Building a Global Consensus: history of the Chordoma Consensus Group

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Background

- Chordoma is a very rare bone malignant tumor

Consensus event on Methodology of Clinical Research in Rare Cancers

Brussels, 10 February 2012

- Clinical decision-making
- Methods to combine evidence
- New study designs
- Surrogate end points
- Organization of studies
Background

- Chordoma is a very rare bone malignant tumor

- New treatments available, but given its rarity the degree of uncertainty remains high and their adoption remains inconsistent across the world, resulting in suboptimal outcomes for many patients.

- Treatment of chordoma patients involves many different specialists

- Special need for a common language to be used by the expert of different fields a global consensus around the management of patients with chordomas a tool to guide and support the discussion with agencies/regulators
ESMO Consensus Conference Sarcoma guidelines update

Milan, 9-10 December 2013
ESMO Consensus Conference
Sarcoma guidelines update

Milan, 9-10 December 2013

expansion of clinical practice guidelines
on chordoma

position paper on tx of chordoma
ESMO Consensus Conference
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expansion of clinical practice guidelines
on chordoma

Bone sarcomas: ESMO Clinical Practice Guidelines for
diagnosis, treatment and follow-up†
The ESMO / European Sarcoma Network Working Group*

major changes
Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

The ESMO/European Sarcoma Network Working Group*

incidence

Primary bone tumours are the 5th most common tumours of all in childhood and adolescence and present in 1 in 10,000 per year. Epidemiologically, 1% of all bone tumours occur in adults. The incidence of osteosarcoma is similar in adults and children, but 15 years is a peak age of incidence, with a male:female ratio of 2:1. The incidence is highest in Asian populations, whereas incidence in children is lower.

Chordomas are very rare tumours, arising from the remnants of the notochord into the sacrum (50%), skull base (30%), mobile spine (20%); extraskeletal cases have also been reported but are extremely rare.

Median age is 60 years, but skull base presentations can also affect a younger population, including children and adolescents. Chordoma is a low-grade, locally invasive malignancy. Dedifferentiated cases are observed in 5% of patients. The metastatic potential of chordoma is ~30%. Metastases usually appear late in the natural history of disease, mostly after local recurrence. Chordoma prognosis is more related to local aggressiveness than to metastases. Chordoma is a tumour showing notochordal differentiation. Brachyury is a transcription factor involved in notochord differentiation and is the diagnostic hallmark for conventional chordoma [84]. Dedifferentiated chordomas may lose brachyury expression. Immunohistochemistry positivity for brachyury is strongly recommended to confirm diagnosis.

Due to the rarity and long natural history of the disease, the quality of evidence available for more common tumour types is currently beyond reach for chordoma. In fact, only a few phase II trials are available and most published data are from case series and/or retrospective.

Chordomas need a multidisciplinary approach in referral centres and/or referral networks, with a multidisciplinary team including expert pathologists and radiologists, surgeons familiar with musculo-skeletal tumours and site of surgery, expert radiation oncologists with access to hadron facilities, expert medical oncologists, and a palliative care team. All diagnostic and therapeutic procedures should be discussed in the multidisciplinary expert team.

MRI is the best modality for local staging. CT scan should be used in the case of diagnostic doubt. Chordoma should be differentiated from benign notochordal lesions and, if radiological appearance is typical for these, biopsy is not recommended unless the lesion changes with time [85].

Preoperative core-needle biopsy is recommended. The biopsy track needs to be included in the surgical resection. In the case of chordoma, the standard approach includes the sacropelvic pedicle and the rectum.
Brachyury (involved in notochord dedifferentiation; diagnostic hallmark; IHC positivity for brachyury strongly recommended)

Need of a multidisciplinary approach in referral centers and/or referral networks, with a multidisciplinary team

Level of evidence as available for more common tumor types is currently beyond reach for chordoma

MR is the best modality for local staging

Chordoma should be differentiated from BNCT (if radiological appearance is typical, biopsy is not recommended unless the lesion changes)
Biopsy
(Preoperative core-needle biopsy recommended; biopsy track to be included in the surgical resection; preop biopsy can be avoided in selected cases in skull base chordoma)

