University Journal of Medicine and Medical Specialities

ISSN 2455- 2852 2019, Vol. 5(6)

IMATINIB IN THE TREATMENT OF ADENOID CYSTIC CARCINOMAS OF THE HEAD AND NECK

JEBAKARUNYA RAMI REDDY
Department of Radio Therapy,CHRISTIAN MEDICAL COLLEGE

Abstract : INTRODUCTION Adenoid cystic carcinomas in head and neck region are quite rare. Majority of them originate from minor salivary glands. Adenoid cystic carcinomas are well known for their indolent biological nature, protracted clinical course and late onset of distant metastases. Surgery is the mainstay of treatment. In recurrent or metastatic disease, chemotherapy is an available option. Several biological agents such as Imatinib have been tried with variable success rates in these patients.We report a case series of seven patients diagnosed to have recurrent or metastatic adenoid cystic carcinomas with CD 117 positivity, who had failed after receiving initial treatment.

METHODS AND MATERIALS

This was a retrospective study done on patients who were diagnosed to have adenoid cystic carcinoma in the last ten years and treated with Imatinib in the
department of Radiotherapy. There were 7 patients who were started on Imatinib. All the patients had histologically proven disease and CD 117 positivity .They all had either loco regionally advanced or metastatic disease. The data was collected from patient records. Blood investigations, radiological investigations were done in all the patients during follow up. Radiological assessment was done using RECIST criteria and CTCAE version 4 criteria were used for toxicity assessment. RESULTS

Out of seven patients, data for response assessment was available for five patients. Among them three patients had stable disease and two patients had progressive disease. Imatinib was well tolerated in all patients.

CONCLUSION

Imatinib is an available treatment option in the treatment of recurrent or metastatic adenoid cystic carcinomas of the head and neck.

Keyword : Adenoid cystic carcinoma, Imatinib Adenoid cystic carcinomas (ACC) are rare tumors arising from the secretory glands contributing to a major portion of minor salivary, parotid and submandibular gland malignancies(1). They are the most common malignancies of the minor salivary glands (2). They also arise in major salivary glands of the head and neck. Although the typical site of origin is salivary glands they also arise in the ceruminous glands, lacrimal glands and excretory glands of the genital tract. They represent 10 to 15 % of the histology of head and neck tumors(3). Approximately 22 % of malignant salivary gland tumors are ACC's occurring predominantly in minor salivary glands(4). The overall 5 – year, 10 year and 15 year survival estimates from literature are 90.34 %, 79.88% and 69.22 % respectively(5). Adenoid cystic carcinomas are well known for their protracted clinical course and late onset of distant metastases. The biological behavior is poorly understood and there is no definite evidence of treatment in adjuvant, locally advanced and metastatic settings. Various pathologic factors, clinical variables have been studied to identify the prognostic indicators of the outcomes. Among the clinical variables clinical stage, particularly tumor size has proven to be a reliable determinant of local control and survival (6). Tumor site has been shown to be of significance, with tumors of the nasal cavities and sinuses being associated with poorer outcomes(7). The studied pathological factors so far have included grade, margins of resection and perineural invasion. Tumour grade has been a poorer indicator of outcome (6). Positive margins and perineural invasion have been showed to be adverse predictors of outcome in patients with ACC(8). More search for further prog nostic indicators have explored the possible relevance of molecular markers in salivary gland tumours in general and as well in ACC. Some markers include epidermal growth factor receptor(EGF-R), HER -2, HER -3,p 53 and proliferating cell nuclear antigen(PCNA) (9–12). There is some data that shows there is no prognostic value for c –kit or PDGFR beta expression. Optimum management of ACC is always a matter of controversy because of the paradoxical nature of the disease being both neurotropic and infiltrative, still having an indolent protracted course. Radical surgery is the main stay of treatment, combined therapy with radiation has led to superior results in many studies (13,14). Radiation alone in locally advanced disease has been palliative and rarely achieved curativity (14). However, some authors have insisted that surgery alone might be sufficient in early tumours where wide margins can be obtained without major functional loss, reserving radiation therapy in cases where there are mandatory pathological indications(15). These cancers have poor response to chemotherapy as they are slow growing tumours. Various cytotoxic agents such as fluorouracil, anthracyclines, platinum compounds have been tried with limited success(16–19). Systemic chemotherapy has modest effect on adenoid cystic carcinoma. Thirty percent of patients responded to 5 FU based chemotherapy in one study(16). But there was not much response in another study which used Cisplatin and 5 Flourouracil(17). In another study Cisplatin and Vinorelbine was beneficial with better control rates(20). A later study by the same

