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Treatment Response and Locoregional Control in Locally Advanced Oral Cavity Cancers with Concurrent Chemoradiation and Radiation Alone

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Abstract

Aim: To clinically determine the treatment response and locoregional control in locally advanced oral cavity cancers with concurrent chemoradiation and radiation alone. *Materials and Methods:* This study was carried out in department of Radiotherapy, MNJ Institute of Oncology & Regional Cancer Center, Hyderabad from October 2010 to April 2012. A total of 50 patients with histologically proven squamous cell carcinoma of oral cavity was enrolled in this study. In this prospective study, patients were randomized to receive either chemoradiation alone (arm –A) or radiotherapy alone (arm-B). Response rate & locoregional control are primary end points, toxicity profile and feasibility are secondary end points. *Inclusion Criteria:* Patients with age < 60 years, both sexes. Patients with histologically proven advanced squamous cell cancer of the oral cavity (stage III & IV). Karnofsky's performance scale ≥ 70. Haematopoietic : Hemogram >10 gm /dl, Total WBC count > 6000/mm^3 and Platelet count > 1,00,000/ mm. Renal: Serum creatinine ≤1.5 mg/dl (or) creatinine clearance ≥ 60 ml/min, Hepatic : Bilirubin ≤ 1.5 times upper limit of Normal (ULN), AST (or) ALT < 2 times of ULN. Alkaline phosphate ≤ 1.5 times ULN , Normal chest X-ray. *Exclusion Criteria:* Patients with age above 60 years. History of previous treatment with any of the following modalities–Surgery, radiotherapy, chemotherapy. Patient with distant metastasis. Hemoglobin <10 gm%. Associated co-morbid conditions: Untreated tuberculosis, Uncontrolled diabetes mellitus and Uncontrolled Hypertension. *Results:* In this prospective study conducted from October 2010 to April 2012, a total of 50 patients proven cases of squamous cell carcinoma of oral cavity were enrolled, 25 patients in chemoradiation (arm-A) and 25 in radiotherapy alone (arm-B). Out of which 2 patient dropped out in arm-A. 23 patients in chemoradiation arm received cisplatin 40 mg/m^2/ week for 6 cycles with Radiotherapy (66 Gy in 33 Fr 2 Gy/Fr, 5 days in a week) and 25 patients in radiation alone arm received 66 Gy in 33 Fr 2 Gy/Fr, 5 days in a week. There was good balance in prognostic factors, including performance status, tumor and nodal stages and histology between the two arms. buccal mucosa is predominant site of distribution in both arms. TNM Stage in arm-A, among 23 patients, 8 were in stage III and 11, 4 in stage IVA and IV B and in arm-B, out of 25patients, 8 in stage III and 13, 4 in stage IV A and IV B, respectively with a probability value (P=0.94) for stage. All the 100% patients in both arms completed the radiation procol that is 66 Gy in 33 Fr 2 Gy/Fr, 5 days in a week for 6.5 weeks. In arm-B (n=23), when compliance to chemotherapy considered, majority completed 6 cycles of chemotherapy. 87% (20/23) patients completed the full course of 6 cycles of chemotherapy. Only 13%(3/23) patients received cycles of chemotherapy. The complete response of primary tumor with T3 stage in chemoradiation arm was seen in 65%(5/8)and partial response in 35% (3/8) of the patients. The corresponding figures in the radiation alone arm were 50%(4/8) and 50% (4/8) respectively. The complete response seen in patients with T4a and T4b tumors in chemoradiation arm was 45%(5/11), 30%(1/4) and partial response was 55%(6/11) , 70%(3/4) while in the radiation alone arm, it is 35%(5/13), 20% complete response and 65% (8/13). 80% partial response. The median time to response from the end of the radiation was 3 months. *Conclusion*: Despite statistical insignificance locoregional control (tumor response) is superior (numerical benefit) with concurrent chemoradiation as compared to radiotherapy alone in locally

advanced head and neck malignancies (oral cavity).

Keywords: Oral Cavity; Chemoradiation.

Introduction

Oral cancers are heterogenous group of cancers arising from different parts of oral cavity with different predisposing factors, prevalence and treatment outcomes.

