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META-ANALYSİS

Effect of rituximab on primary central nervous system lymphomas: A meta-analysis

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Purpose: It is aimed to show the use of rituximab provides survival advantage in this article.
Method: Computer based literature research using PubMed/Medline database by two independent investigators (VK, GY). The initial Pubmed search with combined term of (rituximab) AND (primary central nervous lymphoma, rituximab, survival) resulted in 422 returns through January 31, 2017. English was used as the screening language and only human studies were investigated.
Results: A total of 535 patients were included in the meta-analysis. 346 (64.7%) of the patients were male and 189 (35.3%) were female. Female/male ratio was determined as 0.55. Rituximab was used in the first-step treatment in all patients. Pooled hazard ratio was evaluated for the overall survival (OS) and showed that adding Rituximab to the treatment was related to OS (HR, 0.537; 95% CI, 0.391 - 0.737; P:<0.001. Publication bias was not detected for OS (Begg's test, P:0.286; Egger test, P:0.171). Publication bias was not shown in the Funnel Plot graphic for OS.
Conclusion: The fact that all the studies included in our meta-analysis were retrospective, was the most important restrictive factor of this study. However, our study result supports combination use of rituximab in PNCSL patients and is important in terms of directing clinics.

Rituksimab'ın primer santral sinir sistemi lenfomaları üzerindeki etkisi: Bir metaanaliz

Amaç: Bu makalede rituksimab kullanımının sağkalım avantajı sağladığını göstermek amaçlanmıştır.
Yöntem: İki bağımsız araştırmacı (VK, GY) tarafından PubMed / Medline veri tabanı kullanılarak bilgisayar tabanlı literatür araştırması. (Rituximab) AND (birincil merkezi sinir lenfoma, rituximab, sağkalım) terimiyle ilk Pubmed araştırması, 31 Ocak 2017'ye kadar 422 geri dönüşle sonuçlandı. Tarama dili olarak İngilizce kullanıldı ve sadece insan çalışmaları araştırıldı.
Bulgular: Meta-analize toplam 535 hasta dahil edildi. Hastaların 346'sı (% 64,7) erkek, 189'u (% 35,3) kadındı. Kadın / erkek oranı 0,55 olarak belirlendi. Tüm hastalarda birinci basamak tedavide Rituximab kullanıldı. Havuzlanmış tehlike oranı genel sağkalım (OS) için değerlendirildi ve tedaviye Rituximab eklenmesinin OS ile ilişkili olduğunu gösterdi (HR, 0.537;% 95 CI, 0.391 - 0.737; P: <0.001. OS için yayın yanlılığı saptanmadı (Begg's testi, P: 0.286; Egger testi, P: 0.171) Yayın yanlılığı OS için Funnel Plot grafiğinde gösterilmemiştir.
Sonuç: Meta analizimize dahil edilen tüm çalışmaların geriye dönük olması bu çalışmanın en önemli kısıtlayıcı faktörüdür. Ancak çalışma sonucumuz, rituksimabın PNCSL hastalarında kombinasyon kullanımını desteklemektedir ve kliniklerin yönlendirilmesi açısından önemlidir.

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Primary central nervous system lymphoma (PCNSL) is a rare sub-type of aggressive Non-Hodgkin Lymphomas (NHL) and it constitutes 2-3% of all brain tumors [1]. PCNSL may hold in the brain, spinal cord, leptomeninges or the eye. 90% of PCNSL patients consist of Diffuse Large B-cell lymphoma (DLBCL) patients. Other rare types are Burkitt's lymphoma, T-cell lymphoma and low-grade B-cell lymphoma [2]. Optimal treatment is limited in PNCSL as the blood brain barrier blocks the passage of many drugs to the brain. Therefore, survival is worse compared to other lymphomas that hold in peripheral lymphoid and visceral organs [3].

Although there is no consensus yet on standard treatment, high-dose methotrexate (HD- MTX) and radiotherapy are frequently used in PCNSL treatment [4]. Radiotherapy has been used in PCNSL treatment for a long time. However, standard-dose radiotherapy has side effects such as cognitive dysfunction, brain atrophy, leukoencephalopathy, endocrine disorders and dementia [5]. Rituximab is an antibody of human/murine chimeric glycolyzed immunoglobulin (Ig) G1 structure. Specifically, it bonds to CD20, which is a transmembrane protein in lymphocytes [6]. It was first used in relapsed/refractory indolent NHL treatment. Later, it was used also in the treatment of hematologic malignancy [7].

