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Systematic or Meta-analysis Studies

Systemic therapy in the management of recurrent or metastatic salivary duct carcinoma: A systematic review

M.J.M. Uijen[a], G. Lassche[a], A.C.H. van Engen-van Grunsven[b], Y. Tada[c], G.W. Verhaegh[d], J.A. Schalken[d], C.M.L. Driessen[a], C.M.L. van Herpen[a,*]

[a] Department of Medical Oncology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Department of Pathology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[c] Department of Head and Neck Oncology and Surgery, International University of Health and Welfare Mita Hospital, Tokyo, Japan
[d] Department of Urology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands

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ABSTRACT

Background: Salivary duct carcinoma (SDC) is an aggressive subtype of salivary gland cancer. Approximately half of SDC patients will develop recurrences or metastases. Therapeutic palliative therapy is therefore often needed. The majority of SDC tumors expresses the androgen receptor (AR) and one-third expresses human epidermal growth factor receptor 2 (HER2), both are potential therapeutic targets. The aim of this paper is to systematically review and summarize the evidence on systemic palliative therapy for SDC and to provide treatment recommendations.

Materials and methods: Electronic libraries were systematically searched with a broad search strategy to identify studies where SDC patients received systemic therapy. Due to the rarity of SDC no restrictions were placed on study designs.

Results: The search resulted in 2014 articles of which 153 were full-text analyzed. Forty-five studies were included in the analysis, which included in total 256 SDC patients receiving systemic therapy. Two phase 2 trials primarily including SDC patients were identified. The majority of the studies were case series or case reports, resulting in an overall low quality of available evidence. Based on studies including ≥ 5 SDC patients, objective responses to HER2 targeting agents were observed in 60–70%, to AR pathway agents in 18–53% and to chemotherapy in 10–50%.

Conclusion: For AR or HER2 positive SDC, agents targeting these pathways are the cornerstone for palliative treatment. Regarding chemotherapy, the combination of carboplatin combined with a taxane is best studied. Regarding other targeted agents and immunotherapy evidence is anecdotal, limiting formulation of treatment recommendations for these antineoplastic agents.

Introduction

Salivary duct carcinoma (SDC) is one of the 22 subtypes of salivary gland cancer (SGC), and has histological and immunohistochemical similarities with high grade intraductal and ductal carcinoma of the breast [1]. SDC is most prevalent in the parotid gland and approximately one third of the cases arises from a pleomorphic adenoma (carcinoma ex pleomorphic adenoma) [2,3]. SDC comprises approximately 4–10% of all SGC and distinguishes itself from many of the other subtypes by its often very aggressive behavior [4–7]. The latter is reflected in the median overall survival rate after diagnosis, which ranges between 48 and 79 months [2,8,9]. In the case of resectable disease, patients will initially be treated with curative intent consisting of complete resection of the primary tumor often combined with a lymph node neck dissection, and in most cases followed by postoperative radiotherapy. At presentation, many patients already have regional lymph node involvement (49–72%), with a median number of 4 tumor positive lymph nodes (range 0–97), which negatively affects the overall survival [2,3,9]. Additionally, distant metastases are present at diagnosis in around 4–10% of the patients or arise relatively briefly in the course of the disease (median 16 months until presence of distant metastases) [2,3,9,10].

In total, around half of all patients will develop distant metastases, mostly in the lungs (54% of patients with distant disease), bones (46%),

* Corresponding author at: Department of Medical Oncology, Radboud University Medical Center, Geert Grooteplein Zuid 8, Nijmegen, P.O. box 9101, the Netherlands.
E-mail address: Carla.vanherpen@radboudumc.nl (C.M.L. van Herpen).

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lymph nodes (approximately 40%), liver (approximately 25%) and brain (18%) [2,11]. In patients with recurrent or metastatic disease median overall survival is only 5 months when best supportive care is given [12]. These numbers show the urgent unmet need for palliative systemic treatment in these patients.

Potential targets for systemic therapy are the androgen receptor (AR) and human epidermal growth factor 2 receptor (HER2). SDC show positivity for these receptors in approximately 78–96% and 29–46% of the cases, respectively [2,13,14]. Described mutations include mutations in *TP53* (53–68%), *PIK3CA* (18–26%) and *HRAS* (16–23%), although not yet all of these mutations are druggable. The mutational landscape of SDC, with an overall tumor mutational burden of 1.7 mutations/megabase, might reveal other potential targets for systemic therapy. Overall, potentially actionable genetic alterations are present in 61% of the cases [13,15,16]. Within the immunological microenvironment of SDC other clues might be present that rationalize immunotherapy treatment. For instance, 30–60% of SDC shows immunohistochemical positivity for the programmed death ligand 1 (PD-L1) [17,18].

The rarity of SDC hampers performance of clinical trials. This limits the available evidence on the most effective treatment strategy, despite the fact that approximately half of all SDC patients will be considered for palliative systemic therapy during the course of their disease. Therefore the aim of this paper is to systematically summarize and review the available evidence on treatment outcome of palliative systemic therapy in SDC patients, and to make treatment recommendations based on the findings.

