MADRID 2017 ESMO congress

2015 ESMO Translational Research Fellowship Report

Evaluation of c-MET expression and inhibition in squamous cell carcinoma of the head and neck

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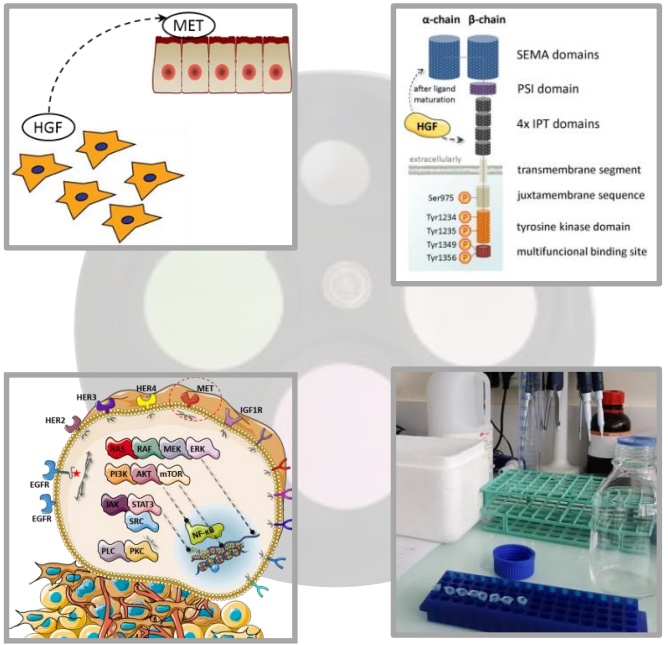

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Disclosure of Potential Conflicts of Interest

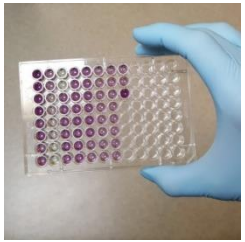
- No conflicts of interest.

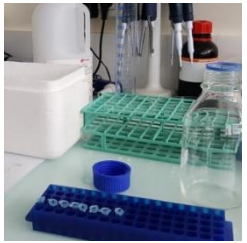
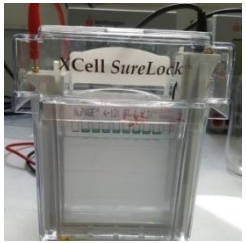
Towards the fellowship

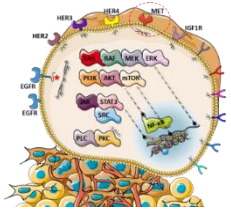
- 2009-2012: very rare hemato-oncological diseases
- 2013: the European Cancer Congress in Amsterdam
- Head and Neck Oncology
- 2014: **ESMO** Clinical Unit Visit
  Professor Jan B. Vermorken
  Antwerp University Hospital, Belgium
- 2015: **ESMO** Translational Research Unit Visit
  Second University of Naples, Italy
- 2015-2016: **ESMO** Translational Research Fellowship
  Professor Sandrine Faivre
  Bichat-Beaujon University Hospital in Paris, France

Why translational research

- learning new skills
- laboratory work
- data interpretation
- early clinical trial design
- team work
- new professional contacts
- exploring new lands...





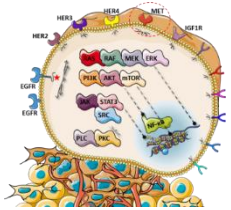
The c-MET project
- objectives -

Primary objectives were to:

- (p1) evaluate c-MET immunohistochemical expression in SCCHN patients
- (p2) assess whether c-MET receptor may become a new therapeutic target in SCCHN

Secondarily, we aimed to:

- (s1) further characterize the c-MET-overexpressing population
- (s2) characterize selected SCCHN cell lines with the evaluation of c-MET inhibition
- (s3) evaluate c-MET inhibition in fresh tumour explants
- (s4) identify new biomarkers for c-MET inhibition

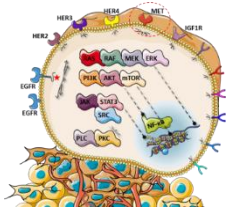


The c-MET project
- methods -

(p1) Evaluation of immunohistochemical expression in SCCHN patients

- (p1a) systematic review of available literature on c-MET immunohistochemistry in SCCHN and meta-analysis of aggregate data: “Is c-MET a prognostic factor in head and neck cancer?”

- (p1b) retrospective review of patient data in a cohort of 100 cases treated at the Bichat Hospital from 2009 to 2011 including:
  - immunohistochemical staining using anti-c-MET antibody at the Bichat Hospital
  - manual c-MET quantification at the Bichat Hospital
  - quantification of cytoplasmic and membrane receptors separately
  - expressing the obtained results as MetMab score or H-score

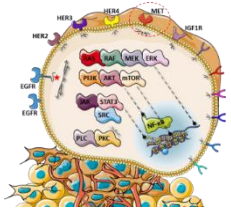


The c-MET project

- methods -

(p2) Assessment whether c-MET receptor may become a new therapeutic target in SCCHN

- (p2a) preparation of an literature review on c-MET signalling to support the rationale of the project and increase the efficacy of data collection
- (p2b) review of available literature on c-MET cross-talks with other pathways to analyse possible combinations with EGFR antagonists
- (p2c) research in the field of immunotherapy to analyse the results of recent trials with novel drugs which may possibly be exploited in combinations with c-MET inhibitors
- (p2d) review of treatment guidelines in recurrent/metastatic SCCHN, as this would probably be the first cohort to receive a c-MET inhibitor
- (p2e) focus on issues related to advanced age, as these patients would probably form a substantial part of those treated with a c-MET inhibitor



The c-MET project

- results -

Outline

- Towards the fellowship
- Why translational research
- The c-MET project
- ➢ Results & publications
- Conclusions