Due to its high molecular weight, intravenous rituximab is used in PCNSL expressing CD-20 as in systemic lymphomas, despite the fact that its passage to the central nervous system is not good. Studies about the use of Rituximab in this area have conflicting results [8]. Despite of developments in optimal systemic treatment, the prognosis of patients is poor [9]. The purpose of this meta-analysis is to indicate whether addition of rituximab to treatment PCNSL contributes to survival.

METHOD

Research Strategy

Computer based literature research using PubMed/Medline database by two independent investigators (VK, GY). The initial Pubmed search with combined term of (rituximab) AND (primary central nervous lymphoma, rituximab, survival) resulted in 422 returns through January 31, 2017. English was used as the screening language and only human studies were investigated.

Inclusion and Exclusion Criteria

The following criteria were used in selecting the studies to be included in the meta- analysis:

- Case reports, case series, reviews, letters, comments were excluded from the study.
- Retrospective studies and randomized controlled studies.
- Studies including patients over 18 and histopathologically diagnosed with PCNSL and using Rituximab were included.
- Studies including non-PCNSL patients using Rituximab were excluded.
- Studies lacking data on impact magnitude of Rituximab in terms of survival in its summary statistics were excluded.
- Duplicate studies were excluded.
- Only English articles were included in the study.

Selection of studies

Whether the studies were suitable for inclusion in the meta-analysis was evaluated by two independent reviewers (MY, VK). The abstracts of all studies identified as a result of screening were read. Full-texts were obtained of articles which were candidates for inclusion in the meta-analysis and summary statistics were extracted from the full-text articles.

Study Population

Patients with PCNSL and using Rituximab were included in the study. In case patients included into different studies by the same investigators were identified, the study with the higher quality was included in the meta-analysis.

Determining the Quality of the Studies

The quality of the studies was determined by two reviewers (GY, VK), independently using Newcastle–Ottawa Quality Assessment Scale, used in evaluating non-randomized studies in which this Scale evaluates the selection of the patient population, study comparability and follow-up and

results of the study. 0 to 9 stars are given to studies under these three topics. 9 star is used as the highest quality in quality evaluation. Non-compliances among investigators were eliminated by jointly evaluating non-conforming studies after evaluations and compromise was reached on all items.

Data Extraction

Data from studies included in the meta-analysis were extracted by independent reviewers. Non-compliances among investigators were eliminated by joint evaluation after data extraction and compromise was reached on all items. The following data were obtained from the studies included in the meta-analysis.

- Basic information on the study, name of first author, publication year, country of study,
- Study design,
- Demographic data such as gender distribution of the patients,
- Applied treatments, the stages of the patients included in the study,
- Impact magnitude of Rituximab on survival.

Statistical Analysis

The primary objective of the statistical analyses we used in our study is to investigate the effect of adding Rituximab in PCNSL treatments, on survival. Hazard Ratio (HR) has been calculated with a 95% Confidence Interval for each study. Cases where HR>1 and 95% Confidence Interval did not include 1, were accepted as significant. In cases without reported HR, HR was calculated using the abstract statistics obtained from data extraction.

Homogeneity was evaluated using $\chi 2$-based test of homogeneity test and inconsistency index (I2). Cases where $p< 0.10$ or I2 >50% were accepted for Heterogeneity $\chi 2$. The results were presented using fixed model. Cases where the p value for the summary HR is <0.05 were accepted as statistically significant. Publication bias was examined by using Egger's regression intercept, Begg-Mazumdar rank correlation analysis, and a visual inspection of funnel plot. Statistical analyses were carried out using Comprehensive Meta-analysis V 3.0 (Biostat, Englewood, NJ).

Study Eligibility

The flowchart of the articles included in the meta-analysis is shown in Figure 1.