Globally, there is a wide variation in incidence and mortality of oral cancers in different regions around the world with an annual incidence of over 3,00,000 cases of which 62% arise in developing countries with highest rates found in Melensia. In comparison with US population, where oral cavity represents only about 3% of malignancies. It accounts for over 30% of all cancers in India [1]. Oral cancers mainly effects middle aged and elderly people, but recently, it has been observed that there is increased incidence of oral cavity cancers among young adults (tongue cancer). Predominance in males. Traditional therapy for locoregionally advanced squamous cell head and neck cancer consists of surgery followed by postoperative radiotherapy.

Although this approach is curative in intent, majority of patients develop locoregional recurrence at the primary or regional site within the first two years of treatment. Hence only 30% of stage III and stage IV head and neck cancers are cured and the five year survival rate remains below 40%. In addition, the frequently aggressive surgical procedures, though technically feasible, results in significant long term anatomic, functional, and psychological sequelae in the surviving patient. This has led to the development of organ-preserving treatment strategies. Patients with advanced stage head and neck cancer are also at risk of developing distant metastases, though this occurs less frequently than does locoregional failure. Finally surviving patients are at a life long risk of developing a second malignancy, which results from field carcinogenesis in the aero-digestive tract caused by long term exposure to alcohol and tobacco, and need medical surveillance for other potentially related diseases. To improve head and neck cancer treatment outcomes, alternative modalities like concurrent chemotherapy with radiotherapy and altered fractionation radiation schedules are being tested in various head and neck trials. Concomitant chemo radiotherapy has frequently been studied in advanced stage III and stage IV head and neck cancers patients or in those with unresectable disease. Several recent studies and meta analyses have indicated superior locoregional control and / or survival rates after concomitant chemo radiotherapy when compared with radiotherapy alone. Thus, a concomitant chemoradiation approach seems to be superior to both radiotherapy alone and the sequential chemotherapy and radiotherpy approach. Munro AJ et al [2]. performed a meta-analysis of the published results from 54 randomized controlled trials of chemotherapy in head and neck cancer. They found an overall benefit to adding chemotherapy of 6.5% (3.7% for induction, 12.1% for concomitant, adjuvant chemotherapy was not assessed). Single agent chemotherapy given synchronously with radiotherapy increased survival by 12.1%.

Materials and Methods

This study was carried out in department of Radiotherapy, MNJ Institute of Oncology & Regional Cancer Center, Hyderabad from October 2010 to April 2012. A total of 50 patients with histologically proven of Squamous Cell Carcinoma of oral cavity was enrolled in this study. In this prospective study, patients were randomized to receive either chemoradiation alone (arm –A) or radiotherapy alone (arm-B). Response rate & locoregional control are primary end points, toxicity profile and feasibility are secondary end points.

Inclusion Criteria

Patients with age < 60 years, both sexes. Patients with histologically proven advanced squamous cell cancer of the ora cavity (stage III & IV). Karnofsky's performance scale ≥ 70. Haematopoietic: Hemogram >10 gm/dl, Total WBC count > 6000/mm^3 and Platelet count >1,00,000/mm. Renal: Serum creatinine ≤ 1.5 mg/dl (or) creatinine clearance ≥ 60 ml/min, Hepatic: Bilirubin ≤ 1.5 times upper limit of Normal (ULN), AST (or) ALT < 2 times of ULN. Alkaline phosphate ≤ 1.5 times ULN , Normal chest X-ray.

Exclusion Criteria

Patients with age above 60 years. History of previous treatment with any of the following modalities – Surgery, radiotherapy, chemotherapy. Patient with distant metastasis. Hemoglobin <10 gm%. Associated co-morbid conditions: Untreated tuberculosis, Uncontrolled diabetes mellitus and Uncontrolled Hypertension.

Pre-Treatment Evaluation

A complete detailed history which includes presenting complaints, past history, family history, personal history and socio-economic history with emphasis on personal habits like tobacco and alcohol consumption. General physical examination including height, weight and performance status.Systemic examination. Local examination & staging . Complete blood picture (as in criteria). Renal function test- Blood urea and serum creatinine (1.5 mg /dl). Liver function test (as in criteria). Biopsy from the primary tumor and/or FNAC of metastatic lymph nodes. Complete dental examination & dental extraction of the decayed and loose tooth under antibiotic cover. Chest X-ray. (PAview). X-ray mandible. (Panorex/Lateral oblique view). CT scan /MRI scan. (optional).