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Oncology reviews

Understanding c-MET signalling in squamous cell carcinoma of the head & neck

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Contents

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ABSTRACT

c-MET is a membrane spanning receptor tyrosine kinase for hepatocyte growth factor (HGF) also termed scatter factor. Transmitting signals from mesenchymal to epithelial cells, the HGF/c-MET axis mediates a range of biological processes that stimulate proliferation, motility, invasiveness, morphogenesis, apoptosis, and angiogenesis. Aberrant c-MET signal transduction favours tumorigenesis with the acquisition of invasive and metastatic phenotypes. Biological functions of c-MET may strongly vary according to microenvironmental changes, which occur at different stages of tumorigenesis and include also HGF/c-MET activation in stromal cells. In this review, we focused on abnormalities in non-nasopharyngeal squamous cell carcinoma of the head & neck. While the prevalence of c-MET mutations and amplifications ranges 0–25%, c-MET upregulation can be found in the majority of squamous head & neck carcinomas. Despite marked heterogeneity in published scoring methods, immunohistochemical overexpression of c-MET has been typically linked to advanced stages and associated with impaired survival and/or resistance to radiotherapy, chemoradiotherapy, and cetuximab. Experimental studies in cell lines and patient-derived xenografts using various c-MET antagonists (both as single-agents and in combination with cytotoxic and epidermal growth factor receptor [EGFR]-directed agents) yielded promising results, albeit benefit in clinical trials remains to be demonstrated. Consequently, selecting more active agents and integrating them effectively in studies, which incorporate predictive biomarkers such as c-MET gene mutations, amplifications, and overexpression, remains challenging. Further investigations should increase emphasis on disentangling the role of tumour-stromal interactions and analyse their potential as modifiers of drug response.

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Letter to the editor

c-MET-mediated resistance to EGFR inhibitors in head and neck cancer: How to move from bench to bedside

Mesenchymal–epithelial transition factor (c-MET), found on melanocytes, endothelial cells, and epithelial tissues, is a membrane spanning receptor tyrosine kinase for hepatocyte growth factor (HGF), produced by elements of mesenchymal origin. The receptor-ligand pair controls diverse biological activities including cell proliferation, motility, invasiveness, morphogenesis, apoptosis, and angiogenesis. Consequently, aberrant signal transduction may trigger tumorigenesis with the acquisition of invasive and metastatic phenotypes. Several HGF and c-MET antagonists have been tested in phase I–III trials for the treatment of different cancer types, albeit without any definite clinical benefit so far [1,2]. Currently, the epidermal growth factor receptor (EGFR)-inhibitor cetuximab represents the only approved targeted agent in squamous cell carcinoma of the head and neck (SCCHN). However, the majority of patients present with primary or acquired EGFR resistance mediated by various mechanisms comprising also the c-MET cascade [3].

With great interest we read the article by Tepper et al. published in this journal. The authors demonstrated that HGF could partially reverse the antiproliferative effects induced by gefitinib. Interestingly, the restored HGF-mediated viability correlated with c-MET expression as determined by ribonucleic acid (RNA) sequencing [4]. Building on knowledge of crosstalk between signalling pathways, the findings of Tepper et al. give further evidence on c-MET involvement in resistance of SCCHN to EGFR inhibitors. Herein, we provide a brief insight into this topic outlining future directions for clinical integration of HGF and c-MET inhibitors in combination protocols with anti-EGFR drugs.

In non-small-cell lung cancer, *c-met* proto-oncogene amplification emerged as one of the key mechanisms of secondary resistance to EGFR tyrosine kinase inhibitors (TKIs) when *in vitro* data showed that c-MET inhibition can reverse EGFR resistance conferred by this genetic aberration [5,6]. In SCCHN, crosstalk between c-MET and EGFR has also been well established. Besides the important observation reported by Tepper et al., experimental studies in cell lines and patient-derived xenografts documented an enhanced effect of dual blockade using c-MET (SU11274, PF2341066, PF04217903) and EGFR TKIs (erlotinib, gefitinib) [7–9]. Moreover, cetuximab-resistance was linked to c-MET upregulation in cell line models as well as in tumour specimens of recurrent and/or metastatic SCCHN treated with single-agent cetuximab or cetuximab-based combinations [10,11]. Despite favourable laboratory data, results from randomized trials exploring anti-c-MET/anti-EGFR combinations in different cancer types were rather disappointing, often crossing futile boundaries. As seen in Table 1, most studies were conducted in lung cancer evaluating tivantinib, an oral small-molecule c-MET inhibitor, or onartuzumab, a humanized monoclonal anti-c-MET antibody. However, when looking at the outcomes from a wider perspective, a trend towards improved response rate (5 out of 8 trials), progression-free (5/8), and overall survivals (6/8) is evident with the MARQUEE trial demonstrating, as the only one, statistically significant differences in overall response rate and median progression-free survival [12–19]. Taken together, the findings indicate a promising biological activity delivered by these molecularly targeted doublets.

Then, what hurdles could impede successful translations from bench to bedside? First, cytotoxic properties of tivantinib seem to be independent of the HGF/c-MET signalling abrogation. On the other hand, they may involve molecular cascades activated by c-MET [15]. In oral cancer cells, Xi et al. hypothesized that blocking of focal adhesion kinase and induction of caspase-dependent apoptosis are responsible for the suppression of cell growth and colony formation elicited by tivantinib [20]. In broad terms, tested drugs often exhibit multi-target effects, which are not yet fully understood and should be regarded as possible confounding factors. Furthermore, the studies by Yoshioka et al. and Eag et al. suffered from insufficient statistical power to detect survival differences [18,19]. This was due to a premature termination in the case of the ATTENTION trial and it also holds true for the following, third, point [18]. Caution should be paid when interpreting exploratory subgroup analyses, since they usually contain small number of patients, are observational in their nature, and may thus be misleading. Three trials (Spigel, 2013; Scagliotti, 2015; Eng, 2016) suggested a potential survival advantage in patients with c-MET-high status by immunohistochemistry [13,15,19]. Unfortunately, a large phase III trial evaluating the addition of tivantinib to erlotinib in pretreated c-MET positive non-small-cell lung cancer cases did not confirm this assumption [14]. Nevertheless, in the era of personalized medicine, adoption of biomarker-based patient stratification is essential and failure to do so may undesirably mask clinical benefits. Correlating with poor clinical outcomes, c-MET overexpression still remains a promising candidate for this role, but the need for a scoring method appropriately defining high c-MET status and overcoming intrinsic tumour heterogeneity creates an imperative for future investigations [1,2,15]. Another consideration is the molecular profile of cancer, which can change over time leading to substantial differences between the original diagnostic tissue and re-biopsy as a consequence of selection pressure during anti-cancer therapies [21]. Finally, biological behaviour of c-MET may strongly vary according to microenvironmental perturbations. Apart from its impact on malignant cells, activation of the HGF/c-MET axis mediates important cellular functions in different stromal compartments including endothelial cells, mesenchymal elements, and lymphocytes [22].