Supportive care
(To be incorporated in treatment from the beginning)

Surgery, quality of surgical margins, RT
(most important prognostic factor; when feasible, en-bloc R0 resection is standard treatment and sequelae acceptable/acceptable by the patient

If en-bloc R0 resection is not feasible, definitive RT alone should always be considered as a valid alternative

For skull base and upper cervical tract chordoma, R1-R2 surgery plus RT is the treatment of choice
For sacral chordoma, surgery should definitely be offered as the first choice in case chordoma arises from S4 and below. Surgery should always be discussed in the context of other alternatives for tumors originating above S3 due to mobidity

Hadrons physically superior and in terms of non-target radiation to photons. They should be considered the treatment of choice. Advanced technology photons could be used in case of unavailability or non-accessibility of protons and ions and every time they show similar dose distribution to the target and critical structures.

Due to the relative radiation resistance of chordomas, a high-dose up to at least 74GyE in conventional fractionation (1.8-2GyE) for photon- and proton therapy is required.
**Indications for definitive RT**
(unresectable disease; inoperable patients; neurological impairment not accepted by the patient; R2 or R1 resections)

**Metastatic disease**
(surgery/RFA/stereotactic RT of metastases in selected cases; chemotherapy inactive, but in case of high-grade dedifferentiated chordoma; uncontrolled evidence that Imatinib is beneficial in terms of PFS; data on the activity of EGFR and VEGFR inhibitors)

**FU**
(6 monthly MR of the primary site for the first 4 years suggested, then yearly until at least 10 years. No consensus on the usefulness/frequency of imaging for other sites of metastatic disease)
ESMO Consensus Conference
Sarcoma guidelines update

position paper

“Building a global consensus approach to chordoma:
a position paper from the medical and patient community”

aim
of fostering a consensus approach to the disease
ESMO Consensus Conference Sarcoma guidelines update

position paper

“Building a global consensus approach to chordoma: a position paper from the medical and patient community”

40 authors from 12 countries

2 pts; 3 path & biologist; 2 radiologists; 8 radiation therapists; 18 surg (NCH, ENT, orthopedic and general surgeons); 6 oncologists; 1 statistician
Building a global consensus approach to chordoma: a position paper from the medical and patient community

Stacchiotti et al., Lancet Oncol 2015

Chordomas are very rare bone malignancies that have had a shortage of effective treatments for a long time. New treatments are now available for both the local and the metastatic phase of the disease, but the degree of uncertainty in selecting the most appropriate treatment remains high and their adoption remains inconsistent across the world, resulting in suboptimum outcomes for many patients. In December 2013, the European Society for Medical Oncology (ESMO) convened a consensus meeting to update its clinical practice guidelines on chordoma. ESMO also hosted a parallel consensus meeting on chordoma that included more than 40 chordoma experts from several disciplines and from both sides of the Atlantic, with the contribution and sponsorship of the Chordoma Foundation, a global patient advocacy group. The consensus reached at that meeting is shown in this position paper.

Introduction

Chordomas are rare cancers, which have long been in need of more effective treatments. Innovative treatment approaches have been developed in the past 20 years, but evidence generated by available studies is weak. Therefore, the degree of uncertainty in selecting the most appropriate treatment remains high and adoption of the new treatments remains inconsistent across the world, which results in suboptimum outcomes for many patients.

In December 2013, the European Society for Medical Oncology (ESMO) convened a consensus meeting to update its clinical practice guidelines on chordoma, with the aim being to expand the chordoma section. Recognizing the special need for a global consensus around the management of patients with chordoma, ESMO hosted a parallel meeting that included chordoma experts from several disciplines and from both sides of the Atlantic, with the contribution and sponsorship of patient advocacy group the Chordoma Foundation.

Quality of existing evidence

At present the quality of evidence available for chordomas is considerably stronger than for chordomas. No phase 3 randomized clinical studies and only a few phase 2 trials are available, and most reported clinical evidence is based on retrospective case series. Thus, a degree of uncertainty needs to be accepted when considering regulatory matters and clinical decision making. The approval of sintel by the US Food and Drug Administration and the European Medicines Agency for the similarly rare dermatofibrosarcoma protuberans on the basis of a retrospective case report and subsequently, 5 years afterwards, a single phase 2 study should provide a relevant precedent.