When all the investigations were within normal limits, patient's written consent was taken after explaining the nature of disease, its treatment and side effects in his own vernacular language. Patient were counseled about the ill effects of tobacco and alcohol consumption and asked to discontinue the same. Patients were also counseled regarding maintaining good oral hygiene throughout the treatment.

A prospective comparative study with total 50 patients – 25 patients in each arm.

In Arm –A, Chemoradiation (cisplatin 40 mg/m^2 / weekly for 6 cycles plus RT).

In Arm –B, Radiotherapy alone (66 Gy in 33 Fr 2 Gy/Fr, 5 days in a week).

In both arms – external beam radiation was delivered by simulating the patient supine with the head on a head rest device, Palpable neck disease should be outlined with wires. For tongue cancers, a bite block may be used to depress the tongue down and away from the palate, allowing easier avoidance of the palate and preventing bolus effect from closure of the mouth. Immobilize with a thermoplastic head (± shoulders) mask. Machine used were patients were treated on LINAC machine with SSD 100 cm. Target Volume was initial tumor volume consists of primary tumor, involved lymph nodes and possible sub-clinical disease. The irradiation field is reduced to include only the gross disease and involved lymph nodes by shielding the spinal cord after 44 Gy in 22 Fr. Depending on the primary tumor site, patients were treated with ipsilateral anterolateral wedge pair technique or two parallel opposed lateral fields or three field technique i.e., two parallel opposed lateral fields and a low neck field (AP) with central block when required. Simulation X-ray film was taken for verification of radiation portals and necessary corrections were made before the start of treatment. The radiation dose delivered was 66 Gy in 33 Fr (2 Gy/Fr, 5 days in a week) in 6.5 weeks. The spinal cord was shielded after 44 Gy in 22 Fr in some cases depending upon the initial treatment technique used.

In chemoradiation arm, single agent cisplatin given concurrently with radiotherapy (66 Gy in 33 Fr. / 2 Gy/5week over 6-7 weeks. The dosage used was 40 mg/m2 weekly for 6 cycles. Premedication with dexamethasone, ranitidine and anti-emetics like granisetron were given before cisplatin infusion. Adequate hydration consisting of dextrose normal saline added with KCl and MgSo4 was given before cisplatin infusion to prevent renal toxicity. Cisplatin calculated according to patient body surface area was added to normal saline and is given over 1 hour IV infusion. It is followed by radiotherapy within one hour after completion of infusion. Post chemotherapy hydration is given with ringerlactate to all the patients. Myelosuppression and renal toxicity is evaluated by doing complete hemogram, blood urea and serum creatinine weekly.

Chemotherapy induced toxicity like nausea, vomiting and renal and hematological toxicities were assessed as per the Common Terminology Criteria for Adverse Events (CTCAE v4.0). The first follow-up was done at 4-6 weeks after the completion of treatment. During follow up the patients were assessed for response of the primary and the node are noted down. Follow-up of the patient was made once in 3 months thereafter till date of analysis.

Results

A total of 50 patients proven cases of squamous cell carcinoma of oral cavity were enrolled, 25 patients in chemoradiation (arm-A) and 25 in radiotherapy alone (arm-B). Out of which 2 patient dropped out in arm-A. 23 patients in chemoradiation arm received cisplatin 40 mg/m^2/week for 6 cycles with Radiotherapy (66 Gy in 33 Fr 2 Gy/Fr, 5 days in a week) and 25 patients in radiation alone arm received 66 Gy in 33 Fr 2 Gy/Fr, 5 days in a week. There was good balance in prognostic factors, including performance status, tumor and nodal stages and histology between the two arms.

In arm-A, the mean age was 46.5yrs and in arm-B, the mean age was 49.2 years and overall pooled mean age for study population was 47.9 years with a probability value (P=0.29) for age. In arm-A among 23 patients , 16 patients were male and 7 were female and in arm-B 15 patients were male and 10 patients

were female with a probability value (P=0.49) for sex. Approximately male to female ratio is 2:1 in both arms.