In SCCHN, all the above mentioned issues are relevant and should be carefully addressed in the design of future trials.

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Szturz P, Raymond E, Faivre S.
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Letter to the editor

Letter to the editor referring to the publication entitled "The role of antagonists of the PD-1: PD-L1/PD-L2 axis in head and neck cancer treatment" by Pai et al.

As addressed by Pai with co-workers in their comprehensive review, novel immunotherapeutic strategies using immune checkpoint inhibitors represent a promising area of research in squamous cell carcinoma of the head and neck (SCCHN) [1]. Results from a phase III trial and preliminary data from three early clinical studies demonstrated the efficacy of monoclonal antibodies against programmed death-1 (PD-1) receptor (nivolumab, pembrolizumab) and its ligand PD-L1 (durvalumab) as second-line treatments in the recurrent and/or metastatic (R/M) setting. With relatively low incidence of serious adverse events, these agents elicited durable responses even in patients with refractory disease. Moreover, nivolumab, as the first drug ever, significantly improved overall survival (OS) by 2.4 months compared with investigator's choice (single-agent chemotherapy or cetuximab) [1–4]. From a broader perspective, these pioneering studies have important implications for future trial design with one of the challenges being the selection of appropriate clinical endpoints associated with benefits of immune checkpoint inhibitors.

Generally, patients with R/M-SCCHN progressing on first-line platinum-based therapy have a very poor outcome. Prospective studies of second-line chemotherapy typically showed median progression-free survival (PFS) or time to progression around 2 months and median overall survival between 4 and 6 months with response rates usually not exceeding 10% [5–9]. Unfortunately, randomized trials exploring various epidermal growth factor receptor (EGFR) inhibitors in the same clinical setting confirmed these bleak figures. Table 1 summarizes results achieved by the EGFR antagonists and compares them with those immunotherapy trials where data on objective response and survival were reported [2–4,7–9]. Across the three included studies using PD-1-directed agents, response rates (13.3–17.7%), median OS (7.5–8 months), and median PFS (2.0–2.1 months) were similar, with the former two outcome measures surpassing the aforementioned figures yielded by cytotoxic and anti-EGFR drugs. However, this was not the case of PFS, which was nearly as low as placebo rates, and in the randomized trial of nivolumab, it even scored numerically worse than PFS of investigator's choice. Thus, in contrast to response rate, PFS values do not sufficiently indicate the considerable impact of PD-1 inhibitors on OS in patients with R/M-SCCHN.

The most plausible explanation for this observation is related to the class-specific plateau shape of the tail of the survival curve apparent in the recent immunotherapy trials listed in Table 1. This phenomenon, responsible for longer median OS without affecting PFS, reflects the following two findings. First, the onset of response induced by immune checkpoint inhibitors is often delayed compared with historical controls treated with cytotoxic chemotherapeutics. In both KEYNOTE-012 and KEYNOTE-055 trials, median time to response equalled 2 months (range, 2–17 and 2–5, respectively), whereas patients who respond to chemotherapy often do so already within once month, i.e. after the first cycle [2,3,10]. Secondly, most of the responses were durable. At the time of data cut-off, 65% (22/34) and 75% (12/16) of the responding patients enrolled in KEYNOTE-012 and KEYNOTE-055, respectively, had an ongoing response [2,3].

Table 1
Second-line trials[a] of PD-1 and EGFR inhibitors in recurrent and/or metastatic squamous cell carcinoma of the head and neck.

Study, year of publication/data presentation	Phase	Number of patients	Treatment arms	Response rate (%)	Median survival (months)	
					PFS/TTP	OS
KEYNOTE-012 (NCT01848834), 2016 [2]	Ib	192	Pembrolizumab	17.7	2.0	8.0
KEYNOTE-055 (NCT02255097), 2016 [3]	II	92[c]	Pembrolizumab	17.4	2.1	8.0
CHECKMATE-141 (NCT02105636), 2016 [4]	III	361	Nivolumab	13.3[c]	2.0	7.5[c]
ZALUTE (NCT00282031), 2011 [7]	III	286	Methotrexate/docetaxel/cetuximab	5.8	2.3	5.1
			Zalutumumab + BSC	6.3	2.3[c]	6.7
ECOG 1302 (NCT00088907), 2013 [8]	III	270	Methotrexate/BSC	1.1	1.9	5.2
			Docetaxel + gefitinib	12.5	3.5	7.3
			Docetaxel + placebo	6.2	2.1	6.0
LUX-Head & Neck 1 (NCT01345682), 2015 [9]	III	483	Afatinib	10.2	2.6[c]	6.8
			Methotrexate	5.6	1.7	6.0

PD-1, programmed death-1; EGFR, epidermal growth factor receptor; BSC, best supportive care; PFS, progression-free survival; TTP, time to progression; OS, overall survival.
[a] Where response rates, progression-free survival/time to progression, and overall survival were reported, and the majority of participants received at least one prior systemic line.
[b] Number of evaluable patients.
[c] Significant differences.

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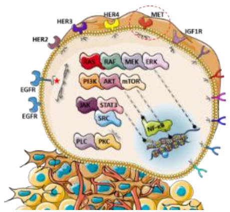
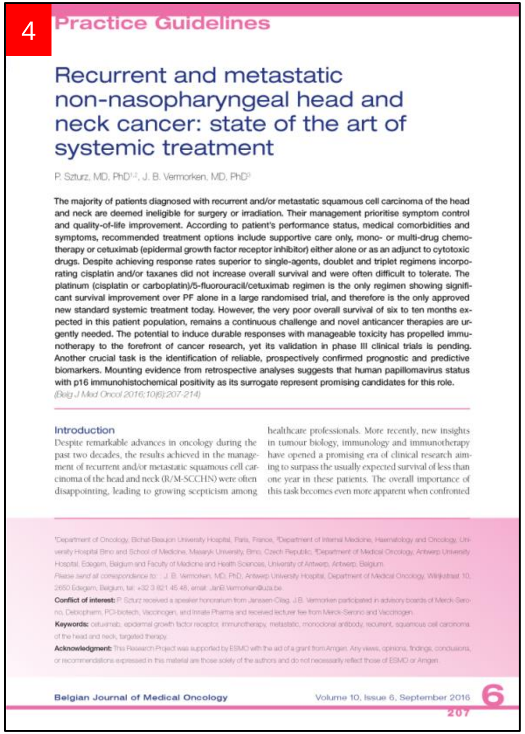