group reported minimal activity with Paclitaxel and carboplatin (19). Surgery followed by radiotherapy is the only curative treatment when feasible. There is no option for advanced, recurrent or metastatic disease. Other options such as biological therapy has to be explored and standardized. Expression of KIT, a transmembrane receptor (145 – 165 kd) tyrosine kinase has been reported to be present in ACC. This receptor is the product of the proto onco gene c – kit and is detected by the immunohistochemical staining for CD 117. This receptor is of the same subclass as of platelet derived growth factor and colony stimulating factor. The exact mechanisms of gene mutation in c – kit activation is not known(21). Because the mutations observed in exon 11 and exon 17 involved in c – kit activation in GIST were not observed in salivary gland tumours. Imatinib (formerly known as STI 571) is a derivative of the 2 – phenyl amino pyramidine series of protein tyrosine kinase inhibitors. It has been shown to inhibit potently the tyrosine kinases of ABL, the platelet derived growth factor receptor (PDGFR), and the receptor for c – kit.

Imatinib has been approved by FDA for use in patients with CML (22). It also has been evaluated in a number of other tumours expressing c – kit or PDGFR, such as GISTs, small cell lung cancer with different levels of efficacy.

It has been approved by the US FDA in patients with advanced stage as it has shown significant disease regression(23). On the contrary it has not shown much benefit in a phase 2 study in small cell lung cancer. In view of c – kit positivity Imatinib has been tried in locally advanced, metastatic and recurrent adenoid cystic carcinomas. Imatinib has been tried in few patients and tested in phase 2 trials also. In a phase 2 trial done by Raphael et al(24). Imatinib was started in 10 patients, out of which 2 patients had stable disease for 11 – 14 months and rest of them had progressive disease. In another phase 2 trial done in Princess Margaret hospital (4). Nine patients had stable disease (which persisted for more than six months in only two patients) and 6 patients had progressive disease. They did not find any major activity and the study was closed. In another study which reported four treated cases, only one patient exhibited stable disease for 6 months and the rest had no response(25). On other hand which reported two cases(26), one patient had local recurrence and was started on Imatinib after which he had partial response and underwent re surgery after which the patient had lived for 20 months without disease. The other patient had locally advanced disease and had achieved partial response after initiation of Imatinib which is stable for more than 15 months. We have offered this biological therapy in few of our patients and would wish to present our experience.

PRIMARY OBJECTIVE:

The primary objective was to determine the response to Imatinib

SECONDARY OBJECTIVE:

1. To determine the duration of response (progression free survival)
2. To evaluate the safety and tolerability of Imatinib

PATIENTS AND METHODS:

This was a retrospective study done on patients who were diagnosed to have adenoid cystic carcinoma in the last ten years and treated with Imatinib in the department of radiotherapy. There were 35 patients treated from 2003 – 2013 and among them Imatinib was started in 7 patients. All the patients had histologically proven disease and CD 117 was positive in all of them. They all had either loco regionally advanced or metastatic disease. The data was collected from the Outpatient charts, discharge summaries and the medical reports. Follow up was available for all the patients. All of them underwent response assessment with clinical examination, chest x rays and computerized tomography scans. The information regarding the demographic data tumors characteristics, initial stage, initial treatment received, temporal profile of development of metastases, duration of Imatinib received were collected and analyzed. Imatinib was started in patients with disease recurrence or metastases those tumors had CD 117 positivity. Patients were started with a dose of 400 mg per day except for one patient where it was started at 250 mg per day and then increased to 400 mg after one week. Dose escalation was done for one patient (800 mg once a day) and later decreased to 400 mg once a day due to haematological toxicity. Complete blood counts, liver functiontest and creatinine were checked in all patients before starting therapy and on a monthly basis. The toxicity was graded according to CTCAE criteria version 4. Follow up was done every 3 months and the clinical and radiological assessment were done during each visit. The responses were classified according to the criteria proposed by the Response Evaluation Criteria in Solid Tumours Committee (RECIST)(27).

