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Édito

Par Christian Cailliot, Directeur R&D UNICANCER et le Pr François-Régis Bataille, Directeur général ICO Angers/Nantes

Le développement clinique des nouveaux traitements innovants et l'élaboration de nouvelles stratégies thérapeutiques, issus du monde académique comme de celui du privé, entrainent une complexification importante de la recherche clinique. Cette évolution nécessite une structuration et une professionnalisation des équipes approfondies ainsi que des investissements plus lourds. R&D UNICANCER, en tant qu'acteur majeur de la recherche académique nationale, doit s'adapter aux nouveaux standards de qualité et à la réglementation en matière d'essais cliniques. Ainsi la formation permanente des équipes opérationnelles aux nouvelles avancées thérapeutiques permet à notre structure de répondre aux attentes de nos institutions, des cliniciens, et au final des patients eux-mêmes.

C'est pourquoi l'année 2014 a été marquée par une réorganisation de R&D UNICANCER :

— Le regroupement de la Pharmacovigilance, les Affaires réglementaires, l'Assurance qualité et l'Audit et en un seul département, dirigé par le Dr Pierre-Henri Bertoye.

— La création d'un département de données médicales : ESME (Epidémio. et Stratégie Médico-économique) sous la direction du Dr Mathieu Robain. Son objectif est de constituer et exploiter de larges bases de données de « vrai vie » sur chaque pathologie cancéreuse afin d'améliorer à termes la prise en charge thérapeutique des patients.

— La création d'un département Développement et partenariats, piloté par Anne-Laure Martin, pour renforcer nos collaborations aussi bien avec les acteurs publics, académiques que privés. Son objectif est de mettre sur pied des programmes de recherche ambitieux et ainsi de promouvoir la recherche en cancérologie, dans un paysage où les efforts de soutien à la recherche au niveau national sont très sensiblement en baisse.

— Et enfin, un département des Opérations cliniques étoffé pour répondre à nos besoins grandissants en matière d'essais cliniques et dont la direction a été confiée tout récemment à Carole Desseaux.

Cette restructuration permet à R&D UNICANCER d'acquérir une masse critique, d'asseoir son savoir-faire, et ainsi de renouveler la confiance des cliniciens, afin de mener ensemble une recherche clinique de qualité. Ainsi, 2014 a été pour R&D UNICANCER une nouvelle année de forte croissance, marquée par :

— La création de nouveaux groupes transversaux : le Groupe soins de support en partenariat avec l'AFSOS, sous la présidence du Pr Yvan Krakowsky ; le Groupe de recherche en radiothérapie, UNITRAD, présidé par le Pr David Azria ; un comité scientifique et éthique pour le programme ESME dont la présidence a été confiée au Dr David Pérol.

— Le lancement de nouveaux essais cliniques: SAFIR 02 poumon, en collaboration avec l'IFCT, et SAFIR 02 sein ; AcSé Vemurafenib en collaboration avec l'INCa et la fondation ARC ; des essais sur des tumeurs orphelines : BEVABEL dans les tumeurs de Bellini, et REGOBONE dans les sarcomes osseux

— La labélisation par l'INCa du groupe de recherche en gériatrie, GERICO, et du groupe d'étude des cancers urogénitaux, GETUG

— De nombreuses communications et publications dont vous trouverez le détail ci-après.

L'année 2015 devra confirmer les orientations prises en 2014 afin de pouvoir offrir aux Centres en particulier, et aux établissements de soins d'une façon générale, toujours plus de services mutualisés (*medical writing*, audits de qualité, rédaction des appels à projets, prise en charge des aspects réglementaires et de pharmacovigilance, délégation de promotion…) afin de les soutenir dans la conduite d'une recherche dynamique et innovante. Enfin 2015 verra le développement proactif de collaborations internationales avec les grands groupes coopérateurs et les institutions de recherche dans le monde.

Grâce à cette restructuration profonde, R&D UNICANCER devrait être mesure d'ici la fin de l'année de lancer son premier appel à projet. Celui-ci s'orientera sans doute vers une voie de recherche prometteuse pour de nombreuses années : l'immunothérapie adoptive dans le traitement du cancer.

French breast cancer intergroup UNICANCER
UCBG

Communications écrites

Identification by array comparative genomic hybridization of a new amplicon on chromosome 17q highly recurrent in BRCA1 mutated triple negative breast cancer. (Toffoli S *et al.*; Breast Cancer Res. 2014 Nov 22;16(6):466.)