The c-MET project

- results -

Outline

- Towards the fellowship
- Why translational research
- The c-MET project
- ➢ Results & publications
- Conclusions



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Practice Guidelines

Recurrent and metastatic non-nasopharyngeal head and neck cancer: state of the art of systemic treatment

P. Szturz, MD, PhD[1,2], J. B. Vermorken, MD, PhD[3]

The majority of patients diagnosed with recurrent and/or metastatic squamous cell carcinoma of the head and neck are deemed ineligible for surgery or irradiation. Their management prioritise symptom control and quality-of-life improvement. According to patient's performance status, medical comorbidities and symptoms, recommended treatment options include supportive care only, mono- or multi-drug chemotherapy or cetuximab (epidermal growth factor receptor inhibitor) either alone or as an adjunct to cytotoxic drugs. Despite achieving response rates superior to single-agents, doublet and triplet regimens incorporating cisplatin and/or taxanes did not increase overall survival and were often difficult to tolerate. The platinum (cisplatin or carboplatin)/5-fluorouracil/cetuximab regimen is the only regimen showing significant survival improvement over PF alone in a large randomised trial, and therefore is the only approved new standard systemic treatment today. However, the very poor overall survival of six to ten months expected in this patient population, remains a continuous challenge and novel anticancer therapies are urgently needed. The potential to induce durable responses with manageable toxicity has propelled immunotherapy to the forefront of cancer research, yet its validation in phase III clinical trials is pending. Another crucial task is the identification of reliable, prospectively confirmed prognostic and predictive biomarkers. Mounting evidence from retrospective analyses suggests that human papillomavirus status with p16 immunohistochemical positivity as its surrogate represent promising candidates for this role.

(Belg J Med Oncol 2016;10(6):207-214)

Introduction

Despite remarkable advances in oncology during the past two decades, the results achieved in the management of recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN) were often disappointing, leading to growing scepticism among healthcare professionals. More recently, new insights in tumour biology, immunology and immunotherapy have opened a promising era of clinical research aiming to surpass the usually expected survival of less than one year in these patients. The overall importance of this task becomes even more apparent when confronted

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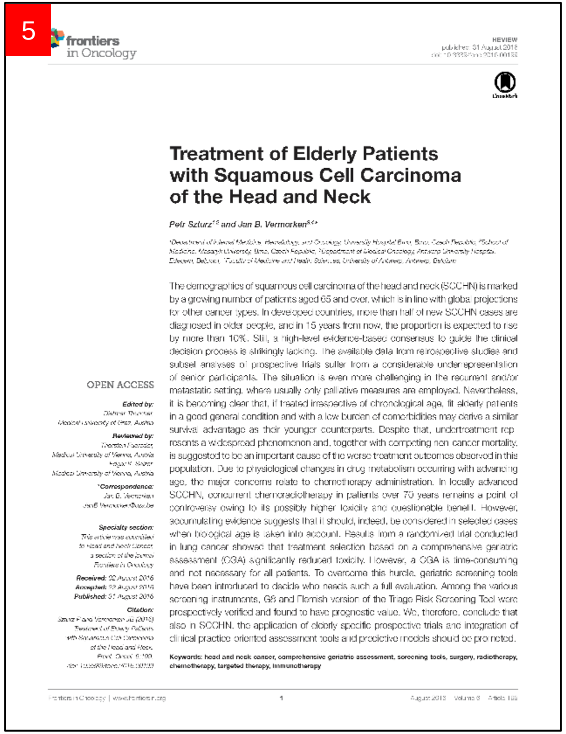
Sztutz P, Vermorken JB.
Belg Journal of Medical Oncology 2016.



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frontiers in Oncology

REVIEW

Treatment of Elderly Patients with Squamous Cell Carcinoma of the Head and Neck

Petr Szturz and Jan B. Vermorken

OPEN ACCESS

The demographics of squamous cell carcinoma of the head and neck (SCCHN) is marked by a growing number of patients aged 65 and over, which is in line with global projections for other cancer types. In developed countries, more than half of new SCCHN cases are diagnosed in older people, and in 15 years from now, the proportion is expected to rise by more than 10%. Still, a high-level evidence-based consensus to guide the clinical decision process is strikingly lacking. The available data from retrospective studies and subset analyses of prospective trials suffer from a considerable underrepresentation of senior participants. The situation is even more challenging in the recurrent and/or metastatic setting, where usually only palliative measures are employed. Nevertheless, it is becoming clear that, if treated irrespective of chronological age, fit elderly patients in a good general condition and with a low burden of comorbidities may derive a similar survival advantage as their younger counterparts. Despite that, undertreatment represents a widespread phenomenon and, together with competing non cancer mortality, is suggested to be an important cause of the worse treatment outcomes observed in this population. Due to physiological changes in drug metabolism occurring with advancing age, the major concerns relate to chemotherapy administration. In locally advanced SCCHN, concurrent chemoradiotherapy in patients over 70 years remains a point of controversy owing to its possibly higher toxicity and questionable benefit. However, accumulating evidence suggests that it should, indeed, be considered in selected cases when biological age is taken into account. Results from a randomized trial conducted in lung cancer showed that treatment selection based on a comprehensive geriatric assessment (CGA) significantly reduced toxicity. However, a CGA is time-consuming and not necessary for all patients. To overcome this hurdle, geriatric screening tools have been introduced to decide who needs such a full evaluation. Among the various screening instruments, G8 and Flemish version of the Triage Risk Screening Tool were prospectively verified and found to have prognostic value. We, therefore, conclude that also in SCCHN, the application of elderly specific prospective trials and integration of clinical practice oriented assessment tools and predictive models should be promoted.

Keywords: head and neck cancer, comprehensive geriatric assessment, screening tools, surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy

Sztutz P, Vermorken JB.
Frontiers in Oncology 2016.

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e (with author names and affiliations)

Prognostic value of c-MET in head and neck cancer: a systematic review and meta-analysis of aggregate data

Running head: Prognostic value of c-MET in head and neck cancer

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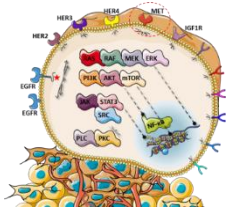

Parallel projects
- results -

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VOLUME 35 • NUMBER 20 • JULY 10, 2017
JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

How Standard Is Second-Line Cetuximab in Recurrent or Metastatic Head and Neck Cancer in 2017?