Methods

Search strategy

Articles were identified by conducting a search of the following electronic databases: PubMed (MEDLINE), Embase and the Cochrane library. The last search was conducted on the 29th of September 2019. The full search strategy can be found in supplementary tables 1 and 2. No restriction was placed on year of publication. All article types and study designs were included. This includes experimental clinical trials and observational data (case series and case reports), since this is recommended for systematic reviews of rare diseases [19]. All relevant studies were selected, regardless of the language of the article.

In addition, several clinical trial registries (clinicaltrials.gov, WHO International Clinical Trials Registry Platform, EU clinical trial register, ISRCTN and Australia and New Zealand Clinical Trial Registries) were searched for relevant studies or ongoing trials. Backward citation was performed by manually checking the reference lists from articles and reviews that were deemed relevant. Forward citation of the articles yielded from this search strategy was tracked using Web of Science.

Inclusion criteria

Studies were considered eligible for inclusion if at least one patient with incurable locally advanced, recurrent or metastatic (R/M) SDC was treated with systemic therapy as main therapy. See Table 1 for further details on the inclusion criteria.

Exclusion criteria

Articles were excluded if systemic therapy was administered as adjuvant or neoadjuvant treatment. Articles describing treatment of SDC of non-salivary gland origin were excluded. Studies reporting on SDC patients besides other types of SGC were only included if the results of the subgroup of SDC patients was reported separately, unless the proportion of SDC patients exceeded 80% or if the treatment outcome of the SDC group could otherwise be determined (e.g. if no responses were observed in the entire study population). Studies in which systemic treatment was given in combination with local therapy (e.g. radiotherapy) were excluded.

Studies were assessed for eligibility independently by two reviewers (MU, GL). Data extraction was performed by one reviewer and integrally verified by a second. Disagreements were resolved by consensus or by consulting a third reviewer if deemed necessary (CvH).

Analysis

A meta-analysis was not possible due to heterogeneity in study designs, treatment types and outcomes of interest, so a narrative analysis was conducted.

Quality of evidence

Broad inclusion criteria and heterogeneity of included study designs limited the use of validated risk of bias tools. Bearing the principles of the GRADE approach in mind, an estimation of the overall quality of evidence was made [20].

Results

The search strategy resulted in 2014 hits up to the 29th of September 2019. The abstracts of these 2014 studies were screened for eligibility, yielding 153 manuscripts. Full text screening of these manuscripts resulted in 45 included studies (Fig. 1): nine phase 2 trials, one phase 1 trial, six case series and twenty-nine case reports [12,21–62]. No phase 3 studies were identified. In these 45 studies, in total 256 SDC patients were included who received systemic therapy for R/M disease. Several patients received multiple lines of therapy. All prospective studies and retrospective studies including ≥ 5 SDC patients are summarized in Tables 2 and 3, respectively. The additional studies (mainly case reports) can be found in supplementary table 3.

Hormonal therapy

One phase 2 trial studied the efficacy of combined androgen blockade (CAB) with leuprorelin acetate and bicalutamide in 36 patients (of which 64% with metastatic disease and 36% with unresectable locally advanced or locoregional recurrent disease) with

Table 1
PICO search strategy.

Population	Patients with incurable locally advanced salivary duct carcinoma, or incurable locoregional recurrences of salivary duct carcinoma or metastasized salivary duct carcinoma.
Intervention	Systemic therapy (e.g. chemotherapy, immunotherapy, hormonal therapy or targeted therapy)
Comparison	Not applicable
Outcome	Any of the following; - objective responses: e.g. objective response rate (complete and partial responses) or stable disease or duration of response (e.g. progression free survival) or - subjective responses (pain relief, symptom improvement) or - survival data (median progression free survival, overall survival).

