and recurrent meningiomas currently have limited treatment options due to the difficulty for surgical management. This study offers another perspective addressing the efficacy and safety results with the use of hydroxyurea. In our review, hydroxyurea showed good result in preventing tumor progression, particularly in Grade 1 meningioma. Although the efficacy and safety are still inconclusive due to limited studies, AEs in meningioma patients treated with hydroxyurea are relatively low. Further combination treatment may be used as a multimodal therapy.

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