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Tanguy Y. Seiwert, The University of Chicago Medicine, and the University of Chicago Comprehensive Cancer Center, Chicago, IL
Jan B. Vermorken, Antwerp University Hospital, Edegem, and University of Antwerp, Antwerp, Belgium

Since 2006, cetuximab has been approved by the US Food and Drug Administration for squamous cell carcinoma of the head and neck (SCCHN). The indications comprise single-agent treatment of patients with recurrent or metastatic disease after a platinum-based regimen and use in combination with radiation therapy in newly diagnosed locoregionally advanced SCCHN. In 2011, the approval of cetuximab was extended to cover recurrent or metastatic SCCHN in conjunction with first-line platinum and 5-fluorouracil doublet. In the latter two categories, cetuximab also has been registered in Japan and the European Union. Presently, reimbursement of second-line cetuximab monotherapy for recurrent or metastatic SCCHN is granted in several countries, including the United States.

Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody. It competitively antagonizes natural ligand binding to the extracellular domain of the epidermal growth factor receptor (EGFR). In addition, cetuximab can stimulate antibody-dependent cellular cytotoxicity.[1] As a central signaling node for mitogenic and antiapoptotic transduction pathways, EGFR is commonly expressed on the cell surface of normal and neoplastic tissues. In SCCHN, its upregulation has been linked to worse survival. Of note, no other anti-EGFR drugs directed against either the extracellular part (monoclonal antibodies panitumumab, zalutumumab) or the intracellular domain (tyrosine kinase inhibitors [eg, afatinib, dacomitinib]) of the receptor have demonstrated sufficient clinical benefit in subsequent trials to gain approval from regulatory authorities as a standard treatment option for SCCHN.[2,3] In this respect, both the positive and the negative trials of these targeted agents were conducted in biomarker-undefined patient populations. However, recent evidence suggests that two biologically distinct molecular subsets of SCCHN, human papillomavirus (HPV)-positive and -negative tumors, occur primarily in the oropharynx. In economically developed countries, the incidence of oropharyngeal cancer has been rising steadily over the past three decades, which cover the period of the EGFR-inhibitor SCCHN trials that were not stratified by HPV status. The alarming epidemiologic trend most likely results from increased exposure to HPV infection, which currently is responsible for the majority of cases.

But is it just a matter of classification, or does HPV status have implications for clinical practice? Primarily, the viral positivity confers an important survival advantage in locoregionally advanced oropharyngeal cancer and probably in recurrent or metastatic SCCHN. HPV status can be determined either by HPV genetic material detection or by using p16 immunohistochemistry. The latter represents a surrogate biomarker with a high concordance rate in oropharyngeal cancer (both primary and recurrent) but poor concordance in other anatomic sites where HPV positivity occurs but is uncommon despite p16 positivity. In 2010, a post hoc analysis of the large Radiation Therapy Oncology Group (RTOG) 0129 study, which explored two different fractionation schedules combined with high-dose cisplatin once every three weeks, showed that the subset of patients with HPV-positive locoregionally advanced oropharyngeal cancer, which accounted for approximately 67% of the study population, had a significantly improved 3-year overall survival (82.4%) compared with HPV-negative counterparts (57.1%). The independent prognostic value of HPV/p16 status was confirmed by many others, so at present, HPV/p16 status is considered the single strongest prognostic factor in this disease setting.[4]

In recurrent or metastatic SCCHN, HPV/p16 positivity has been reported in a lower proportion of patients (approximately 10% to 20%), which hampers the interpretation of exploratory subgroup analyses and profiling data. Nevertheless, results from two large prospective trials that explored platinum-based chemotherapy together with cetuximab (the registration EXTREME [Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer] study) or panitumumab (the subsequent SPECTRUM [Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer] study) imply a superior survival outlook among HPV/p16-positive recurrent or metastatic SCCHN.[5-7] Because of the design and small sample sizes in HPV/p16-positive subgroups, the observed benefit is difficult to attribute to a specific tumor site of origin, although the oropharynx again exhibited the highest rate of positive cases. Of note, these findings are in line with a retrospective review of RTOG 0129 and 0522. Compared with patients with p16-negative oropharyngeal cancer, the analysis showed a reduced risk of death in those with p16-positive oropharyngeal cancer, which was maintained even after progression (ie, in recurrent disease).[8]

As opposed to therapy-independent prognostic markers, the predictive markers are helpful in selecting patients for a particular modality, which thus forms the basis for personalized medicine. In locoregionally advanced oropharyngeal cancer, the registration IMCL-9815 (Randomized Phase III Trial to Compare Radiation Therapy Alone With Radiation Therapy and

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CASE REPORT

Long-term remission of locally recurrent oropharyngeal cancer after docetaxel-based chemotherapy plus cetuximab

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Abstract
Background In recurrent head and neck squamous cell carcinoma ineligible for resection or irradiation, treatment aims primarily at symptom control and quality of life enhancement with an expected outcome of 6–12 months. *Methods* In 2005, a male patient, born in 1944, with a second local recurrence of human papillomavirus negative tonsil cancer was enrolled in the EXTREME trial, and randomized to platinum/5-fluorouracil/cetuximab arm resulting in partial remission with progression-free survival of 12 months. The second-line systemic therapy comprised 5 cycles of 3-weekly docetaxel/cisplatin/5-fluorouracil regimen plus weekly cetuximab. *Results* As confirmed on imaging and repeated biopsies, complete response was achieved with disease-free survival of 8 years and follow-up period of 12 years. Severe acute toxicities during the taxane-based chemotherapy plus cetuximab included grade 4 anorexia and grade 3 febrile neutropenia. *Conclusions* Poor tumor differentiation, no weight loss, oropharyngeal location, white race, and particularly the induced complete response were most likely the key favorable prognostic factors in the reported patient. The possibility of a synergistic interaction between taxanes and cetuximab should be further explored.

Keywords Tonsil cancer · Positron emission tomography · Taxanes · Targeted therapy · Epidermal growth factor receptor inhibitor

Deceased: E. Van Marck.