RESULTS:

The median age of the patients was 40 years. There were 5 female patients and 2 male patients. Most of the tumours were arising from the Maxilla and lungs were the common site of distant metastases. The average time to develop metastases from diagnosis was 60 months. Three patients had stable disease and two patients had progressive disease. Out of the three patients who had stable disease, two had lung metastases, one from diagnosis and the other along the course of the disease. The third patients had only local progression. All the three had received prior treatment with chemotherapy and radiotherapy before initiation of Imatinib. They continue to have stable disease after initiation of Imatinib with a PFS of 32 months , 20 months and 10 months respectively. The first patient continues to live 7 years after diagnosis, the second patient 2 years 4 months after diagnosis and the third patient 11 years after diagnosis. Two patients had progressive disease after initiation of the drug with a PFS(progression free survival) of eight months and 6 months respectively. Both of them had received initial treatment with surgery and radiotherapy earlier and later was started on chemotherapy after they progressed with Imatinib. The first patient had both local and distant metastases(renal) and the second also had local as well as distant metastases(lung).

The first patient had surgery before initiation of Imatinib. There was increase in the renal as well as new bone lesions in the first patient and increase in local as well as lung metastases in the second patient after Imatinib. The first patient continues to live for eight years and eight months and the second patient for five years and five months. The median PFS was 10 months in our patients. The response in two patients could not be assessed as the first patient died within three months of initiation and in the second patient Imatinib was started recently.

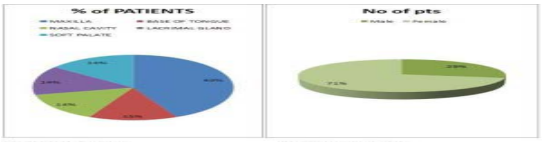

TABLE 1

S.No	Stage at diagnosis	Disease extent at initiation of Imatinib		Response
		Local	Distant	
1	T4aN0M0	Stable disease	Lung metastases	Stable disease
2	T4aN0M1(lung)	Stable disease	Lung metastases	Stable disease
3	T4bN0M1(Bone marrow and skeletal)	Local disease	Bone marrow and Skeletal metastase	Not available
4	T4aN0M0	Local disease	Renal and skeletal	Progressive disease
5	T2N0M0	Disease present	Lung mets	Progressive disease
6	TxN0M0	Stable disease	Lung mets	Stable disease
7	T2N0M0	Stable disease	Lung mets	Not available

CLINICAL CHARACTERISTICS AND RESPONSE TO TREATMENT:

TABLE 2
PATHOLOGICAL CHARACATERISTICS:

Patient No	Close margins	PNI	Grade	CD 117
1	+	-	1	+
2	NA	+	1	+
3	NA	+	3	+
4	+	+	2	+
5	NA	+	2	+
6	+	-	2	+
7	NA	+	1	+

NA – Not available, + = positive, - = negative

TABLE 3:
OTHER TREATMENT RECEIVED:.

	SURGERY	RADIOTHERAPY	CHEMOTHERAPY
1	Total maxillectomy	66 Gy in 33 fractions	6 x CAP*
2	Nil	66 Gy in 33 fractions	6 X CAP*
3	Nil	Nil	Nil
4	Partial excision and laser excision later	66 Gy in 33 fractions	6 X CAP*
5	Partial maxillectomy	66 Gy in 33 fractions	6 X CAP*
6	Excision biopsy and reexcision for four times	25 fractions(complete data not available)	6 X CAP*
7	Excision biopsy	66 Gy in 33 fractions	Nil

*abbreviation – Cisplatin, Adriamycin , Cyclophosphamide

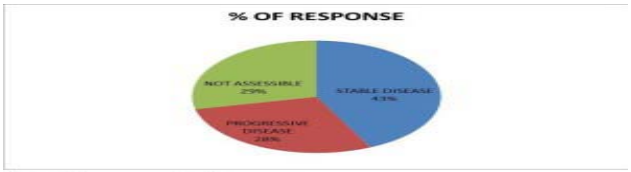

Fig 3: Diagram representing the responses

Fig 4: Progression free survival of all the patients

TOXICITY:

One patient had grade 2 haematological toxicity(anaemia) with a higher dose of 800 mg. The dose was decreased to 400 mg once a day and drug was continued. The other patients tolerated the treatment well.