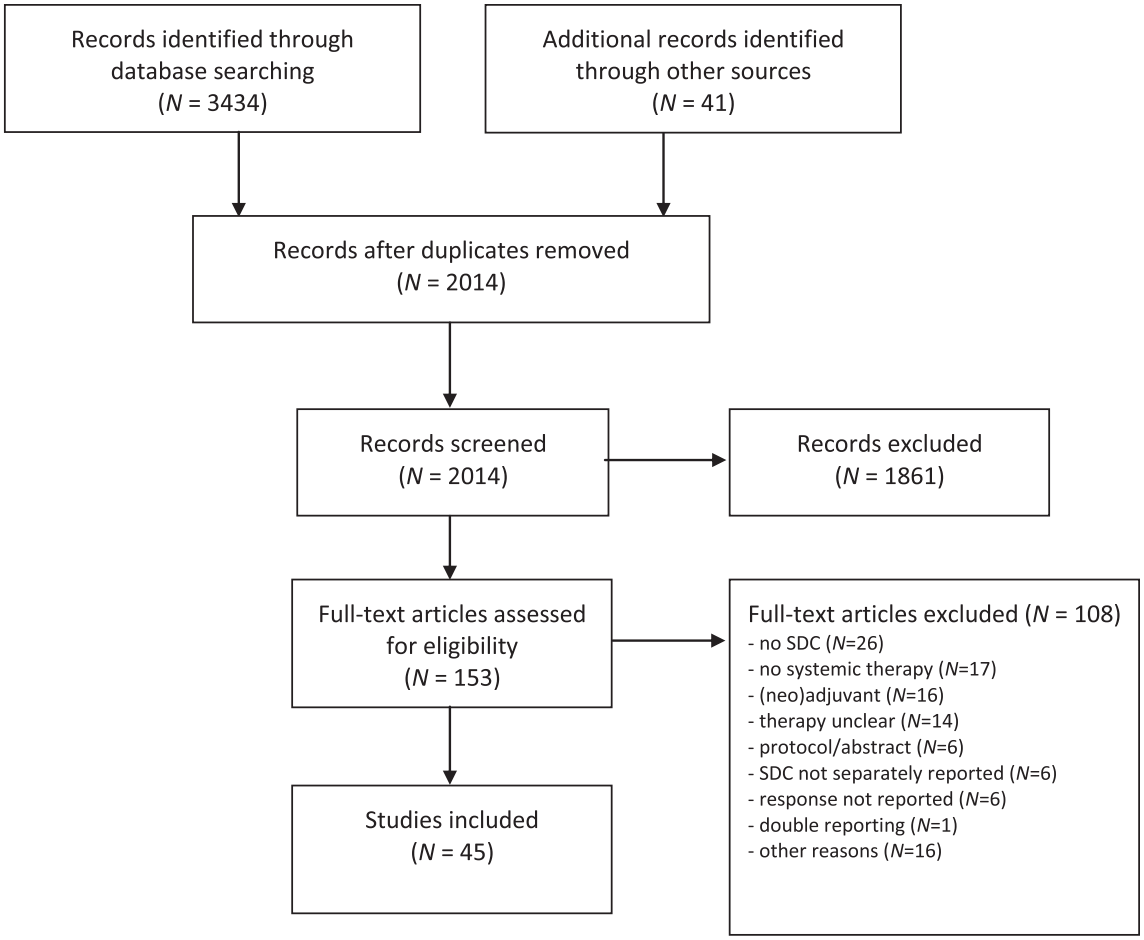

Fig. 1. Flow diagram of search strategy.

advanced AR-positive SGC (94% SDC) [29]. The results were not reported separately for the SDC patients. Objective responses occurred in 42% of the patients (complete response (CR): 11%, partial response (PR): 31%). The clinical benefit rate, defined as CR, PR, or stable disease (SD) ≥ 24 weeks, was 75% with a median progression free survival (PFS) of 8.8 months and overall survival (OS) of 30.5 months (no survival data in historical cohort with other treatments reported).

Three case series reported on a total of sixty AR-positive SDC patients that received androgen deprivation therapy (ADT) [12,45,59]. Patients were treated with either monotherapy (luteinizing hormone-releasing hormone (LHRH) analogues or the AR antagonists: enzalutamide or bicalutamide), or CAB (LHRH analogue and bicalutamide). In the largest of these studies, objective response was seen in 18% of the patients, all PR [12]. In the other two studies objective responses were seen in 53% and 50% [45,59]. Only the largest study reported the clinical benefit rate and compared survival to a best supportive care group. The clinical benefit rate (CR, PR or SD) was 50%. The median OS in ADT treated SDC patients was 17 months, compared to 5 months in the best supportive care group. Additionally, this study reported on eleven SDC patients that received second line ADT (LHRH analogue, either as monotherapy, or combined with bicalutamide and/or a 5-alfa-reductase-inhibitor), after progression on first line ADT. The ten evaluable patients, showed no objective response, but six patients had SD (60%) with a median duration of 9 months [12].

Furthermore, use of ADT in SDC was described in case reports in a total of twelve patients [23–26,31,43,53,57,58,62]. Positive results were described in six patients (1 CR, 2 PR, 1 SD ≥ 6 months, 1 clinical improvement, 1 response on positron-emission tomography (PET) imaging). In addition, one patient was treated with a combination of hormone therapy and chemotherapy; this patient received bicalutamide, leuprolide and paclitaxel, which resulted in PR that was ongoing at 6 months [63].

HER2 targeted therapy

Fifty-seven SDC patients, of which 86% had distant metastases, were treated with the combination of trastuzumab and docetaxel in a phase 2 study including HER2-positive SDC patients [54]. Objective responses were seen in 70% of the patients (14% CR and 56% PR) with a clinical benefit rate of 84% (CR, PR and SD ≥ 24 weeks). PFS and OS were 8.9 months and 39.7 months, respectively.

Another study (case series) evaluated the combination of trastuzumab with paclitaxel and carboplatin and in five HER2-positive SDC patients, all with distant metastases [42]. The objective response rate was 60% (1 CR and 2 PR) with a median duration of response of 18 months.

In case reports, a total of twelve patients received a combination of trastuzumab with docetaxel/paclitaxel [22–24,27,30,34,38,48,56]. Two patients had CR (17%) and eight patients had PR (67%). Duration of responses varied between 3 and 32 months.

Additionally, six patients received a combination of trastuzumab, docetaxel/paclitaxel and carboplatin, which led to 3 PR and 3 CR; little was reported on the duration of the responses [27,35,52,55,60,64].

The combination of trastuzumab and pertuzumab in combination with different types of chemotherapy was given in six SDC patients [23,50,53,58]. The combination of trastuzumab and pertuzumab with chemotherapy ($N = 6$) led to 3 CR, 1 PR, 1 SD and 1 response on PET imaging. Some durations were still ongoing, but ranged from 3 to 17 months.

HER2 targeted therapy was given as monotherapy in three SDC

Table 2
Prospective studies in which SDC patients were included.

