INPLASY PROTOCOL

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None declared.

Effectiveness of Neoadjuvant Molecular-Targeted Chemotherapy in Ameloblastoma - A Systematic Review

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Review question / Objective: **The aim of this article is to obtain an in-depth review of ameloblastoma tumor to determine the available level of evidence and the possible benefit of targeted therapeutics for the treatment of BRAF V600E mutation in ameloblastoma tumor.**
Condition being studied: **Ameloblastoma is an epithelium-derived odontogenic tumour that evolved since the prehistoric era. Ameloblastoma is unique among the odontogenic neoplasms occurring in the jaws, because of its locally invasive behaviour and high recurrence rate. Facial asymmetry, displacement of teeth, malocclusion, and pathologic fractures are some of the asymmetrical features that ameloblastoma is known to cause. If left untreated, they often lead to wide tissue destruction and deformity. For the treatment of ameloblastomas, conventional chemotherapy and radiation have been unexplored or contraindicated and to date, wide surgical resection is the only treatment of choice for ameloblastoma tumours, resulting in post-treatment compromised quality of life in the individuals.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 June 2022 and was last updated on 06 June 2022 (registration number INPLASY202260018).

INTRODUCTION

Review question / Objective: **The aim of this article is to obtain an in-depth review of ameloblastoma tumor to determine the available level of evidence and the possible benefit of targeted therapeutics for the treatment of BRAF V600E mutation in ameloblastoma tumor.**

Rationale: **For the treatment of ameloblastomas, conventional chemotherapy and radiation have been unexplored or contraindicated and to date, wide surgical resection is the only treatment of choice for ameloblastoma tumours, resulting in post-treatment compromised quality of life in the individuals. Molecular and genetic factors**

strongly linked to the dysregulation of multiple genes associated with various pathways mediate the oncogenic transformation of odontogenic epithelium to ameloblastoma. Ameloblastic tissues showed significantly altered cell signalling pathways. Many studies have identified various markers expressed by ameloblastoma, which helps us to understand tumour pathogenesis. The recent identification of altered molecular signalling pathways in ameloblastoma has begun to elucidate mechanisms of oncogenesis, differentiation, tumour progression, and plausible nonsurgical considerations for treatment but not attained completeness due to lack in rhythmic corelation of the cascading effect. Till date, there was no systematic data provided regarding the available chemotherapeutic drugs for ameloblastoma.

Condition being studied: Ameloblastoma is an epithelium-derived odontogenic tumour that evolved since the prehistoric era. Ameloblastoma is unique among the odontogenic neoplasms occurring in the jaws, because of its locally invasive behaviour and high recurrence rate. Facial asymmetry, displacement of teeth, malocclusion, and pathologic fractures are some of the asymmetrical features that ameloblastoma is known to cause. If left untreated, they often lead to wide tissue destruction and deformity. For the treatment of ameloblastomas, conventional chemotherapy and radiation have been unexplored or contraindicated and to date, wide surgical resection is the only treatment of choice for ameloblastoma tumours, resulting in post-treatment compromised quality of life in the individuals.

METHODS

Search strategy: PubMed/MEDLINE, EBSCO, and Web of Science databases for relevant published studies between 1975 and 2021 was performed with Booleans and/or were used along with the following terms “ameloblastoma”, “targeted therapy”, “chemotherapy”, “malignant”, “metastasis”, “BRAF V600E mutation”, “associated mutations”, “pulmonary”, or “relapse”, “recurrence”.

Participant or population: Studies with human subjects, with no limits on age or other demographics.

Intervention: Studies with data that was clearly linked to targeted therapies for AME, MA, and BRAF V600E mutations, and related mutations. Vaccines and herbal medications were not included. Studies were included only when the name and dosage of the targeted medication regimen utilized in the therapy were disclosed.

Comparator: There was no need for a comparator group.

Study designs to be included: Case reports and case series available in full text were included even if they extracted the minimum dataset, including tumour site, histological confirmatory diagnosis, and treatment, due to the paucity of published articles relevant to targeted therapies. Exclusions included systematic reviews, meta-analyses, in vitro research, animal experiments, and abstracts from conferences.

Eligibility criteria: The reviewers only looked at works that had been published or translated into English. Case reports and case series available in full text were included even if they extracted the minimum dataset, including tumour site, histological confirmatory diagnosis, and treatment, due to the paucity of published articles relevant to targeted therapies. Exclusions included systematic reviews, meta-analyses, in vitro research, animal experiments, and abstracts from conferences.

Information sources: A comprehensive electronic retrieval of PubMed/Medline, EBSCO, and Web of Science databases for relevant published studies between 1975 and 2021 was performed. AME (follicular and plexiform, unicystic, peripheral), and MA were the several variants that were included in the review. The Booleans and/

or were used along with the following terms: "ameloblastoma", "targeted therapy", "chemotherapy", "malignant", "metastasis", "BRAF V600E mutation", "associated mutations", "pulmonary", or "relapse", "recurrence". The review also included additional references explored using the reference lists of selected studies, bibliography, and Google Scholar. The PRISMA flowchart for literature screening and selection of studies included in the review is shown in Figure 1. The studies containing relevant information were obtained for full text review after titles and abstracts were screened. Restricted access papers were retrieved using institutional support.

Main outcome(s): We included only those studies of AME/MA reporting the potential use of neoadjuvant targeted therapies. Studies reporting only the tumour size, prevalence, growth of ameloblastic carcinoma, in vitro cell growth or molecular investigations were excluded.

Quality assessment / Risk of bias analysis: Histological diagnosis and detailed disclosure of drug dosage were included in this broad explanatory inquiry of the tool, which is analogous to the detailed criteria we employed during the study selection process. Hence, we chose not to undertake a separate risk of bias evaluation because the items in the tool were most relevant to assessing methodological quality, and this context had already been reviewed and accounted for.

Strategy of data synthesis: Each of the retrieved full-text publications was screened and evaluated independently by the two authors. The evidence based librarianship (EBL) Critical Appraisal Checklist was used by the two reviewers to ensure the quality of the selected studies. Disagreements between the data were examined and resolved by a blinded reviewer to establish concordance. Table 1 illustrates the characteristics of the cases reported and considered in the review. A tool for assessing the methodological quality of case reports/series to be included in a systematic review was employed.

Subgroup analysis: Subgroup analysis was not performed.

Sensitivity analysis: Sensitivity analysis was performed and no error was found.

Country(ies) involved: India.

Keywords: BRAF V600E, MAID regimen, Metastatic ameloblastoma, Molecular targeted therapy, Pulmonary ameloblastoma.

Contributions of each author:

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