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Introduction

Despite advances in primary management of newly diagnosed oropharyngeal cancers, about 40 % of patients develop recurrent diseases most of which are difficult to salvage [1]. In case of a relapsed tumor deemed unsuitable for surgery or irradiation, only palliative strategies like best supportive care, cytotoxic chemotherapy or targeted therapy could be offered with an expected prognosis of 6–12 months [2]. Traditionally, a platinum-based combination has been regarded as the cornerstone of systemic treatment in this particular setting, however, without any proven survival advantage over single-agent methotrexate [3]. Although several phase II studies of three-drug

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Systemic Treatment of Recurrent/ Metastatic Squamous Cell Carcinoma of the Head and Neck

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Petr Szturz and Jan B. Vermorken

Abstract
Most patients with recurrent or metastatic head and neck squamous cell cancers qualify for palliative treatment. The management of these patients includes supportive care only, mono- or multiagent chemotherapy, and more recently targeted therapies. While platinum-based combinations are superior to single-agent therapies in terms of response rate, they are more toxic and so far have not shown to lead to meaningful survival benefit. Attempts to improve on this by using other or additional cytotoxic drugs were unsuccessful in the last 30 years. It was therefore an urgent need to investigate the efficacy of novel anticancer therapies that specifically target the tumor cells in such patients. A recent randomized trial showed that adding cetuximab, an EGFR-directed monoclonal antibody, to a standard platinum-based chemotherapy regimen led to an important survival benefit. Despite the still dismal prognosis, the outcome of this latter trial has changed practice in this category of head and neck cancer patients. The next challenge will be to sort out how to incorporate the numerous targeted agents that are currently studied into the existing treatment strategies, also in consideration of an optimization of their therapeutic index. Human papillomavirus status with immunohistochemical p16 expression as its surrogate marker represents promising prognostic and possibly predictive biomarkers that need to be prospectively validated in future randomized trials.

Keywords
Head and neck • Recurrent • Metastatic • Targeted therapies • Platinum • Monoclonal antibodies • Tyrosine kinase inhibitors • Immunotherapy

42.1 Introduction

Approximately 60–65 % of patients with head and neck cancer can be cured with surgery and/or radiotherapy [1]. While a large proportion of patients presenting with stage I and II squamous cell carcinoma of the head and neck (SCCHN) will remain disease-free after single modality treatment (either surgery or radiotherapy), the majority of patients presenting in a more advanced disease stage, and treated with whatever combined modality approach, will eventually relapse either locoregionally and/or at distant sites. A few patients with a locoregional recurrence can be salvaged by surgery or reirradiation. However, most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment. Treatment options in these patients include supportive care only or, in addition single-agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents.

Treatment choice should be based on factors such as performance status, comorbidity, prior treatment, symptoms, patient preference, and logistics [2]. Goals of treatments in

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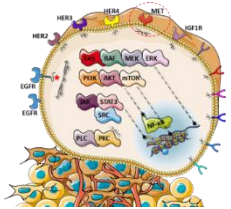

Parallel projects

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Head and Neck Cancers

Gemcitabine-Based Chemoradiation in the Treatment of Locally Advanced Head and Neck Cancer: Systematic Review of Literature and Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Chemotherapy • Concomitant chemoradiotherapy • Gemcitabine • Head and neck cancer • Neoplasms • Oncology • Radiotherapy • Radiation • Toxicity

ABSTRACT

Background. Platinum-based concurrent chemoradiation (CCRT) improves locoregional control and overall survival of locoregionally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN) when compared to radiotherapy alone, but this approach is hampered by significant toxicity. Therefore, alternative ways to enhance the radiation effects are worth investigating. Gemcitabine (2′,2′-difluorodeoxycytidine), in addition to its activity against a variety of solid tumors, including SCCHN, is one of the most potent radiosensitizers, and it has an overall favorable safety profile. In this paper, the clinical experience with gemcitabine-based chemoradiation in the treatment of patients with LA-SCCHN is reviewed.

Methods. We conducted a review of the literature on the clinical experience with radiotherapy combined with either single-agent gemcitabine or gemcitabine/cisplatin-based polychemotherapy for the treatment of patients with LA-SCCHN. We also searched abstract databases of major international oncology meetings from the last 20 years. A meta-analysis was performed to calculate pooled proportions with 95% confidence intervals (CIs) for complete response rate and grade 3–4 acute mucositis rate.

Results. A total of 13 papers were eligible for the literature review. For schedules using a gemcitabine dose intensity (DI) below 50 mg/m² per week, the complete response rate was 80% (95% CI, 79%–93%) with grade 3–4 acute mucositis rate of 38% (95% CI, 27%–50%) and acceptable late toxicity. In one of the studies employing such low DIs, survival data were provided showing a 3-year overall survival of 50%. Compared with DI ≥50 mg/m² per week, there was no difference in the complete response rate (71%; 95% CI, 50%–85%; $p = .087$) but a significantly higher ($p < .001$) grade 3–4 acute mucositis rate of 74% (95% CI, 62%–83%), often leading to treatment interruptions (survival data provided in 8 studies; 3-year overall survival, 27%–68%). Late toxicity consisting mainly of aphagia was generally underreported, with no information about xerostomia and skin fibrosis was scarce.

Conclusion. This review highlights the radiosensitizing potential of gemcitabine and suggests that even very low doses (less than 50 mg/m² per week) provide a sufficient therapeutic ratio and therefore should be further investigated. Refinements in radiation schemes, including intensity-modulated radiation therapy, in combination with low-dose gemcitabine and targeted agents, such as cetuximab, are currently being investigated. *The Oncologist* 2016;21:59–71

Implications for Practice: Cisplatin-based concurrent chemoradiation (CCRT) has become the standard treatment of locally advanced head and neck cancer (LAHNC). This approach is hampered by significant toxicity. This paper reviews the studies using gemcitabine as an alternative radio-sensitizer for CCRT in patients with LAHNC. In this capacity, despite its mild intrinsic toxicity, gemcitabine comes with high rates of severe mucositis when used in dosages exceeding 50 mg/m² per week. CCRT with low-dose gemcitabine provides a sufficient therapeutic ratio, combining clinical activity, similar to the higher-dose regimens, with lower toxicity. Further investigation is warranted.

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Chapter 16
Treatment in the Elderly

Petr Szturz and Jan B. Vermorken

Cancer and Ageing

As documented in many epidemiological studies, there is a marked association between tumour development and ageing. Advanced age is indeed the major risk factor for cancer, which in turn represents the second most common cause of death for persons over 65 years in Europe [1, 2]. In accordance with demographic projections clearly showing the steadily growing number of the elderly people, the global cancer burden will nearly double in the near future. By 2030, up to 22 million new cases (12 million in those 65 years or older) and 13 million cancer deaths (8.4 million in those 65 years or older) are to be expected worldwide each year. Of note, these figures exclude non-melanoma skin cancers, which are frequent and generally well curable [3]. However, the biological landscape of malignant transformation in older adults is far from being straightforward. Besides the dominant role of somatic mutations accumulating over lifetime, other age-related processes promote but also hinder tumourigenesis. Vascular ageing and a decline in circulating levels of various hormones probably counteract neoplastic progression, while it may be fostered by chronic low-grade inflammation and an increased fraction of senescent cells [1]. Interestingly, cancer incidence and mortality were reported to decrease or plateau in the oldest population (over 90 years) owing partly to the selection of less vulnerable individuals [4].