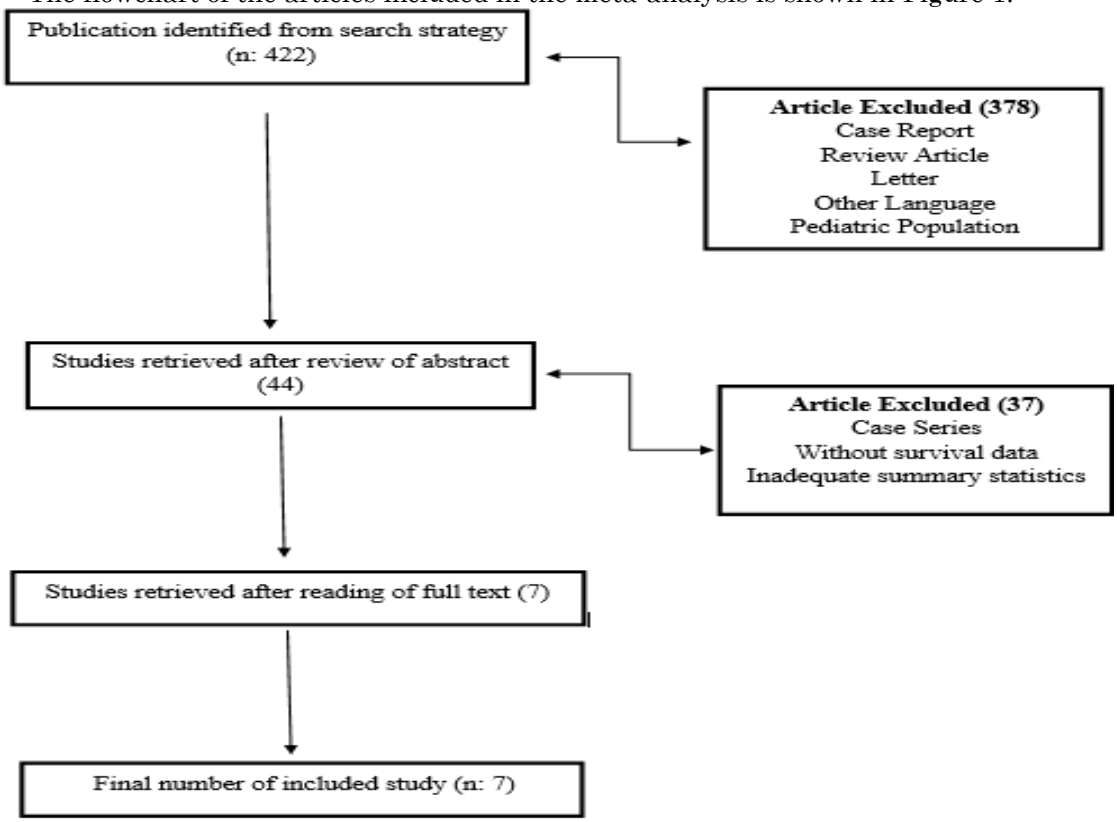

Figure 1: The flow chart of the meta-analysis

The computer-based literature research using PubMed/Medline resulted in a total 422 article. 378 articles were eliminated by evaluating the titles and abstracts after the article screening. The full-texts of the remaining were evaluated. Of the 44 articles whose full-texts were evaluated, 37 were excluded from the meta-analysis due case series, insufficient survival data, insufficient summary statistical data or inclusion of patients diagnosed with secondary central nervous system lymphoma. The 6 articles obtained following this elimination were included in the meta-analysis (Table 1).

Table 1. Details of the studies included in the meta-analysis

Study	Country	Study Design	Number of Patients (Male)	Number of Patients (Female)	Total Number of Patients	Median Age	Treatment	Median Follow-up	HR (OS)	P value (OS)	Study Quality Score	Conclusion	REF
Birnaum T,201 2	Germany	Retrospective	22	14	36	66(39-79)	MTX+I FO+R versus MTX+I FO	18mont h (3- 32)	0,531	0,33	3	NS	
Gregory G, 2013	Australia	Retrospective	68	52	120	65(21-81)	HD-MTX Cytarab in R Radiothrea py İntrathecal MTX	30 month (1-139)	0,512	0,064	5	NS	
Kellogg GR, 2013	USA	Retrospective	24	21	45	59(37-86)	HD-MTX Cytarab in R Radiothrea py İntrathecal MTX	13,8 month (0ne week to 6.4 years)	0,120	0,003	5	S	
Dalia S, 2014	USA	Retrospective	49	40	89	61(17-70)	HD-MTX R Radiothrea py	NR	0,52	0,02	5	S	
Madle M, 2015	Germany	Retrospective	38	43	81	66(42-85)	Various Regime including R	NR	0,049	0,002	4	S	

Determining the Quality of Studies Included in Meta-Analysis

All the 6 studies included in the meta-analysis were retrospective studies. Therefore, the quality evaluation of the studies were performed using Newcastle-Ottawa Scale. In this quality evaluation system 1-3 is considered as low, 4-6 as moderate and 7-9 as high-quality study. The retrospective studies included in the meta-analysis had a median score of 6.