INTRODUCTION

Triple Negative Breast Cancers (TNBC) represent about 12% to 20% of all breast cancers (BC) and have a worse outcome compared to other BC subtypes. TNBC often show a deficiency in DNA double-strand break repair mechanisms. This is generally related to the inactivation of a repair enzymatic complex involving BRCA1 caused either by genetic mutations, epigenetic modifications or by post-transcriptional regulations. The identification of new molecular biomarkers that would allow the rapid identification of BC presenting a BRCA1 deficiency could be useful to select patients who could benefit from PARP inhibitors, alkylating agents or platinum-based chemotherapy. Methods Genomic DNA from 131 formalin-fixed paraffin-embedded (FFPE) tumors (luminal A and B, HER2+ and triple negative BC) with known BRCA1 mutation status or unscreened for BRCA1 mutation were analysed by array Comparative Genomic Hybridization (array CGH). One highly significant and recurrent gain in the 17q25.3 genomic region was analysed by fluorescent *in situ* hybridization (FISH). Expression of the genes of the 17q25.3 amplicon was studied using customized Taqman low density arrays and single Taqman assays (Applied Biosystems).

RESULTS

We identified by array CGH and confirmed by FISH a gain in the 17q25.3 genomic region in 90% of the BRCA1 mutated tumors. This chromosomal gain was present in only 28.6% of the BRCA1 non-mutated TNBC, 26.7% of the unscreened TNBC, 13.6% of the luminal B, 19.0% of the HER2+ and 0% of the luminal A breast cancers. The 17q25.3 gain was also detected in 50% of the TNBC with BRCA1 promoter methylation. Interestingly, BRCA1 promoter methylation was never detected in BRCA1 mutated BC. Gene expression analyses of the 17q25.3 sub-region showed a significant over-expression of 17 genes in BRCA1 mutated TNBC (n=15) as compared to the BRCA1 non mutated TNBC (n=13).

CONCLUSIONS

In this study, we have identified by array CGH and confirmed by FISH a recurrent gain in 17q25.3 significantly associated to BRCA1 mutated TNBC. Up-regulated genes in the 17q25.3 amplicon might represent potential therapeutic targets and warrant further investigation.

Communications orales

SFSPM

Prédiction du risque de récidive avec le test Oncotype DX® chez les patientes atteintes de cancer du sein hormono-dépendant avec atteinte ganglionnaire, traitées par chimiothérapie adjuvante: Résultats de l'étude PACS01. (F Penault-Llorca *et al*.)

CONTEXTE

Les résultats du Récurrence Score® (RS) du test Oncotype DX® permettent d'évaluer le risque d'une récidive à distance et le bénéfice de la chimiothérapie chez les patientes atteintes d'un cancer du sein avec des récepteurs aux œstrogènes positifs (RE+) avec ou sans atteinte ganglionnaire. Nous avons étudié l'impact de la valeur pronostique du RS chez les patientes atteintes d'un cancer du sein hormono-dépendant (RH+) avec atteinte ganglionnaire (N+), traitées par chimiothérapie et hormonothérapie adjuvante, issues de l'étude PACS01.

MÉTHODE

L'étude PACS01 compare le traitement 6 FEC100 (6FEC ; Epirubicine) au traitement 3 FEC 100 suivi de 3 Docétaxel (3FEC-3D) chez 1999 patientes. Après un amendement au protocole, il a été proposé aux patientes RH+ 5 ans d'hormonothérapie (tamoxifène) à l'issue de la chimiothérapie.

L'étude actuelle comprend 530 patientes issues de l'essai principal PACS01 dont le prélèvement tumoral (RE+ par IHC centralisé) était suffisant pour une analyse avec le test Oncotype DX®. L'objectif principal était d'évaluer le lien entre le RS et la survie sans récidive à distance (DRFI). Les critères secondaires étaient la survie sans maladie (DFS) et la survie globale (SG). La durée médiane de suivi était de 7,7 ans.

RÉSULTATS

Parmi les 530 patientes, 209 (39,4%) avaient un RS bas; 159 (30,0%) un RS intermédiaire; et 162 (30,6%) un RS élevé. 74,2% ont été traitées par tamoxifène. Dans l'analyse principale, le RS était un paramètre prédictif significatif de de la survie sans récidive à distance (DRFI) (HR=4,1 pour une différence de 50 points, P<0,001), de la DFS (HR=3,3, p<0,001) et de la SG (HR=5,0, p<0,001).