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Chapter 15
Immunotherapeutic Approaches

Petr Szturz and Jan B. Vermorken

One Hundred Fifty Years of Progress

Not many fields in medicine have seen so sharp fluctuations in attitude of healthcare professionals as cancer immunotherapy. Since the second half of the nineteenth century, there have been several fundamental discoveries leading to either an increase or decrease in its popularity [1, 2]. The first report to document the intriguing involvement of the immune system in cancer development was published more than 150 years ago. In 1863, Rudolf Virchow described immune infiltrates in neoplastic tissues. This finding gave at the same time early evidence for the origin of cancer at sites of chronic inflammation [3]. However, it was not until 1890s that a serious attempt at cancer immunotherapy was made. In 1893, based on a series of ten cases, William B. Coley confirmed that the phenomenon of cancer remission, occasionally occurring in patients with feverish infections, could be reproduced by injecting streptococcal cultures in and around tumours [4]. Subsequently, about 900 patients, mostly diagnosed with inoperable sarcomas, received the "Coley's toxin", but due to severe accompanying fevers and the low perceived cure rates, this approach remained purely experimental [5]. Thus, despite initial high hopes, the following five decades were marked by growing scepticism and even the prophetic hypothesis about tumour recognition by the immune system conceptualized by Paul Ehrlich in 1909 did not receive much attention [6].

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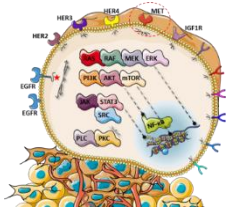

Parallel projects

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Schnitzlerové syndrom

Diferenciální diagnostika, přehled léčebných možností a popis 5 případů léčených anakinrou

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Souhrn

Schnitzlerové syndrom je získané autoinflamatorní onemocnění zatím nejasné etiologie. Pro stanovení této diagnózy byla přijata Strasburská kritéria (neinfekční horečka, chronická kopřivka, změny kostní struktury, leukocytóza a zvýšené hodnoty zánětlivých markerů – CRP a přítomnost monoklonálního imunoglobulinu většinou typu IgM, zcela výjimečně IgG). Léčbou volby pro tuto nemoc je blokáda účinků interleukinu 1. V praxi je nejčastěji využíván antagonista receptoru pro interleukin 1, anakinra. V současnosti se objevují zprávy i o použití dalších léků blokujících účinek interleukinu 1, kanakinumab a rilonacept. Dlouhodobě léčíme 5 pacientů preparátem anakinra (108, 72, 33, 32 a 1 měsíc). U všech nemocných jsme začali s aplikací anakinry v dávce 100 mg 1krát denně. Při dávkování 100 mg 1krát denně vymizely kompletně všechny příznaky u 4 nemocných, pouze u 1 nemocného došlo k ústupu příznaků asi o 75 %, nikoliv však k úplnému vymizení. Tento pacient potřebuje navýšení dávky ve dnech se spontánním zintenzivněním potíží na 2 ampulky denně. U jednoho ze 4 pacientů, u nichž příznaky při dávkování 1krát denně zcela vymizely, se po roce léčby ukázalo dostačující podávat anakinru v 48hodinových intervalech. Delší prodloužení intervalu mezi aplikacemi však netoleruje. V průběhu léčby jsme nezaznamenali žádné nežádoucí účinky anakinry a v průběhu léčby nedochází k poklesu účinnosti, aplikace anakinry jsou stejně účinné jako na začátku léčby. V textu rozvádíme diferenciální diagnostiku Schnitzlerové syndromu.

Klíčová slova: anakinra – autoinflamatorní choroby – kanakinumab – horečka nejasné etiologie (Fever of unknown origin – FUO) – interleukin 1 – kopřivka – kryopyrin asociovaný periodický syndrom (CAPS) – monoklonální gamapatie – rilonacept – Schnitzlerové syndrom – Stillova choroba dospělých

Schnitzler's Syndrome

Differential diagnostics, an overview of therapeutic options and description of 5 cases treated with anakinra

Summary

Schnitzler's syndrome is an acquired auto-inflammatory disease of still unclear origin. The Strasbourg criteria were adopted (non-infectious fever, chronic urticaria, changes in the bone structure, leukocytosis and higher values of inflammatory markers – CRP and presence of monoclonal immunoglobulin mostly of type IgM, very rarely of IgG) to establish this diagnosis. The first-choice therapy for this disease is the blocking of interleukin-1 effects. In practice, the interleukin-1 receptor antagonist, anakinra, is the most commonly used. Currently reports also appear of the use of other medicines blocking the effect of interleukin-1, namely canakinumab and rilonacept. We have been treating 5 patients with anakinra (108, 72, 33, 32 and 1 months) on a long-term basis. In all the patients, we

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kazuistiky

Hodnocení pětileté léčby Erdheimovy-Chesterovy nemoci anakinrou – kazuistika a přehled literatury

Zdeněk Adam , Hana Petrášová, Zdeněk Řehák, Renata Koukalová, Marta Krejčí , Luděk Pour , Eva Veteškníková , Aleš Černák, Sabina Ševčíková , Petr Szturz, Zdeněk Král, Jiří Mayer