Buccal mucosa is predominant site of distribution in both arms. 20 patients (86.9%) in arm-A had a performance status of KPS > 70 and 3 patients (13.1%) had KPS of 80 and in arm-B among 25 patients, 21 patients had KPS of > 70 and 4 patients (16%) had KPS of 80. In arm-A, among 23 patients, 8 were in stage III and 11, 4 in stage IVA and IV B and in arm-B, out of 25patients, 8 in stage III and 13, 4 in stage IV A and IV B, respectively with a probability value (P=0.94) for stage.

When compliance to radiotherapy was considered, all the 100% patients in both arms completed the radiation procol that is 66 Gy in 33 Fr 2 Gy/Fr, 5 days in a week for 6.5 weeks.

In arm-B (n=23), when compliance to chemotherapy considered, majority completed 6 cycles of chemotherapy. 87%(20/23) patients completed the full course of 6 cycles of chemotherapy. Only 13%(3/23) patients received cycles of chemotherapy

Table 1: Demographic distribution in study

Patient characteristics	CT+RT (Arm-A)	RT (Arm-B)
Total No. of patients included in study	25	25
Total No. of patients completed study	23	25
Mean age of diagnosis	46.5	49.2
Age distribution		
20-30	1	1
31-40	7	2
41-50	7	11
51-60	8	11
Sex distribution		
Male	16	15
Female	7	10

Table 2: Primary site distribution and TNM staging of the tumour.

Primary site distribution	CT + RT (Arm-A)	RT (Arm-B)
Buccal Mucosa	14	10
Floor of Mouth	3	3
Hard Palate	4	3
Lip	1	1
Alveolus	1	1
Tongue	1	4
RMT	1	1
Tumour Stage		
T3	8	8
T4a	11	13
T4b	4	4
Nodal Stage		
N0	8	2
N1	10	15
N2a	2	3
N2b	1	2
N3	2	1
TNM Stage		
Stage III	8	8
Stage IVA	11	13
Stage IVB	4	4
Grade of the tumor		
Well differentiated	13	11
Moderately differentiated	10	14

Table 3: Overall compliance to treatment in chemoradiation arm

Parameters	No of Patients (n=23)	Percentage
Radiotherapy	23	100
Chemotherapy(6 cycles)	20	87
Chemotherapy(4cycles)	3	13
RT +CT(6 Cycles)	20	87

The complete response of primary tumor with T3 stage in chemoradiation arm was seen in 65% (5/8) and partial response in 35%(3/8) of the patients. The corresponding figures in the radiation alone arm were 50%(4/8) and 50%(4/8) respectively. The complete response seen in patients with T4a and T4b tumors in chemoradiation arm was 45% (5/11), 30%(1/4) and partial response was 55% (6/11) , 70% (3/4) while in the radiation alone arm, it is 35%(5/13), 20% complete response and 65% (8/13). 80% partial response. The median time to response from the end of the radiation was 3 months.

Mucositis and nausea/vomiting were the most common acute side effects, seen pre-dominantly in chemoradiation. Mucosal toxicity in Grade II and III toxicity 70% and 60.8% in chemoradiation arm and 50 & 40% in radiation alone arm with p=0.2. Out of 23 patients in arm-A 12 patients (52.1%) had grade 3 skin reactions compared to (32%) 8 patients in arm-B with a probability value P=0.13. No one developed hematological or renal toxicity in either arms. Weight loss was seen towards the lateral half of treatment in both arms. At the end of treatment patients developed 21% patients has average weight loss of 4 Kg in CT/RT arm and 12% patients has average weight loss of 2 Kg in RT alone arm, which seems to be due to poor intake because of the debilitating oral mucosal reactions. These patients were admitted and given hydration and enteral feeding till mucositis subsides.

Table 4: Response rate based on TNM stage

T Status	Arm A		Arm B	
	CR	PR	CR	PR
T3	65%	35%	50 %	50%
T4a	45%	55%	35%	65%
T4b	30%	70%	20%	80%
N Status	**Arm A**		**Arm B**	
	CR	PR	CR	PR
N1	80%	20%	70%	30%
N2a	65%	35%	55%	45%
N2b	50%	50%	40%	60%
N3	20%	80%	15%	85%
TNM Status	**Arm A(n=23)**		**Arm B(n=25)**	
	CR	PR	CR	PR
Stage – III	65%	35%	55%	45%
Stage IV –A	45%	55%	35%	65%
Stage IV –B	30%	70%	20%	80%