Study	Design	Patient characteristics	Drugs	Only SDC	*N* of SDC patients (% of total number)	Disease stage*	Prior systemic therapy*	Response*	Median Survival (PFS, OS)*	Remarks
Hormone therapy										
Fushimi et al. [29]	Phase 2	SGC AR+	leuprorelin + bicalutamide	N	34 (94%)	NR	NR	NR	NR	Results total study (*N* = 36): CR: 4 (11%) PR: 11 (31%) SD: 16 (44%) PD: 5 (14%) ORR: 42% [26%-59%] CBR: 75% [58%-88%] (includes SD > 24 weeks) PFS: 8.8 mo, OS: 30.5 mo
HER2 targeted therapy										
Takahashi et al. [54]	Phase 2	SDC HER2+	docetaxel + trastuzumab	Y	57 (100%)	LR: 8 (14%) DM: 49 (86%)	chemo: 20 (35%) ADT: 3 (5%)	CR: 8 (14%) PR: 32 (56%) SD: 14 (25%) PD: 3 (5%)	PFS: 8.9 mo OS: 39.7 mo	ORR: 70% [57%-82%] CBR: 84% [72%-93%] (includes SD > 24 weeks) 14 pts received other treatment after 6 cycli.
Fiedler et al. [28]	Phase 1	Solid tumors HER2+	trasGEX	N	1 (3%)	LR: 1 (100%)	NR	CR: 1 (100%)	PFS: 53 mo**	
Targeted therapy (other targets than AR and HER2))										
Agulnik et al. [21]	Phase 2	SGC EGFR + and/or erbB2+	lapatinib	N	4 (10%)	NR	NR	NR	NR	No objective responses in trial SD > 6 mo: 13/40 pts, but no SDC.
Jakob et al. [33]	Phase 2	SGC	gefitinib	N	3 (8%)	NR	NR	NR	NR	No objective responses in trial Non-ACC cohort: 4 pts SD > 9 mo, unclear if SDC.
Locati et al. [44]	Phase 2	SGC	sorafenib	N	2 (5%)	NR	NR	PR: 1 (50%)	NR	Other SDC patient unclear if PD or SD.
Hyman et al. [32]	Phase 2 basket	Solid tumors BRAF V600 mutation	vemurafenib	N	1 (1%)	NR	NR	CR: 1 (100%)	PFS: 8 mo	
Kim et al. [37]	Phase 2	SGC	nintedanib	N	1 (5%)	NR	chemo: 1 (100%)	SD: 1 (100%)	PFS: 7.3 mo OS: 10.1 mo**	No objective responses in trial.
Chemotherapy										
Licitra et al. [41]	Phase 2	SGC	CAP	N	2 (9%)	LR: 1 (50%) DM: 1 (50%)	NR	PR: 1 (50%) SD: 1 (50%)	PR: PFS: 6 mo, OS: 12 mo SD: PFS: NR, OS: 16 mo	
Laurie et al. [39]	Phase 2	SGC	gemcitabine + cisplatin	N	1 (3%)	NR	NR	PR: 1 (100%)	NR	

AR: androgen receptor, CAP: cyclophosphamide, doxorubicin and cisplatin, CBR: clinical benefit rate, CR: complete response, DM: distant metastases, EGFR: epidermal growth factor receptor, erbB2+: refers to HER2 positivity, HER2: human epidermal growth factor receptor 2, LR: locoregional, mo: months, N: no, NR: not reported, ORR: overall response rate, OS: overall survival, PD: progressive disease, PFS: progression free survival, PR: partial response, pts: patients, SD: stable disease, SDC: salivary duct carcinoma, SGC: salivary gland cancer, trasGEX: second generation monoclonal antibody of trastuzumab, Y: yes.

* only SDC patients are reported.

** (response) ongoing at time of report.

Table 3
Retrospective studies in which ≥ 5 SDC patients were included.