DISCUSSION:

Adenoid cystic carcinoma is a rare tumour of the minor and major salivary glands. Surgical treatment is the mainstay of treatment and radiotherapy when added to patients who have pathological indications (close margins and PNI) has shown to improve the local control rates. Despite this one third of patients fail systemically and effective treatment to tackle this problem is lacking as to date(8). Imatinib was introduce d as a treatment option in ACC due to C- Kit positivity and lack of standardized systemic therapy. It has shown good activity in gastro intestinal stromal tumours and has been approved by FDA for the same. The natural history of our patients were in concordance of those described in the literature. Most of them had a protracted, indolent clinical course and the time to metastasize was almost 5 years(28). In our patients, three patients (42%) exhibited stable disease for 32 months, 20 months and 10 months respectively and two patients (28%) showed progressive disease after PFS of 8 months and 6 months. Our results were in line with the phase 2 studies.

There seem to be correlation between Grade and PNI with the outcome. Patients who had both grade 2 and PNI had progressive disease. One patient who had grade 3 and PNI survived only for three months after diagnosis. This also was suggestive of poor outcomes in patients with sinonasal primaries. In our observation we found that when Imatinib was started in patients who had good local control, they exhibited better outcomes than those who had uncontrolled disease at the primary site, irrespective of the primary treatment received.

There could be many reasons for varying response of Imatinib. One study by Heinrich suggested that mere positivity of C –Kit is not always sufficient to predict response to Imatinib. The basic mutations of the gene and its sensitiveness might help us to determine to select patients for this drug. The limited efficacy of Imatinib in adenoid cystic carcinomas does not mean that targeted therapy has no hope in this tumour. Recent studies have led to the discovery of new targets(new genetic alterations) (29) for the treatment. Due to the scarcity of the patients, large number of patients and further studies are needed for standardization of Imatinib therapy in different settings in adenoid cystic carcinoma.

BIBLIOGRAPHY:

1. Fordice J, Kershaw C, El-Naggar A, Goepfert H. Adenoid cystic carcinoma of the head and neck: predictors of morbidity and mortality. Arch Otolaryngol Head Neck Surg. 1999 Feb;125(2):149–52.
2. Gates GA. Minor salivary gland tumors of the oral cavity. Otolaryngol Clin North Am. 1972 Jun;5(2):283–9.
3. Miglianico L, Eschwege F, Marandas P, Wibault P. Cervico-facial adenoid cystic carcinoma: Study of 102 cases. Influence of radiation therapy. Int J Radiat Oncol. 1987 May;13(5):673–8.
4. Hotte SJ, Winquist EW, Lamont E, MacKenzie M, Vokes E, Chen EX, et al. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. J Clin Oncol Off J Am Soc Clin Oncol. 2005 Jan 20;23(3):585–90.
5. Ellington CL, Goodman M, Kono SA, Grist W, Wadsworth T, Chen AY, et al. Adenoid cystic carcinoma of the head and neck: Incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data. Cancer. 2012 Sep 15;118(18):4444–51.
6. Spiro RH, Huvos AG. Stage means more than grade in adenoid cystic carcinoma. Am J Surg. 1992 Dec;164(6):623–8.
7. Khan AJ, DiGiovanna MP, Ross DA, Sasaki CT, Carter D, Son YH, et al. Adenoid cystic carcinoma: a retrospective clinical review. Int J Cancer J Int Cancer. 2001 Jun 20;96(3):149–58.
8. Garden AS, Weber RS, Morrison WH, Ang KK, Peters LJ. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with