In this report, we grade levels of evidence from I to V and use grades of recommendation from A to D adapted from the system used by the Infectious Diseases Society of America-US Public Health Service Grading System (panel).

Epidemiology

Chordoma is a bone tumour with an annual incidence of 0.1 every 100,000 individuals and prevalence of less than one every 300,000. Chordoma is a tumour showing notochordal differentiation. The notochordal cells in human beings at about 8 weeks in the fetal development, and evidence suggests that chordomas develop from persistent notochordal remnants. Lines of origin are the sacrum (50%), skull base (30%), and mobile spine (20%). Cranial chordomas have also been described but are very rare.

The median age at diagnosis is 60 years, with skull base presentations generally affecting a younger population, including children. The median time from initial symptoms to diagnosis is longer than 2 years, with a clinical presentation as mass that varies according to tumour site of origin. A small number of familial cases of chordoma have been reported, which suggests the potential for genetic predisposition.

Panel: Level of evidence and grade of recommendation

1. Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias or meta-analysis of well-conducted randomized trials without heterogeneity).
2. Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality or meta-analysis of such trials or cross-trials with demonstrated heterogeneity).
3. Prospective cohort studies.
4. Retrospective cohort studies or case-control studies.
5. Studies without control group, case reports, and expert opinions.
   a. Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.
   b. Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.
   c. Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (including adverse events and costs), optional.
   d. Moderate evidence against efficacy or for adverse outcome, generally not recommended.
   e. Strong evidence against efficacy or for adverse outcomes, never recommended.

To distinguish prospectively planned studies from retrospective case series, we assigned the level of evidence V followed by “***” to single-group prospective trials.
Building a global consensus approach to chordoma: a position paper from the medical and patient community


**General principle**

Pathology

Radiology

**Localized disease:** primary tumor, treatment

skull-base/cervical spine

sacrum

thoraco-lumbar

**Loco-regional relapse**

**Advanced disease**

**Follow-up**

**Ongoing studies and future direction**

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Chordomas are rare bone malignancies that have had a shortage of effective treatments for a long time. New treatments are now available for both the local and the metastatic phase of the disease, but the degree of uncertainty in selecting the most appropriate treatment remains high and their adoption remains inconsistent across the world, resulting in suboptimum outcomes for many patients. In December 2013, the European Society for Medical Oncology (ESMO) convened a consensus meeting to update its clinical practice guidelines on chordoma. ESMO also hosted a parallel consensus meeting on chordoma that included more than 40 chordoma experts from several disciplines and from both sides of the Atlantic, with the contribution and sponsorship of the Chordoma Foundation, a global patient advocacy group. The consensus reached at that meeting is shown in this position paper.

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**Quality of existing evidence**

As present the quality of evidence available for more common tumour types is considerably stronger than for chordomas. No phase 3 randomised clinical studies and only a few phase 2 trials are available, and more robust clinical evidence is based on retrospective case series. Thus, a degree of uncertainty needs to be accepted when considering regulatory matters and clinical decision making. The approval of imatinib by the US Food and Drug Administration and the European Medicines Agency for the similarly rare dermatofibrosarcoma protuberans on the basis of a retrospective case series and subsequently, 1 year afterwards, a single phase 2 study should provide a relevant precedent.

In this report, we grade levels of evidence from I to V and use grades of recommendation from A to D adapted from the National Institute for Health and Care Excellence of the United Kingdom and the American Society for Radiation Oncology (ASTRO) guidelines.

**Epidemiology**

Chordoma is a bone tumour with an annual incidence of 0.1 to 1 every 100,000 individuals and prevalence of less than one every 30,000. Chordoma is a tumour showing nuclear and chromosomal differentiation. The notochordal appearance in human beings is about 8 weeks in the fetal development, and evidence suggests that chordomas develop from persistent notochordal elements. Sites of origin are the sacrum (50%), skull base (30%), and mobile spine (20%). Extra-sacral cases have also been described but are rare.