Study	Design	Patient characteristics	Drugs	Only SDC	*N* of SDC patients (% of total number)	Disease stage*	Prior systemic therapy*	Response*	Median Survival(PFS, OS)*	Remarks
Hormone therapy										
Boon et al. [12]	Case series	SDC AR+	bicalutamide +/- goserelin	Y	35 (100%)	LR: 2 (6%) DM: 33 (94%)	no	CR: 0 (0%) PR: 6 (18%) SD: 11 (32%) PD: 17 (50%)	PFS: 4 mo OS: 17 mo	Evaluable: 34/35 pts CBR: 50% Median PFS for pts with PR or SD: 11 mo. 11 pts later received second line ADT (goserelin +/- bicalutamide +/- 5-ARI) Evaluable pts: 10/11 pts. SD: 6 (60%) with median PFS of 9 mo. PD: 4 (40%) CBR: 60%
Viscuse et al. [59]	Case series	SGC AR+	leuprolide +/- bicalutamide or bicalutamide or enzalutamide	N	17 (85%)	NR	no	CR or PR: 9 (53%)	NR	Study included 35 pts, 20 received ADT (17 SDC), 14 chemo (10 SDC) See row below.
Locati et al. [45]	Case series	SGC AR+	bicalutamide + triptorelin	N	8 (47%)	DM: 8 (100%)	chemo: 3 (38%)	CR: 2 (25%) PR: 2 (25%) SD: 3 (37.5%) PD: 1 (12.5%)	NR	Duration responses: CR: 11 and 39 mo PR: 6 and 7 mo SD: 8, 10 and 23 mo
HER2 targeted therapy										
Limaye et al. [42]	Case series	SDC HER2+	paclitaxel + trastuzumab + carboplatin	Y	5 (100%)	DM: 5 (100%)	chemo: 1 (20%)	CR: 1 (20%) PR: 2 (40%) SD: 0 (0%) PD: 2 (40%)	DoR: 18 mo	Study also reports on 8 pts in adjuvant setting.
Chemotherapy										
Nakano et al. [46]	Case series	SGC	paclitaxel + carboplatin	N	18 (47%)	NR	chemo: 2 (11%)	Objective response: 7 (39%)	NR	Objective response was not further specified.
Okada et al. [49]	Case series	SGC	carboplatin + docetaxel	N	12 (50%)	NR	yes: 9 (75%)	CR: 2 (17%) PR: 4 (33%) SD: 3 (25%) PD: 3 (25%)	PFS: 8.0 mo OS: 32.6 mo	Disease stage NR, but target lesions: LR: 3 (35%) DM: 8 (67%)
Viscuse et al. [59]	Case series	SGC	chemo	N	10 (71%)	NR	no	CR: 1 (10%) PR: 0 SD: NR	NR	Different chemo combinations were given. SD: 3/14 pts, unclear if SDC

ADT: androgen deprivation therapy, AR: androgen receptor, CBR: clinical benefit rate, CR: complete response, DoR: duration of response, DM: distant metastases, HER2: human epidermal growth factor receptor 2, LR: locoregional, mo: months, N: no, NR: not reported, OS: overall survival, PFS: progression free survival, PR: partial response, pts: patients, SD: stable disease, SDC: salivary duct carcinoma, SGC: salivary gland cancer, Y: yes, 5-ARI: 5-alfa-reductase-inhibitor.
**(response) ongoing at time of report.
* only SDC patients are reported.

patients. One patient with a parapharyngeal lymph node metastasis received trasGEX (second-generation monoclonal antibody of trastuzumab) in a phase 1 trial and achieved CR, without progression at 53 months follow-up [28]. Two patients received trastuzumab monotherapy, leading to 1 CR, with ongoing duration at 18 months, and 1 SD for 5 months [40,48]. Additionally, four case reports described SDC patients treated with trastuzumab-emtansin (T-DM1) [22,23,53,58]. Two patients achieved PR (duration: 8 and 14 months), the other reports mentioned a clinical response of 12 months and an ongoing CR based on PET imaging at 29 months of follow-up.

Targeted therapy (other targets than AR and HER2)

Five prospective targeted therapy trials, which included SDC patients, focused on tyrosine kinase inhibitors [21,32,33,37,44]. In all these studies, SDC patients comprised ≤ 10% of the total study population. No case series were identified reporting on targeted therapy in SDC patients, only several case reports.

BRAF

The efficacy of vemurafenib was examined in a basket study for solid tumors with BRAF mutations [32]. This study included one SDC patient, which achieved CR lasting for 8 months. Furthermore, one case report described the treatment combination of dabrafenib and trametinib in one SDC patient with a BRAF V600E mutation [43]. The patient showed marked improvement of osseous metastases, but progression occurred at 13 months.

EGFR

Two phase 2 trials in SGC patients studied the effect of EGFR inhibitors (gefitinib, lapatinib) [21,33]. In both trials no objective responses were observed in the entire study population. The trial of gefitinib ($N = 37$) included three SDC patients. In the non-adenoid cystic carcinoma (ACC) cohort (total of 18 patients) four patients did have SD ≥ 9 months, but it is unclear if these were SDC patients [33]. None of the four SDC patients treated with lapatinib had SD > 6 months [21]. In a case report, lapatinib resulted in a complete resolution of skin lesions, with progression after 18 months [22].

VEGFR

The effect of sorafenib and nintedanib (VEGFR inhibitors) was studied in two phase 2 trials in SGC patients [37,44]. Of the two SDC patients in the trial with sorafenib, one had a PR. The other patient did not have an objective response [44]. No objective responses were observed in the nintedanib trial. In the only SDC patient in this trial SD was achieved for 7.3 months [37].

Other targets

In one case report treatment with cabozantinib for two *NCOA-RET* gene fusion positive SDC patients was evaluated. Both patients experienced clinical improvement with no specification of the duration. One case report mentioned treatment with a combination of trastuzumab, lapatinib and bevacizumab, leading to a PR in a single SDC patient. Besides one asymptomatic bone metastasis treated with radiation, the patient had no signs of further progression at 25 months [27]. The combination of temsirolimus and bevacizumab was given to two SDC patients; one patient showed a visual response of skin lesions, and the other patient had a PR for 3 months [51]. One study reported on different targeted therapy approaches in three separate patients (supplementary table 3) [47]. Three PR were observed: one in a patient treated with a combination of BRAF- and MEK-inhibitors, one in a patient treated with a PI3K-inhibitor, and one in a patient treated with TORC1/2 inhibitor with durations of 5, 12 and 3.7 months, respectively.