En analyse multivariée, le RS a fourni des informations pronostiques indépendantes des facteurs cliniques et pathologiques classiques, y compris pour le traitement, l'âge, la taille, le grade tumoral, le nombre ganglions atteints, le type de chirurgie et le score du Ki-67 (P<0,001). Le RS était un facteur prédictif important de la DRFI, la DFS et la SG dans les deux bras de l'essai (p<0,001). On ne retrouve pas d'interaction significative entre le RS et le type de traitement reçu pour la prédiction des récidives à distance (p=0,79).

La DRFI était de 93,7% (intervalle de confiance (IC) à 95%=89,4-96,3) dans le groupe RS bas, de 87,3 (IC95%=81,0-91,6) dans le groupe RS intermédiaire, et de 69,3 (IC95%=61,5-75,8) dans le groupe RS élevé.

La DFS était respectivement de 90,8% (IC95%=86,0-94,1), de 84,9 (IC95%=78,3-89,6), et de 64,6 (IC95%=56,7-71,4) dans le groupe RS bas, intermédiaire et élevé.

La SG était respectivement de 99,0% (IC95%=96,2-99,8), 95,6 (IC95%=90,9-97,9) et 85,6 (IC95%=79,1-90,2) dans le groupe RS bas, intermédiaire et élevé.

CONCLUSION

Dans cette population de patientes atteintes d'un cancer du sein RH+ à haut risque de rechute, N+, ayant reçu une chimiothérapie adjuvante de type 6FEC ou 3FEC-3D, la signature à 21 gènes confirme sa valeur pronostique significative. Ces résultats soulignent la nécessité de cibler les patientes avec un risque résiduel élevé de récidive malgré un traitement de référence et de leur proposer des thérapies additionnelles afin d'anticiper une biologie défavorable ou de potentielles résistances aux traitements (chimiothérapie et/ou hormonothérapie).

ASCO

Prediction of recurrence with the Oncotype DX Recurrence Score in node-positive, HR-positive, breast cancer patients (pts) treated with adjuvant chemotherapy: Results from PACS01 trial (F Penault-Llorca *et al*.)

ESMO

Prediction of recurrence with the Recurrence Score in pre- and post-menopausal patients from the PACS01 trial. (F Penault-Llorca *et al*.)

A phase II trial of Abiraterone acetate plus prednisone in patients with molecular apocrine (HER2-negative) locally advanced or metastatic breast cancer: a UCBG study (A. Gonçalves *et al*.)

SABCS

Circulating tumoral cells (CTC) and endothelial cells (CEC) changes in HER2 negative metastatic breast cancer (MBC) patients treated with first line weekly paclitaxel and bevacizumab: preliminary results of a prospective cohort from the French Breast Cancer InterGroup Unicancer: COMET study (JY Pierga *et al*.)

NEOPAL: a randomized phase II study comparing RCB response to neoadjuvant chemotherapy or letrozole-palbociclib in PAM50 defined postmenopausal luminal breast cancer (PH Cottu *et al*.)

Gastro-intestinal

UNICANCER GASTRO INTESTINAL

Communications écrites

Radiation plus docetaxel and cisplatin in locally advanced pancreatic carcinoma: a non-comparative randomized phase II trial. (Ducreux M *et al*; Dig Liver Dis. 2014 Oct;46(10):950-5)

BACKGROUND

We performed a randomized, non-comparative phase II study evaluating docetaxel in combination with either daily continuous (protracted IV) 5-fluorouracil or cisplatin administered weekly, concurrent to radiotherapy in the treatment of locally advanced pancreatic carcinoma. Results of the docetaxel plus cisplatin regimen are reported.

METHODS

Forty chemotherapy-naive patients with locally advanced pancreatic carcinoma were randomly assigned to receive 5-fluorouracil and docetaxel or docetaxel 20mg/m(2) and cisplatin 20mg/m(2)/week, plus concurrent radiotherapy for 6 weeks. The radiation dose to the primary tumour was 54Gy in 30 fractions. The trial's primary endpoint was the 6 month crude non-progression rate.

RESULTS

51 patients from 7 centres were included in the docetaxel-cisplatin treatment group. Six-month non-progression rate was 39% (95% confidence interval: 26-53). Median overall survival was 9.6 months (95% confidence interval: 2.4-60.7); 6 complete and 8 partial responses were obtained. Six patients survived more than 2 years after their inclusion in the trial. Grade ≥3 toxicity was reported in 63% of patients; no treatment-related death occurred. Severe toxicities were mainly anorexia (22%), vomiting (20%) and fatigue (24%).

CONCLUSIONS

Despite inadequate efficacy according to the main end point, this regimen gave a satisfactory rate of objective response (27%) with tolerable toxicity.

Definitive chemoradiotherapy with FOLFOX *versus* fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. (Conroy T et al. Lancet Oncol. 2014 Mar;15(3):305-14.)