Fig. 1: Shows Grade 1 mucositis

Fig. 2: Shows Grade 2 mucositis

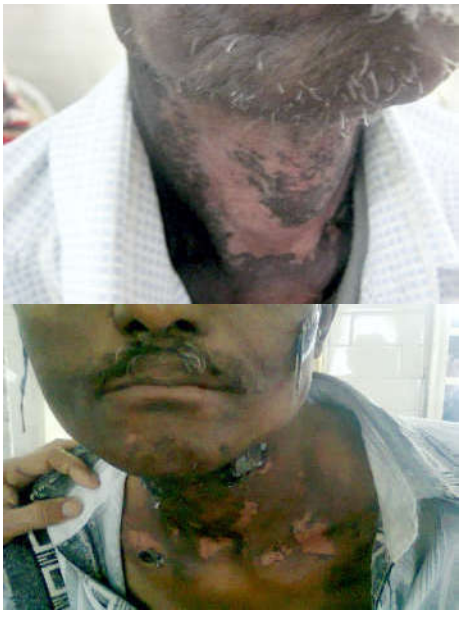

Fig. 3: Shows grade II skin toxicity

Table 5: Adverse effects in study

Acute Toxicity	Grade-1	Grade–2	Grade-3
Arm-A	90%	70%	60%
Arm-B	80%	50%	40%
Skin Toxicity			
Arm A	90%	70%	52.1%
Arm B	80%	55%	32%
Nausea			
Arm A	45%	36%	30%
Arm B	35%	20%	4%
Vomiting			
Arm A	25%	15%	4%
Arm B	4%	--	--

Discussion

Oral cancers constitutes 30% of head & neck cancers. Most of them present at advanced stages where dominant pattern of failure is locoregional. This study is to compare locoregional control and toxicity profile of concurrent chemoradiation with radiation alone in biopsy proven squamous cell carcinoma of oral cavity. The evidence in recommending platinum based concurrent chemoradiation as the standard of care for locoregionally advanced Squamous cell carcinoma head and neck cancers comes from rigorously conducted randomized controlled trials and metaanalysis. The updated metaanalysis of chemotherapy in head and neck cancer (MACH-NC) confirmed the finding of the original report of 4% overall survival benefit with Chemotherapy. It also demonstrated a relative 19% improvement in survival (hazard ratio 0.81, P<0.001) for concomitant therapy translating into an 8% absolute benefit in overall survival with platinum based regimens in the concurrent setting. In this study total of 50 patients enrolled. 25 patients in each arm. Median age group was 47.9 years. Male to female ratio is 2:1. Most of the patients has buccal mucosa as predominant site, this is consistent with literate data review of Gupta et al [3] because of most of them chew betal nut and tobacco, keep the quid in gingio buccal sulcus for longer period of time. In arm-A among 23 patients, 8 were stage III and 11 in IV A and 4 in stage IV B and in arm-B also 8 in stage III and 13 in IV A and 4 in stage IV B. In the present study, out of 50 patients, 23 patients in arm-A and 25 patients in arm-B were available for analysis. In arm-A, majority (87%) completed the intended treatment protocol i.e concurrent chemoradiotherapy, cisplatin (40mg/m^2 /week) for 6 cycles plus RT (66 Gy in 33 Fr 2 Gy/Fr, 5 days in a week). 13% completed only 4 cycles of chemotherapy ,the other two cycles chemotherapy could not be administrated as patient developed, severe mucositis associated with pain, but they completed RT protocol. In radiation alone arm all 25 patients completed the radiation protocol. The mean overall treatment is 54 days. Cisplatin chemotherapy (40mg/m^2) were used in the study, because the intent of adding chemotherapy was to utilize the radio sensitivity property rather than the cytotoxicity of the drug itself. This is consistent with the dose of radio sensitization as quoted in literature (Loredana et al) [4]. Fountzilas G et al [5] with 124 patients conducted phase-III randomized trial with standard fractioned RT alone (Arm-A) with same RT concomitantly with Cisplatin (100 mg/m^2 on D2, D22 and D42) (Arm-B) or carboplatin (7AUC on D2,22, 43) (arm-C). the median overall survival is superior in arm-B compared to the rest 2 arms. David et al [6]. conducted phase-III randomized trial comparing concurrent chemoradiation (3 weekly) with radiotherapy alone and concluded that projection for local control without surgical resection were 77% versus 45% (P<0.001). Three weekly cisplatin at a dose of 100mg/ m2 concurrently with RT is considered to be the standard of care for nonsurgical treatment of advanced head and neck cancers based on several phase III trials. However these protocols has been associated with significant acute and late toxicity. Therefore splitting full dose three weekly cisplatin as weekly cisplatin schedule might decrease toxicity and increase compliance while maintaining dose intensity. F. Kose et al [7] from Baskent University experience concluded that concurrent chemoradiotherapy with weekly cisplatin can be accepted as effective as concurrent chemoradiotherapy with 3 weekly high dose bolus cisplatin. Homma A et al [8] concluded that weekly cisplatin could be easier to manage than three weekly cisplatin because patients can be monitored more regularly for toxicity allowing the schedule to be altered if required. This regimen appears to be a suitable alternative to three weekly high dose cisplatin with concomitant radiotherapy. One of the initial trials using weekly cisplatin in nasopharyngeal

