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Review

Barriers to clinical trial recruitment in head and neck cancer

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SUMMARY

Despite substantial improvements in the treatment of head and neck cancer (HNC) over the last two decades, overall survival rates remain unsatisfactory. The need for improved therapeutic approaches for HNC patients is hampered by low patient recruitment rates in HNC clinical trials, particularly Phase III studies. Based on an analysis of ClinicalTrials.gov, this article identified several potential barriers to patient recruitment in Phase I–III clinical trials of treatments for HNC. Of 694 HNC trials identified on ClinicalTrials.gov from multiple sites worldwide, 91 (13.1%) were identified as either terminated, suspended or withdrawn; 27.5% ($n = 25$) of these did not provide an additional reason for stopping recruitment early. Insufficient accrual was the most common reason provided for trial closure ($n = 23$, 25.3%). Possible reasons for the insufficient accrual rates include the inappropriate designs of these studies given the change in HNC tumour biology in the last 20 years, the low incidence of the disease, and the diversity of treatment standards and referral processes across countries. Given the low numbers of drugs approved for HNC, it is important that barriers to recruitment in this field are addressed to allow new therapies to be successfully validated in completed clinical trials. This review discusses how these accrual challenges may be overcome with changes to clinical trial designs, including their adaptation to specific subgroups, such as human papillomavirus-positive patients.

Introduction

Substantial improvements have been made in the treatment of head and neck cancer (HNC) over the last two decades, with a multidisciplinary treatment schedule now being the standard approach. Treatment options include surgery, concurrent chemoradiotherapy (CCRT), radiotherapy alone, chemotherapy alone, induction chemotherapy followed by radiotherapy or CCRT, or targeted agents, depending on the primary site of the tumour and disease stage [1]. In the locoregionally advanced setting, overall survival (OS) rates vary depending on the characteristics of the patient (e.g. tumour stage, human papillomavirus (HPV) association, site of tumour) [2–6]. OS in recurrent and/or metastatic patients is only around 7 months [7]. In Europe, the OS rate for HNC patients, irrespective of disease stage, is 72% at 1 year and 42% at 5 years, with 5-year OS rates being lower in men than women (39% vs. 51%) and lower in patients aged ⩾75 years versus those aged 15–45 years (35% vs. 54%) [8]. Therefore, ongoing studies are investigating new therapeutic approaches that may improve the standard of care in HNC patients.

A large number of oncology clinical studies face accrual and retention challenges [9], and this has been described as the ultimate inefficiency in the success of clinical trials. In a previous analysis, 419 Cancer Therapy Evaluation Program (CTEP)-approved National Cancer Institute (NCI)-sponsored Phase I–III, nonpediatric clinical trials activated between 2000 and 2004 were investigated for an 8-year period [10]. Successful trials were those achieving 100% of the minimum accrual goal. A large percentage of these trials did not achieve the minimum projected accrual (37.9%); this was particularly the case for Phase III trials ($n = 34/48$; 70.8%). Of the 29 Phase III trials closed to accrual, 18 (62.1%) did not attain the accrual goal. Moreover, this analysis showed that there is an inverse relationship between long clinical trial development and poor accrual performance [10]. In another analysis, 26.7% of 149 CTEP-approved Phase III nonpediatric trials led by the NCI failed to achieve at least 90% of their accrual objectives owing to inadequate accrual, varying from 13% of breast cancer trials to 37.5% of trials in women with genital tract tumours [9]. These data highlight the accrual challenge in Phase III cancer studies, which is a problem mirrored in HNC clinical trials. However, it is unknown whether specific barriers exist in HNC trials per se, or if the barriers observed in oncology

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trials in general contribute to the lack of patient enrolment in this disease setting. Based on an analysis of ClinicalTrials.gov and TrialTrove, this article assesses the potential barriers to patient recruitment in clinical trials of treatments for HNC.

Methods

On 8 August 2013, an initial ClinicalTrials.gov advanced search was carried out to identify all currently registered Phase 0–IV trials investigating HNC, regardless of trial status. The advanced search fields were defined as: Conditions – Head and neck cancer; Recruitment – All studies; Study type – Interventional studies; Phase – All phases. These search findings were further analysed to identify HNC trials that were listed as 'Completed' or 'Closed'. 'Closed' trials included those that were designated as 'terminated' (study stopped recruiting or enrolling participants early and will not start again; participants are no longer being examined or treated), 'suspended' (study stopped recruiting or enrolling participants early, but may start again) or 'withdrawn' (study stopped recruiting before enrolling its first participant).

Trials included in the final analysis were defined as closed Phase I–III trials (terminated, suspended or withdrawn) investigating interventional therapies (including targeted therapy, immunotherapy, chemotherapy, gene therapy and radiotherapy) in the treatment of patients with HNC (including head and neck squamous cell carcinoma [HNSCC], cancers of the oral cavity, larynx, oropharynx, hypopharynx, nasopharynx and salivary glands). All lines of treatment were allowed, including neoadjuvant, induction, definitive (with or without surgery or chemoradiotherapy), adjuvant, maintenance, first-line, second-line, further-line and palliative therapy. Exclusion criteria included trials not designed primarily as HNC trials (e.g. trials including various types of solid tumours in addition to HNC), trials not designed primarily to measure the efficacy and safety of the therapy (e.g. studies focusing on management of disease side effects), behavioural studies, investigations of devices or procedures, imaging studies, vaccines, dietary supplements, and observational studies. TrialTrove was also utilised to determine target and actual patient accrual.