The median age at diagnosis is 60 years, with skull base presentations generally affecting a younger population, including children. The median time from initial symptoms to diagnosis is longer than 2 years, with a clinical presentation of acute pain that varies according to tumour site of origin. A small number of familial cases of chordoma have been reported, which suggests the potential for genetic predisposition.
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General principle
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Advanced disease
Follow-up
Ongoing studies
and future direction

Stacchiotti et al, Lancet Oncol 2015
“Ongoing studies and future direction

With new targeted therapies, response has often been non-dimensional, though substantial changes in tumor tissue have been documented radiologically. Therefore, new tumor response criteria are needed. Potential alternatives include growth modulation index, PET response, changes in tumor contrast up-take and minor decrease in tumor size, and circulating tumor DNA. QoL needs to be investigated in all studies. Since the rarity of the disease makes high-power randomized clinical trials challenging, uncontrolled studies, case series analyses and even case reports should be regarded as contributing to available evidence. Observational studies merit attention in the disease, as they have the ability to provide external controls for future uncontrolled studies.”
ESMO Consensus Conference Sarcoma guidelines update

“Ongoing studies and future direction

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Raccomandazioni degli esperti per la diagnosi e il trattamento del chordoma

Hans Keulen
28 LUGLIO 1957 - 29 OTTOBRE 2015

Questo opuscolo rivolto ai pazienti è dedicato alla memoria di Hans Keulen, membro del Consiglio e coordinatore europeo della Chordoma Foundation. Hans si è dedicato instancabilmente alla nostra causa, al servizio della comunità di pazienti affetti da chordoma, promuovendo la ricerca e assistendo diversi pazienti europei. Gli siamo grati per averci ispirato con il suo ottimismo, il suo coraggio e la sua grande passione nel tentativo di migliorare le cure a disposizione dei pazienti. Siamo profondamente rammaricati per la sua perdita e, in suo onore, continueremo a perseguire la ricerca di trattamenti efficaci per questa patologia, ad assistere i pazienti nelle loro scelte e a sostenere affinché possano prendere le decisioni migliori per la loro salute.
Chordoma study end-points, FDA meeting
Chicago 5.2014
Workshop on methodology of clinical studies on rare cancers ESMO/EMA meeting: chordoma as a model for very rare cancers
London 10.2014
RCE/EMA workshop on Chordoma, Londra 4.2015
The compassionate and off-label use of new drugs is widespread in chordoma with a very discordant access to potentially active treatments among different European countries.
Advanced disease ...

Imatinib

Italy, 648/96
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Stacchiotti et al, Lancet Oncol 2015

The group will hopefully continue to operate as a global medical and patient community with the goal to maintain and develop a consensus approach to this rare tumor.
General principle
Pathology
Radiology
Localized disease: primary tumor, treatment
skull-base/cervical spine
sacrum
thoraco-lumbar
Loco-regional relapse

“Detailed recommendations about the management of recurrences are omitted from this publication and will be the subject of a subsequent consensus meeting and publication.”
Chordoma Community Conference, Milan, 22.11.2015
Milan, 23 October 2015

II Consensus Conference

(Looco-regional relapse, Supportive care, QoL)

>60 experts
(Europe, Japan, US)
Chordoma, position paper on local relapse under preparation

Chordoma Foundation
>60 Experts (EU, US, Japan)
end 2016
EMA comments ...

- (Early) scientific advise almost for free for rare disease
- Extension of patent for the given rare indication
- Check other EMA rules for rare diseases
- Ok quality of life as primary end-point (see ruxolitinib in polycythemia registrative study)
- Ok for growth modulation index
- Ok for random with imatinib as comparator
- Ok for response evaluation criteria other than RECIST
- Ok for randomized trial for two observational arms (PGC)? Not replied
- PGC Composite end-points? > Why not? See Castlemann study
- PGC Registry and data: can be incorporated in the evaluation of activity of a new drug? > better than nothing, especially to inform prior in study design
- Adaptive licensing