Chemotherapy

In total, three SDC patients received chemotherapy in prospective clinical trials [39,41]. Two received CAP (cyclophosphamide, doxorubicin and cisplatin) and one patient was treated with gemcitabine and cisplatin. CAP resulted in one PR and one SD; gemcitabine combined with cisplatin resulted in PR. Little was reported regarding the duration of the responses (table 2).

Three case series reported on the effect of chemotherapy in SDC patients. A total of 40 SDC patients were treated with chemotherapy in these studies. In two studies patients were treated with a combination of carboplatin and a taxane (docetaxel/paclitaxel) [46,49]. The combination of carboplatin and paclitaxel ($N = 18$) resulted in objective responses in 39% of the patients, and the combination of carboplatin with docetaxel ($N = 12$) resulted in objective response in 50%. One study reported on the use of several different chemotherapeutics in 10 SDC patients, mainly platinum-based regimes [59]. One patient (10%) achieved CR (treatment schedule unclear), but there were no other objective responses reported.

Additional SDC case reports mentioned the effect of different combinations of chemotherapy in seven patients [24,30,43,48,61]. Three out of these seven patients had PR (one on CAP, one with cisplatin + vinorelbine, one with cisplatin + docetaxel). In addition, in one case report first line treatment of cisplatin and 5-fluorouracil combined with cetuximab was given, leading to a CR that lasted 3 months. As second line cisplatin and 5-fluorouracil (5-FU) were replaced by tegafur-gimeracil-oteracil potassium (which also contains a 5-FU prodrug), which led to SD ongoing at 7 months [36].

Immunotherapy

One case report describing the use of immunotherapy in a SDC patient was identified. This patient received nivolumab as second line therapy [43]. Dosage and efficacy were not reported; the patient stayed on therapy for 3 months and treatment was discontinued due to severe fatigue.

Quality of evidence

Using the GRADE approach on the gathered evidence of systemic therapy in SDC led to low or very low quality of evidence, as was expected in this rare disease. This is mainly due to study designs and methodology of the studies. There were no sound prospective studies with an appropriate control group. Therefore, most studies used PFS and OS as surrogate endpoints to indicate increased overall survival benefit. Although the rarity of SDC limits sound patient accrual, 2 prospective trials have been performed in which a large proportion of included patients were SDC patients. These studies did not predefine the sample size [29,54]. Earlier performed studies on SGC generally included a more heterogeneous groups of SGC patients, limiting their usefulness to draw conclusions on efficacy in each included subtype (indirectness of evidence).

Efficacy of systemic therapy strategies that have been examined in larger studies (> 10 patients) show consistency in effect size. ADT shows objective response rates of 42% in the only prospective study that has been performed, which is comparable to the 50% and 53% response rate reported in retrospective studies. Trastuzumab combined with taxane chemotherapy showed objective responses in 70% of the patients in retrospective data, which is comparable to the 84% when combining the objective responses reported in several case reports. The combination of carboplatin with taxane chemotherapy shows comparable results in two retrospective studies, with objective responses of 39% and 50%. Efficacy of other targeted therapy approaches remains unclear, as evidence is anecdotal and mainly derived from single case reports.

Discussion

Main findings

In this systematic review, evidence of use of different systemic therapy approaches in R/M SDC is summarized. SGC is a heterogeneous and rare disease, and SDC is only one of many subtypes. This impedes treating physicians' search for the best treatment for their patients as it is hard to get an overview of the known evidence. This review aimed to aid in this search and is, to our best knowledge, the first systematic review presenting all known evidence specifically for systemic therapy approaches in R/M SDC patients through a broad search (although other reviews have summarized evidence for SGC in general, thus including SDC) [65–67].

Due to the rarity of the disease most studies had small sample sizes and included not only SDC patients, but a broader range of SGC patients. However, recently two relatively large prospective studies have been performed [29,54]. Overall, given the close histologic resemblance of SDC to high grade intraductal and ductal carcinoma of the breast and the analogy with prostate cancer due to the omnipresence of the AR pathway activation, investigated therapeutic strategies closely mimic treatment of these common cancers (e.g. ADT and HER2 targeted therapy) [1,68–70].

Comparing systemic treatments

No prospective randomized studies comparing different systemic treatments in SDC patients have been performed. Retrospectively, one study compared first-line ADT versus chemotherapy. Selection between these regimes was mainly based on availability of AR testing at the time of patient encounter, possibly introducing bias in the comparison [59]. Median overall survival was comparable between first-line ADT and first-line chemotherapy, but as most patients received other lines of therapy after progression on the first line of ADT/chemotherapy effect size of both interventions is hard to establish. An ongoing phase 2 study is currently evaluating the efficacy of chemotherapy versus ADT in patients with advanced, AR-positive SGCs (EORTC-1206, NCT01969578).