RESULTS

Characteristics of the patients

A total of 535 patients were included in the meta-analysis. 346 (64.7%) of the patients were male and 189 (35.3%) were female. Female/male ratio was determined as 0.55. Rituximab was used in the first-step treatment in all patients.

Overall Survival, Disease-Free Survival, Event-Free Survival

Pooled hazard ratio was evaluated for the overall survival (OS) and showed that adding Rituximab to the treatment was related to OS (HR, 0.537; 95% CI, 0.391 - 0.737; P:<0.001; Figure 2).

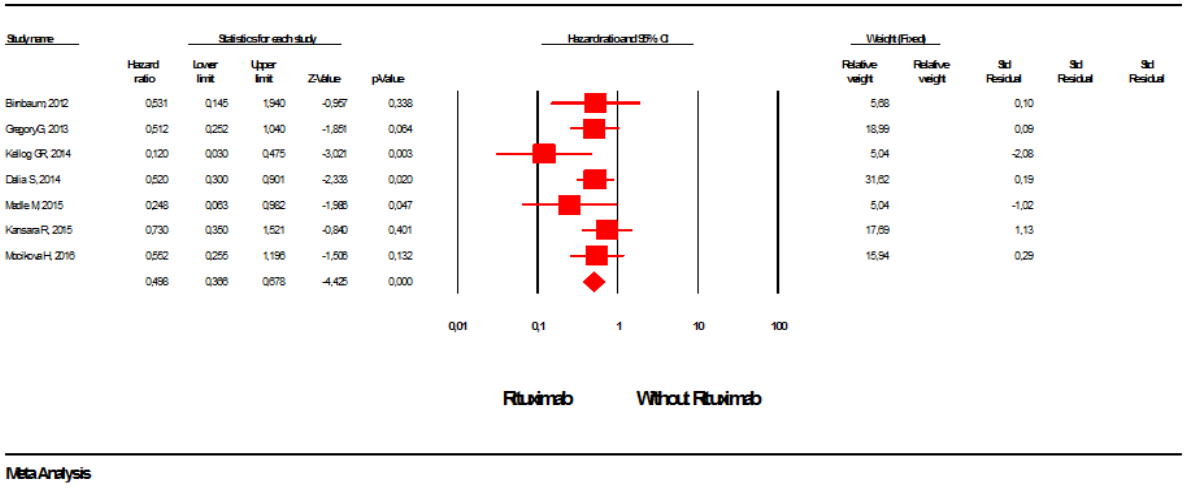

Figure 2. Meta-analysis of overall survival (OS) among patients receving Rituximab

Publication Bias

Publication bias was not detected for OS (Begg's test, P:0.286; Egger test, P:0.171). Publication bias was not shown in the Funnel Plot graphic for OS (Figure 3).

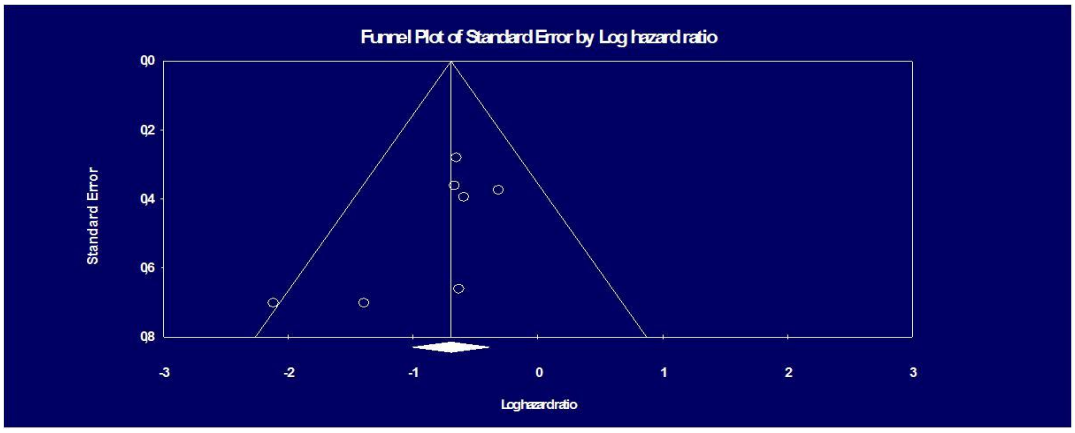

Figure 3. Publication bias determination using funnel plot for OS

DISCUSSION

Most of the studies conducted on use of rituximab in PCNSL are retrospective. These studies also have conflicting results. In this study we have shown that use of rituximab provides survival advantage.