carcinoma reported by Chan et al [9] in this trial 5 year overall survivalwas 70.3% vs. 58.6% (P=0.049) for the chemoradiotherapy and Radiotherapy arm. Boulmay et al [10] regarding validation of weekly dose cisplatin combined with radiotherspy in locally advanced head and neck cancers, concluded that concomitant weekly CDDP with full course radiation is feasible, tolerable, higly active and compliant. Z.A Otty et al, in a retrospective analysis, efficacy of weekly cisplatin 40 mg/m2 in definitive adjuvant chemoradiation of head and neck cancers concluded that survival figures and toxicity profile of low dose cisplatin are comparable to historical controls using high dose regimens. Kerstein M et al, in chemoradiation for locally advanced oral cavity cancers. Study data support the use of primary chemoradiotherapy as a viable treatment option for patients with advanced oral cavity cancers, survival is high and overall function for the majority of patients is satisfactory. Patients with T4 oral tongue cancer may be spared total glossectomy. In the more recent phase-III randomized trial Sharma et al [11], reported improved response rate 79.2% Vs. 69.7% (p <0.05) and 3 years overall survival 62% vs. 42% (p=0.024) for concurrent weekly cisplatin as compared to radical radiotherapy alone. This however are achieved at a cost of increased grade III to IV toxicity (40% vs. 16%, P< 0.05). Mucosal toxicity concerned 14 patients (60.8%) in arm-A had grade 3 mucositis comparative to 10 patients (40%) in arm-B. Out of 23 patients in arm-A 12 patients (52.1%) had grade 3 skin reactions compared to (32%) 8 patients in arm-B. In chemoradiation arm 36% has grade 2 nausea and 15% had grade 2 vomiting compared to 20% & 0% in Radiotherapy alone arm. 21% patients has average weight loss of 4 Kg inchemoradiation arm and 12% patients has average weight loss of 2 Kg in RT alone arm. Patients were admitted in wards and given supportive care whenever required. The overall treatment response in stage III (65% complete response and 35% partial response), stage IV (37.5% complete response and 62.5% partial response) in chemoradiation arm compared to stage III (55% complete response and 45% partial response). Stage IV (27.5% complete response and 72.5% partial response) in radiation alone arm. In this study,the overall complete response in chemoradiation arm and radiotherapy alone arm was 47.8% vs 36%, with probability p=0.41. Despite of improvement in tumour response in terms of locoregional control in chemoradiation arm compared to radiation alone arm, the p value was statistically not significant, due to limited number of population in this study. Long term follow-up was not feasible. Hence conclusion is not possible on the parameters like late toxicity, disease free survival and overall survival. This study was limited by its small number and short follow up and hence further studies comparing concurrent chemotherapy with radiotherapy in advanced oral cavity cancers will be of value in reaching a consensus.

Conclusion

Despite statistical insignificance locoregional control (tumor response) is superior (numerical benefit) with concurrent chemoradiation as compared to radiotherapy alone in locally advanced head and neck malignancies (oral cavity). Concomitant weekly cisplatin with full course radiation is feasible, tolerable and compliant. The toxicity with concomitant chemoradiotherapy is in acceptable limits and can be medically managed with supportive care.

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