Results

A total of 694 Phase 0–IV HNC trials were identified on ClinicalTrials.gov, irrespective of trial status, approximately 14 years since ClinicalTrials.gov was made publicly available in February 2000. Of the trials identified, 218 (31.4%) were listed as completed, and 91 (13.1%) Phase I–III trials were listed as terminated, suspended or withdrawn (herein referred to as closed trials). The 91 closed trials form the basis for this article.

Overall, HNSCC (including but not limited to cancer of the oral cavity, oropharynx, hypopharynx and/or larynx) was the most frequent patient population studied ($n = 66$, 72.5%), followed by nasopharyngeal carcinoma in eight trials (8.8%; Table 1). The majority of the closed trials were in patients with locoregionally advanced disease ($n = 47$, 51.6%) or recurrent/metastatic disease ($n = 42$, 46.2%), and investigated the specified therapy regimens as either first-line treatment ($n = 38$, 41.8%) or second-line treatment ($n = 34$, 37.4%) in these settings. Over half ($n = 53$, 58.2%) of the trials included sites located in the US, 19.8% ($n = 18$) included countries in Europe, and 11.0% ($n = 10$) included countries in Asia. Over one-third ($n = 35$, 38.5%) of the trials in this analysis received industry funding.

Of the 91 closed HNC studies (listed as suspended, terminated or withdrawn), 27.5% ($n = 25$) did not provide a reason for stopping recruitment early, including seven of the eight trials in nasopharyngeal carcinoma (Table 1). Insufficient accrual (including designations of low/slow/poor accrual, accrual problems and lack of recruitment) was the most common reason provided for trial closure, with 25.3% ($n = 23$) of the total closed trials citing this reason. The other most common reasons for closure were loss of funding/support (12.1%), safety concerns (8.8%) and lack of efficacy (6.6%).

Half of the 23 trials citing insufficient accrual as the reason for closure were Phase II studies ($n = 12$; 52.2%); four (17.4%) Phase III trials were terminated due to low accrual (Table 2). Overall, 65.2% ($n = 15$) of the trials achieved less than 50% of the estimated target accruals. Seven of these trials achieved $\leqslant$10% of the target accrual, with three trials having terminated or withdrawn without a single patient enrolled more than a year after trial initiation. Nearly half

Table 1
Characteristics of terminated, suspended or withdrawn Phase I–III clinical trials in head and neck cancer.

	Trials, *n* (%)
Total	91 (100.0)
Reason for trial closure	
Unknown/no reason disclosed	25 (27.5)
Low accrual	23 (25.3)
Loss of funding/support	11 (12.1)
Safety concerns	8 (8.8)
Lack of efficacy	6 (6.6)
Other reasons[a]	18 (19.8)
Location[b]	
US	53 (58.2)
Europe	18 (19.8)
Asia	10 (11.0)
Central and South America	1 (1.1)
Australia	3 (3.3)
Canada	3 (3.3)
Israel	2 (2.2)
Not provided	13 (14.3)
Patient population	
Head and neck squamous cell carcinoma	66 (72.5)
Nasopharyngeal carcinoma alone	8 (8.8)
Oral cavity/oropharyngeal carcinoma alone[c]	7 (7.8)
Laryngeal carcinoma alone[d]	3 (3.3)
Hypopharyngeal carcinoma alone[e]	2 (2.2)
Salivary gland carcinoma alone	2 (2.2)
Other[f]	3 (3.3)
Disease stage	
Locoregionally advanced[g]	47 (51.6)
Recurrent/metastatic	42 (46.2)
Other[h]	2 (2.2)
Treatment setting[i]	
First-line	38 (41.8)
Second-line	34 (37.4)
Induction/neoadjuvant	10 (11.0)
Adjuvant	7 (7.8)
Maintenance	2 (2.2)

[a] Other includes studies listed as temporarily stopped for assessment or ongoing but not recruiting, or studies that were terminated due to changes in sponsor disease focus or other corporate changes, changes in patient eligibility, principal investigator left the institution, study site closure or failure to open, drug formulation issues, US Food and Drug Administration hold, met study endpoint early, or listed as administratively complete with no other clarification.
[b] Trials performed in multiple countries are listed under more than one country category.
[c] Including cutaneous/lip and oral cavity ($n = 1$).
[d] Including laryngopharyngeal ($n = 1$).
[e] Including + base of tongue ($n = 1$) and + larynx ($n = 1$).
[f] Including upper aerodigestive tract carcinomas ($n = 1$), adenoid cyst carcinoma ($n = 1$), and paranasal sinus cancer ($n = 1$).
[g] Includes early stage and locoregionally advanced nasopharyngeal carcinoma ($n = 1$).
[h] Including dysplastic carcinoma in situ ($n = 1$) and stage I–III supraglottic laryngeal cancer ($n = 1$).
[i] In trials including patients eligible for different lines of treatment, only the primary line under investigation is included.