Kasara et al. showed that survival in PCNSL where rituximab was used together with HD-MTX, was better compared to patients who used only HD-MTX [10]. There are studies that reported results contrary to this study that supported our meta-analysis. Mocikova et al. detected that adding rituximab to MTX did not provide OS advantage. Patients registered to the Czech Lymphoma Study Group (CLSG) registry during 2002-2012 were included in this study. HD-MTX was administered with or without rituximab and later WBRT was implemented on the patients. Although PFS was shown in the study results, OS advantage could not be shown [11]. Madle et al. investigated the impact of rituximab on OS in PCNSL where high-dose chemotherapy was used with our without rituximab prior to autologous stem cell transplantation (ASCT). In this study, first-step treatment was identified as rituximab use in addition to whether or not ASCT was implemented and age-independent prognostic factors [12].

In their study, jointly evaluating secondary central nervous system lymphomas together with PCNSL patients, Kellogg et al. determined that rituximab use as an independent prognostic factor by taking into consideration treatment modalities such as WBRT, intrathecal MTX, HD- MTX, Rituximab, CHOP, MVP or cytarabine using multivariate Cox regression analysis [13].

In their retrospective study, Gregory et al. detected that in PCNSL patients being older than 60 years, having an ECOG performance score greater than 1 and high LDH were poor prognostic factors [14]. They found cytarabine and rituximab use to be associated with better OS. Birnbaum et al. have investigated the effects of adding rituximab to MTX and ifosfamide combination in a retrospective single center study [15]. In this study, rituximab was shown to significantly increase complete remission ratio (100.0 vs. 68.4%, P=0.02). PFS was evaluated in this study but OS was not. Use of rituximab was shown to provide significant PFS advantage.

Blood brain barrier constitutes an obstacle for therapeutic agents in PCNSL. Rituximab has poor passage to the central nervous system due to the size of the rituximab molecule [16]. Therefore, small nano-particles are tried as a new strategy as drug deliverers. Saesoo et al. have used anti-CD20 consisting of super magnetic iron oxide nano-particles in an in-vitro model consisting of cell culture in their study [17]. As a result, they have shown that rituximab successfully passed through the blood brain barrier and had activity against lymphoma.

In their meta-analysis, Song et al. have shown the contribution of rituximab to survival similar to our meta-analysis (OR 2.87, 95% CI 2.02-4.08, P < 0.00001) [18]. In this study, the complete remission (OR 1.70, 95% CI 1.17-2.46, P = 0.005), and the 2-year Progression-Free Survival (PFS) (OR 2.11, 95% CI 1.08-4.11, P = 0.03) of rituximab was also shown, which are not included in our study.

Bromberg et al. have presented (at the 59th American Society of Hematology Annual Meeting and Exposition) their international randomized phase 3 HOVON 105/ALLG NHL 24 study including 199 patients, where they investigated the activity of rituximab added to MBVP induction chemotherapy (high-dose MTX, BCNU, teniposide, and prednisone) regime in PCNSL [19]. PFS or OS impact of adding rituximab could not be shown in this study. Dalia et al. have shown the OS advantage of HD-MTX use in their retrospective study where they evaluated PCNSL patients treated in a single center [20]. They therefore asserted that HD-MTX use should constitute the backbone of the treatment in first-step treatment in PCNSL patients. Additional contribution could not be shown of intrathecal chemotherapy or radiotherapy added to HD-MTX treatment. Also, OS contribution could also not be shown of rituximab added to HD-MTX. There are few prospective studies on rituximab use in PCNSL patients. The fact that the treatment regime used in the study of Bromberg et al. was different, could have led to this result.

The fact that all the studies included in our meta-analysis were retrospective, was the most important restrictive factor of this study. However, our study result supports combination use of rituximab in PNCSL patients and is important in terms of directing clinics.

Teşekkür: *Yok.*

Çıkar çatışması: *Yok.*

Finans: *Yok.*

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