BACKGROUND

Definitive chemo-radiotherapy is a curative treatment option for oesophageal carcinoma, especially in patients unsuitable for surgery. The PRODIGE5/ACCORD17 trial aimed to assess the efficacy and safety of the FOLFOX treatment regimen (fluorouracil plus leucovorin and oxaliplatin) *versus* fluorouracil and cisplatin as part of chemoradiotherapy in patients with localised oesophageal cancer.

METHODS

We did a multicentre, randomised, open-label, parallel-group, phase 2/3 trial of patients aged 18 years or older enrolled from 24 centres in France between Oct 15, 2004, and Aug 25, 2011. Eligible participants had confirmed stage I-IVA oesophageal carcinoma (adenocarcinoma, squamous-cell, or adenosquamous), Eastern Cooperative Oncology Group (ECOG) status 0-2, sufficient caloric intake, adequate haematological, renal, and hepatic function, and had been selected to receive definitive chemoradiotherapy. Patients were randomly assigned (1:1) to receive either six cycles (three concomitant to radiotherapy) of oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, bolus fluorouracil 400 mg/m^2, and infusional fluorouracil 1600 mg/m^2 (FOLFOX) over 46 h, or four cycles (two concomitant to radiotherapy) of fluorouracil 1000 mg/m^2 per day for 4 days and cisplatin 75 mg/m^2 on day 1. Both groups also received 50 Gy radiotherapy in 25 fractions (five fractions per week). Random allocation to treatment groups was done by a central computerised randomisation procedure by minimisation, stratified by centre, histology, weight loss, and ECOG status, and was achieved independently from the study investigators. The primary endpoint was progression-free survival. Data analysis was primarily done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00861094.

FINDINGS

134 participants were randomly allocated to the FOLFOX group and 133 to the fluorouracil and cisplatin group (intention-to-treat population), and 131 patients in the FOLFOX group and 128 in the fluorouracil and cisplatin group actually received the study drugs (safety population). Median follow-up was 25.3 months (IQR 15.9-36.4). Median progression-free survival was 9.7 months (95% CI 8.1-14.5) in the FOLFOX group and 9.4 months (8.1-10.6) in the fluorouracil and cisplatin group (HR 0.93, 95% CI 0.70-1.24; p=0.64). One toxic death occurred in the FOLFOX group and six in the fluorouracil-cisplatin group (p=0.066). No significant differences were recorded in the rates of most frequent grade 3 or 4 adverse events between the treatment groups. Of all-grade adverse events that occurred in 5% or more of patients, paraesthesia (61 [47%] events in 131 patients in the FOLFOX group *vs* three [2%] in 128 patients in the cisplatin-fluorouracil group, p<0.0001), sensory neuropathy (24 [18%] *vs* one [1%], p<0.0001), increases in aspartate aminotransferase concentrations (14 [11%] *vs* two [2%], p=0.002), and increases in alanine aminotransferase concentrations (11 [8%] *vs* two [2%], p=0.012) were more common in the FOLFOX group, whereas serum creatinine increases (four [3%] *vs* 15 [12%], p=0.007), mucositis (35 [27%] *vs* 41 [32%], p=0.011), and alopecia (two [2%] *vs* 12 [9%], p=0.005) were more common in the fluorouracil and cisplatin group.

INTERPRETATION

Although chemoradiotherapy with FOLFOX did not increase progression-free survival compared with chemoradiotherapy with fluorouracil and cisplatin, FOLFOX might be a more convenient option for patients with localised oesophageal cancer unsuitable for surgery.

Results in the elderly with locally advanced rectal cancer from the ACCOR12/PRODIGE 2 phase III trial: tolerance and efficacy. (François E *et al*. Radiother Oncol. 2014 Jan;110(1):144-9)

BACKGROUND

Rectal cancer predominantly affects the elderly. Unfortunately, this age category is under-represented in clinical trials because clinicians are loath to include patients with a high risk of comorbidity.

PATIENTS AND METHODS

An exploratory analysis of the ACCORD12/PRODIGE 2 phase III trial was carried out to retrospectively compare the benefit of neoadjuvant chemotherapy between the elderly (≥70 years; n=142) and younger patients (<70 years; n=442), this analysis was not preplanned in the study protocol. Patients with histologically confirmed resectable stage T3 or T4 rectal adenocarcinoma were eligible with an age limit of 80 years.