Several studies evaluated the efficacy of ADT. Only in the study of Boon *et al.* the majority of patients received bicalutamide monotherapy. The results of this study are less favorable compared to studies where the majority of patients received a LHRH analogue with or without bicalutamide (CAB). In prostate cancer, where the role of ADT has been examined extensively, LHRH analogues are recommended as standard of care when hormonal therapy is advised [71]. The role of bicalutamide is less prominent, although a large study showed a small survival advantage when bicalutamide is added to LHRH analogues [72]. This suggests, for male patients, that treatment with a LHRH analogue with or without bicalutamide is the reasonable choice over bicalutamide monotherapy (although bicalutamide monotherapy has the advantage of libido and sexual potency retention) [73]. The registration of novel AR targeted drugs even widens the options for AR targeted therapy in SDC [74]. For female patients, bicalutamide monotherapy might still be considered due to lower physiological testosterone levels, but pretreatment measurement of testosterone would be advisable. Additional ADT treatment optimization might arise from research on the mutational landscape of SDC, which reveals several potential resistance mechanisms to androgen receptor blockade, including AR-V7 splice variants and *FOXA1* mutations [16].

HER2 targeted therapy has previously shown positive results in breast cancer and has subsequently been explored for other malignancies with HER2 expression, including SDC [69,75]. In SDC the combination of trastuzumab and chemotherapy showed impressive response rates in a phase 2 clinical trial, which makes this combination a good choice in the palliative treatment of HER2-positive SDC patients [54]. In breast cancer, the addition of pertuzumab to trastuzumab plus docetaxel has also shown favorable results. In a phase 3 study, PFS was 18.5 months (OS 56.5 months) for the group with addition of pertuzumab, compared to 12.4 months (OS 40.8 months) for the control group (placebo, trastuzumab, docetaxel) [76,77]. These results provide a rationale for addition of pertuzumab to trastuzumab plus docetaxel in SDC patients, although the high response rates for this combination in SDC makes it more difficult to study the potential additive value of pertuzumab as it already is a very effective regime.

Treatment recommendations

To guide treatment decisions it is recommended to test for AR and HER2 in all SDC patients. Especially in R/M disease this is a prerequisite, although ADT might also be important in the adjuvant setting [78]. AR should be assessed by immunohistochemistry (IHC), ideally AR positivity should be scored similar to the scoring method of prospective trial of Fushimi et al. [29], where AR positivity was evaluated just like the estrogen and progesterone receptors in accordance with the American Society of Clinical Oncology/College of American Pathologists guidelines for the evaluation of breast cancer predictive factors [79]. However, preliminary results indicate that functional AR-pathway activation measurements on mRNA level might better predict response on ADT [80]. HER2 status should be assessed by both IHC and *in situ* hybridization (ISH) and interpreted following the guidelines for HER2 assessment in breast cancer [81]. Remarkably, response rate of HER2 targeted therapy in HER2 + SDC patients is high (70%), even compared to response rate in HER2 + breast cancer patients (41.3%) [54,82]. Whether lower HER2 expression in SDC patients could potentially be sufficient for clinical response to HER2 targeted therapy needs further investigation.

In case of both AR and HER2 positivity (approximately 30% of the patients), AR targeted strategies or HER2 targeted therapy have not yet been compared head-to-head. Indirect comparison of these treatments in different (prospective and retrospective) studies hints toward superior response rates and OS for HER2 targeted therapy combined with taxane chemotherapy compared to ADT therapy [29,54]. Especially in SDC patients with visceral metastases, extensive or rapidly progressive disease, a HER2 targeted agent in combination with a taxane is recommended over ADT as first line therapy [83]. In addition, expected side effects might steer the choice between these therapies. ADT related side effects include bone loss, metabolic changes, gynecomastia, muscle loss and hot flashes [84]. Upon HER2 targeted therapies (combined with taxane chemotherapy) hematological toxicity can be expected, as well as various other symptoms such as anorexia and fatigue [54,69]. Furthermore cardiotoxicity is an important side effect that can occur during HER2 targeted treatment.

As first line HER2 targeted therapy, trastuzumab combined with chemotherapy is the preferred choice based on the available evidence [54]. Evidence supporting the addition of pertuzumab to the first-line treatment is limited, further research is warranted [23,50,53,58]. Recently, preliminary results from a phase 2 basket study in SGC patients were reported on ASCO. In total 10 HER2 + SGC patients received trastuzumab emtansine (TDM-1) treatment [85]. Nine patients showed objective responses (90%), including 5 complete responses after prior trastuzumab, pertuzumab and ADT. Based on these promising results, TDM-1 should be considered for patients who progressed after trastuzumab +/- pertuzumab. TDM-1 might even be considered as first-line treatment since the response rates of this study seem higher (90%) than the response rates of trastuzumab (60–70%), although trastuzumab has been studied in larger patient populations compared to TDM-1.

Recently, another HER2-targeted therapy, the antibody-drug conjugate trastuzumab deruxtecan (T-DXd), led to clinical responses in HER2 + SDC patients. In this phase I study in various solid malignancies 8 SGC patients were included. Two patients with SDC had PR upon treatment with T-DXd and two SDC patients had SD (other responses were not reported) [86].

When initiating ADT, the combination of a LHRH analogue with

Table 4
Dosage recommendations.