radiation. Int J Radiat Oncol Biol Phys. 1995 Jun 15;32(3):619–26.9. Shintani S, Funayama T, Yoshihama Y, Alcalde RE, Ootsuki K, Terakado N, et al. Expression of c-erbB family gene products in adenoid cystic carcinoma of salivary glands: an immunohistochemical study. Anticancer Res. 1995 Dec;15(6B):2623–6.
10. Sugano S, Mukai K, Tsuda H, Hirohashi S,Furuya S, Shimosato Y, et al. Immunohistochemical study of c-erbB-2 oncoprotein overexpression in human major salivary gland carcinoma: an indicator of aggressiveness. Laryngoscope. 1992 Aug;102(8):923–7.
11. Cho KJ, Lee SS, Lee YS. Proliferating cell nuclear antigen and c-erbB-2 oncoprotein expression in adenoid cystic carcinomas of the salivary glands. Head Neck. 1999 Aug;21(5):414–9.
12. Papadaki H, Finkelstein SD, Kounelis S, Bakker A, Swalsky PA, Kapadia SB. The role of p53 mutation and protein expression in primary and recurrent adenoid cystic carcinoma. Hum Pathol. 1996 Jun;27(6):567–72.
13. Simpson JR, Thawley SE, Matsuba HM. Adenoid cystic salivary gland carcinoma: treatment with irradiation and surgery. Radiology. 1984 May;151(2):509–12.
14. Vikram B, Strong EW, Shah JP, Spiro RH. Radiation therapy in adenoid-cystic carcinoma. Int J Radiat Oncol Biol Phys. 1984 Feb;10(2):221–3. 15. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. Management of minor salivary gland carcinomas. Int J Radiat Oncol. 1996 Jun 1;35(3):443–54.
16. Tannock IF, Sutherland DJ. Chemotherapy for adenocystic carcinoma. Cancer. 1980 Aug 1;46(3):452–4.
17. Hill ME, Constenla DO, A'Hern RP, Henk JM, Rhys-Evans P, Breach N, et al. Cisplatin and 5- fluorouracil for symptom control in advanced salivary adenoid cystic carcinoma. Oral Oncol. 1997 Jul;33(4):275–8.
18. Vermorken JB, Verweij J, de Mulder PH, Cognetti F, Clavel M, Rodenhuis S, et al. Epirubicin in patients with advanced or recurrent adenoid cystic carcinoma of the head and neck: a phase II study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol Off J Eur Soc Med Oncol ESMO. 1993 Nov;4(9):785–8.
19. Airoldi M, Fornari G, Pedani F, Marchionatti S, Gabriele P, Succo G, et al. Paclitaxel and carboplatin for recurrent salivary gland malignancies. Anticancer Res. 2000 Oct;20(5C):3781–3.
20. Airoldi M, Pedani F, Succo G, Gabriele AM, Ragona R, Marchionatti S, et al. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. Cancer. 2001 Feb 1;91(3):541–7.
21. Holst VA, Marshall CE, Moskaluk CA, Frierson HF Jr. KIT protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. Mod Pathol Off J United States Can Acad Pathol Inc. 1999 Oct;12(10):956–60.
22. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diag osed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003 Mar 13;348(11):994–1004.
23. Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res Off J Am Assoc Cancer Res. 2002 Oct;8(10):3034–8.
24. Pfeffer MR, Talmi Y, Catane R, Symon Z, Yosepovitch A, Levitt M. A phase II study of Imatinib for advanced adenoid cystic carcinoma of head and neck salivary glands. Oral Oncol. 2007 Jan;43(1):33–6.
25. Ochel H-J, Gademann G, Röcken C, Wördehoff H. Effects of imatinib mesylate on adenoid cystic carcinomas. Anticancer Res. 2005 Oct;25(5):3659–64.
26. Alcedo JC, Fábrega JM, Arosemena JR, Urrutia A. Imatinib mesylate as treatment for adenoid cystic carcinoma of the salivary glands: report of two successfully treated cases. Head Neck. 2004 Sep;26(9):829–31. in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer Oxf Engl 1990. 2009 Jan;45(2):228–47.
28. Matsuo M, Rikimaru F, Higaki Y. [Clinical study on 72 cases of adenoid cystic carcinoma]. Nihon Jibiinkoka Gakkai Kaiho. 2013 Jan;116(1):10–6.
29. Frierson HF Jr, El-Naggar AK, Welsh JB, Sapinoso LM, Su AI, Cheng J, et al. Large scale molecular analysis identifies genes with altered expression in salivary adenoid cystic carcinoma. Am J Pathol. 2002 Oct;161(4):1315–23.