Souhrn

Erdheimova-Chesterova nemoc je histiocytární neoplazie ze skupiny non-Langerhans-cell histiocytóz, je tvořena infiltráty pěnitých histiocytů. Tyto patologické histiocyty produkují prozánětlivé cytokiny. Proto je Erdheimova-Chesterova choroba nazývána inflamatorní histiocytární neoplazií. Nemoc, u prováděná klinickými projevy systémové zánětlivé odpovědi nebo B symptomy. Při zobrazovacích vyšetřeních jsou typické osteosklerotické změny postihující diafýzy a metafýzy dlouhých kostí dolních končetin a dále fibrotizující změny postihující stěnu aorty a cévy z ní odstupující. Dále jsou typické perineální fibrotické změny, které se šíří v retroperitoneu. Mohou způsobit závažné komplikace – hydronefrózu se všemi jejími důsledky. Léčba této nemoci nebyla v přechozích letech uspokojivá. Klasická chemoterapie ani glukokortikoidy neprinášejí zásadní a dlouhodobé zlepšení. Z cytostatik je účinný pouze 2-chlorodeoxyadenozin (kladribin), ale ne u všech pacientů. Pouze u jednoho z našich 2 pacientů jsme dosáhli 2-chlorodeoxyadenozinem kompletní remise, která trvá více než 2 let, zatímco u popisovaného pacienta vedl kladribin sice ke zmenšení infiltrátů v CNS, ale nevedl k ústupu aktivity nemoci v jiných lokalizacích dle PET/CT s aplikací radiofarmaka fluorodeoxyglukózy (FDG). Dalším účinným lékem pro pacienty s Erdheimovou-Chesterovou nemocí je interferon α. Jeho dlouhodobé podávání je však spojeno s četnými nežádoucími účinky a u popisovaného pacienta jsme jej proto nezkoušeli. Zavedení blokátoru receptoru interleukinu 1, anakinry, do léčby přineslo novou naději pro tyto nemocné. Popisujeme pacienta, u něhož prošlá léčba anakinrou již více než 5 let. Pacient si aplikuje 1 ampulku, 100 mg podkožně denně. Tato léčba úplně odstranila systémové B symptomy a odstranila bolestivost a vedla k normalizaci všech nálezů, které signalizovaly systémovou zánětlivou reakci. Efekt léčby je pravidelně sledován CT zobrazením břišní duteiny a FDG-PET/CT vyšetřením. V průběhu 5 let léčby anakinrou postupně ustupovaly fibrotické změny v retroperitoneu, jak dokumentují obrazy v textu. Při low-dose CT zobrazení, které bylo součástí PET/CT vyšetření, byla patrná četná osteosklerotická ložiska ve skeletu, zvláště v dolních končetinách, se zvýšenou akumulací ^{18}F-fluorodeoxyglukózy (FDG). Osteosklerotická ložiska zůstávají při opakovaných vyšetřeních stále dobře zřetelná. V počátku 5 let se ale akumulace FDG v nich snižila, jak dokumentují obrazy v textu. Léčba anakinrou má charakter udržovací léčby. U popsaného pacienta se nepodařilo prokázat mutaci BRAFV600E, takže léčbou vemurafenibem jsme netestovali. Závěr: Anakinra vedla k ústupu fibrózních změn v retroperitoneu a vymizení B symptomů a k poklesu a mizení akumulace FDG při FDG-PET/CT vyšetření.

Klíčová slova: anakinra – Erdheimova-Chesterova choroba – kladribin – retroperitoneální fibróza – vemurafenib

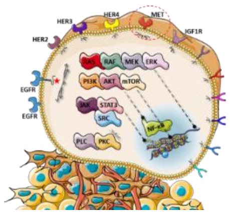
Evaluation of five years of treatment of Erdheim-Chester disease with anakinra: case report and overview of literature

Summary

Erdheim-Chester disease is a histiocytic neoplasm of diseases from the group of non-Langerhans-cell histiocytoses, formed by infiltrates of foamy histiocytes. These pathological histiocytes produce pro-inflammatory cytokines. Therefore Erdheim-Chester disease is called inflammatory histiocytary neoplasm. The disease is accompanied by clinical symptoms of systemic inflammatory response, i.e. B symptoms. Imaging examinations detect typical osteosclerotic changes affecting diaphyses and metaphyses of the lower long bones and fibrotic changes which affect the aorta wall and the vessels leading from it. Also characteristic are perineal fibrotic changes spreading in the retroperitoneum. They can cause serious complications – hydronephrosis with all its consequences. The therapy for

Vnitř Lék 2016; 62(10): 822–832

Adam Z,...,Szturz P et al.
Vnitr Lek 2016.



Parallel projects

- results -

Outline
- Towards the fellowship
- Why translational research
- The c-MET project
- ➢ Results & publications
- Conclusions

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Léčba 14 případů Castlemanovy nemoci: zkušenosti jednoho centra a přehled literatury

Zdeněk Adam[1], Petr Szturz[1], Marta Krejčí[1], Renata Koukalová[2], Eva Michalková[1], Zdeněk Řehák[2], Eva Pourová[3], Luděk Pour[1], Pavlína Volfová[1], Viera Sandecká[1], Zdeňka Čermáková[4,9], Leoš Křen[5], Filip Sokol[5], Ivo Hanke[6], Igor Penka[6], Hana Petrášová[7], Sabina Ševčíková[8], Zdeněk Král[1], Jiří Mayer[1]

Souhrn

Castlemanova choroba je termín pro reaktivní lymfocytární a plazmocytární proliferaci, která se vyskytuje buď ve formě lokalizované, unicentrické, obvykle bez systémových příznaků, nebo ve formě generalizované, multicentrické, obvykle se systémovými příznaky (www.vzacne-diagnozy.cz). …

Klíčová slova: anémie chronických chorob – Castlemanova choroba – hyperproteinemie – lenalidomid – polyklonální hypergamaglobulinemie – rituximab – siltuximab – talidomid

Vnitř Lék 2016; 62(4): 287–298

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16

KAZUISTIKA

Ložisková amyloidóza v dutině nosní

Localized Amyloidosis Involving the Nasal Cavity

Koukalová R.[1], Szturz P.[2], Svobodová I.[3], Stulík J.[4], Řehák Z.[1]

Souhrn

…

Klíčová slova
nosní polyp – amyloidóza – ložisková amyloidóza – pozitronová emisní tomografie – PET/CT

Summary

…

Key words
nasal polyp – amyloidosis – localized amyloidosis – positron-emission tomography – PET/CT

http://dx.doi.org/10.14735/amko2016216

216 Klin Onkol 2016; 29(3): 216–219

Koukalová R, Szturz P et al.
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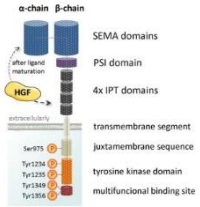

Conclusions

- c-MET overexpression is a common finding in head and neck cancer (46% moderate, 64% strong).
- At least moderate overexpression is associated with advanced disease and shorter survival.
- c-MET represents a promising therapeutic target in head and neck cancer.
- It is also a promising predictive biomarker for c-MET targeting.