Tumor characteristics SDC	Treatment	Drug(s)	Dosage	Duration	Rationale
AR +	ADT	leuprorelin + bicalutamide	- Leuprorelin acetate s.c. 3.75 mg every 4 weeks or 11.25 mg every 12 weeks - Bicalutamide 80 mg OD	Until PD	Dosage from prospective clinical trial of Fushimi et al. [29]
HER2 +	HER2-targeted + chemotherapy	trastuzumab + docetaxel	Every 3 weeks: - Trastuzumab i.v.: loading fose 8 mg/kg, followed by 6 mg/kg - Docetaxel: 70 mg/m^2 Patients ≥ 70 years of age: reduce docetaxel to 55 mg/m^2	6 cycles Consider continuation of combination or trastuzumab monotherapy	Dosage from prospective clinical trial of Takahashi et al. [54]
n.a.*	Chemotherapy	paclitaxel + carboplatin	Every 3 weeks: - carboplatin: AUC = 6 - paclitaxel: 200 mg/m^2	The median number cycles was five (range: 2–12)	Dosage from retrospective trial of Nakano et al. [46]
n.a.*	Chemotherapy	docetaxel + carboplatin	Every 3 weeks: - carboplatin: AUC = 5 - docetaxel: 70 mg/m^2	6 cycles	Dosage from retrospective trial of Okada et al. [49]

AR: androgen receptor, ADT: androgen deprivation therapy, HER2: human epidermal growth factor receptor 2, OD: once daily, n.a: not applicable, i.v.: intravenously, PD: progressive disease, SDC: salivary duct carcinoma, s.c.: subcutaneously.

* These treatments could be considered for HER2 negative patients, in HER2 + patients chemotherapy should be combined with HER2-targeted agents.

bicalutamide is preferred over monotherapy in terms of response rate and PFS, although CAB has higher rates of (mild) adverse events. When considering chemotherapy in HER2 negative SDC, although still limited, most evidence exists for efficacy of carboplatin in combination with taxane chemotherapy in SDC, but CAP chemotherapy may be considered as an alternative. Practical guidelines and dosage recommendations are listed in table 4.

In addition, patients might benefit from other targeted therapies as positive results have been described in small numbers of patients. This requires testing for genetic alterations (e.g. for patients not (longer) eligible for ADT or HER2 targeted strategies) known to be targetable with targeted agents. Whole exome or targeted sequencing of 31 SDC tumors showed potentially druggable targets in 61% of these tumors [87]. Although this also includes amplification of *ERBB2* (35%), which would likely have been identified through alternative tests: IHC and FISH, other relevant mutations such as *PIK3CA* (23%), *HRAS* (23%) or *BRAF* V600E mutations were identified in a substantial amount. Patients with PIK3CA or HRAS mutations might benefit from PI3K inhibitors and/or tipifarnib and patients with *BRAF* mutations might benefit from treatment with vemurafenib, since these therapies showed antitumor effects in patients with other malignancies [32,88,89]. Preferably, such treatments should be examined in a clinical trial setting. This also applies for immunotherapy; more research is required to establish the effect of immunotherapy in SDC patients. A recent study provided more insight in the immune microenvironment of SDC, which might aid in the selection of precision immunotherapy. Through transcriptomic analyses it is indicated that the SDC does not escape immune responses by excluding T-cells, in fact SDC has relatively high levels of immune cell infiltration. The immune evasive capacity appears to rely on high expression of T-cell checkpoints and high levels of T cell dysfunction [90].

Strengths and limitations

In this systematic review all known evidence for systemic treatment strategies in R/M SDC is identified and summarized through a thorough and broad literature search following systematic review guidelines. However, the strength of our treatment recommendations is severely impacted by the low quality of the overall evidence synthesis. Included and described studies are mostly limited to retrospective data, consisting of case series and case reports. This bears the risk of substantial publication bias and limits drawing firm conclusions.

Conclusion

This systematic review exposes an overall paucity in well performed studies on efficacy of treatment strategies in R/M SDC, although there is an urgent unmet clinical need in this patient category with a dismal prognosis. The evidence that is present is of low quality and the vast majority of cases is retrospectively analyzed, although recently relatively large prospective studies (> 30 SDC patients) have been published (2018 and 2019) [29,54]. The available knowledge points towards a strategy in which testing for activation of the AR and HER2 pathway is a prerequisite in choosing the right treatment option. In AR-positive patients, ADT should be the first line whereas in HER2 + patients HER2 based treatment with trastuzumab, combined with a taxane is the reasonable first choice. Upon progression in HER2 + SDC trastuzumab-emtansine is another promising strategy. Treatment decisions in patients co-expressing AR and HER2 should be guided by clinical factors, but we advocate use of HER2 targeted treatment in most patients. When chemotherapy is considered in HER2 negative patients, the combination of carboplatin with a taxane should be considered. Eligibility of patients for treatment with specific targeted therapies depends on presence of mutations targetable with currently registered drugs or drugs under investigation in basket trials. Testing for these targets is therefore recommended.

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Author contributions

MU developed the search strategy and ran the electronic searches. MU and GL acted as reviewers, contributed to the results and discussion and wrote the manuscript.

AvE, YT, GV, JS and CD: contributed to the methodology and writing the manuscript.

CvH oversaw the project, acted as a third reviewer and contributed to writing the manuscript.

All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CvH: Advisory (institution): Bayer, Bristol-Myers Squibb, Ipsen, MSD, Regeneron. Research grant (institution): Astra Zeneca, Bristol-Myers Squibb, MSD, Merck, Ipsen, Novartis, Sanofi. MU: nothing to declare. GL: nothing to declare. AvE: nothing to declare. CD: nothing to declare. YT: nothing to declare. GV: nothing to declare. JS: nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2020.102069.

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