RESULTS

Overall, the two age categories did not statistically differ in terms of patient's clinical and tumor baseline characteristics. Preoperative chemoradiotherapy leads to more severe grade 3/4 toxicities (25.6% *vs* 15.8%, p=0.01) and more permanent stomas (33.3% *vs* 22.8%, p=0.014) in elderly patients who were less often operated on than younger patients (95.8% *vs* 99.0%, p=0.008). The relative number of interventions per surgery type (p=0.18), treatment efficacy in terms of R0 resection rate (88.6% *vs* 90.6%; p=0.54) and complete pathological response (14.7% *vs* 16.9%; p=0.55) were nearly identical between the two categories.

CONCLUSION

Altogether these results warrant the development of specific optimal therapeutic strategies for the elderly.

GETUG

UNICANCER Getug

Communications écrites

Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. (Fizazi K *et al.*; Lancet Oncol. 2014 Dec;15(13):1442-50)

BACKGROUND

Poor prognosis germ-cell tumours are only cured in about half of patients. We aimed to assess whether treatment intensification based on an early tumour marker decline will improve progression-free survival for patients with germ-cell tumours.

METHODS

In this phase 3, multicentre, randomised trial, patients were enrolled from France (20 centres), USA (one centre), and Slovakia (one centre). Patients were eligible if they were older than 16 years, had evidence of testicular, retroperitoneal, or mediastinal non-seminomatous germ cell tumours based on histological findings or clinical evidence and highly elevated serum human chorionic gonadotropin or alfa-fetoprotein concentrations that matched International Germ Cell Cancer Consensus Group poor prognosis criteria. After one cycle of BEP (intravenous cisplatin [20 mg/m(2) per day for 5 days], etoposide [100 mg/m(2) per day for 5 days], and intramuscular or intravenous bleomycin [30 mg per day on days 1, 8, and 15]), patients' human chorionic gonadotropin and alfa-fetoprotein concentrations were measured at day 18-21. Patients with a favourable decline in human chorionic gonadotropin and alfa-fetoprotein continued BEP (Fav-BEP group) for 3 additonal cycles, whereas patients with an unfavourable decline were randomly assigned (1:1) to receive either BEP (Unfav-BEP group) or a dose-dense regimen (Unfav-dose-dense group), consisting of intravenous paclitaxel (175 mg/m^2 over 3 h on day 1) before BEP plus intravenous oxaliplatin (130 mg/m^2 over 3 h on day 10; two cycles), followed by intravenous cisplatin (100 mg/m^2 over 2 h on day 1), intravenous ifosfamide (2 g/m^2 over 3 h on days 10, 12, and 14), plus mesna (500 mg/m^2 at 0, 3, 7 and 11 h), and bleomycin (25 units per day, by continuous infusion for 5 days on days 10-14; two cycles), with granulocyte-colony stimulating factor (lenograstim) support. Centrally blocked computer-generated randomisation stratified by centre was used. The primary endpoint was progression-free survival and the efficacy analysis was done in the intention-to-treat population. The planned trial accrual was completed in May, 2012, and follow-up is ongoing. This study is registered with ClinicalTrials.gov, number NCT00104676.

FINDINGS

Between Nov 28, 2003, and May 16, 2012, 263 patients were enrolled and 254 were available for tumour marker assessment. Of these 51 (20%) had a favourable marker assessment, and 203 (80%) had an unfavourable tumour marker decline; 105 were randomly assigned to the Unfav-dose-dense group and 98 to the Unfav-BEP group. 3-year progression-free survival was 59% (95% CI 49-68) in the Unfav-dose-dense group *versus* 48% (38-59) in the Unfav-BEP group (HR 0.66, 95% CI 0.44-1.00, p=0.05). 3-year progression-free survival was 70% (95% CI 57-81) in the Fav-BEP group (HR 0.66, 95% CI 0.49-0.88, p=0.01 for progression-free survival compared with the Unfav-BEP group). More grade 3-4 neurotoxic events (seven [7%] *vs* one [1%]) and haematotoxic events occurred in the Unfav-dose-dense group compared with in the Unfav-BEP group; there was no difference in grade 1-2 febrile neutropenia (18 [17%] *vs* 18 [18%]) or toxic deaths (one [1%] in both groups). Salvage high-dose chemotherapy plus a stem-cell transplant was required in six (6%) patients in the Unfav-dose-dense group and 16 (16%) in the Unfav-BEP group.

INTERPRETATION

Personalised treatment with chemotherapy intensification reduces the risk of progression or death in patients with poor prognosis germ-cell tumours and an unfavourable tumour marker decline.

Prognostic Factors for Survival in Noncastrate Metastatic Prostate Cancer: Validation of the Glass Model and Development of a Novel Simplified Prognostic Model. (Gravis G *et al*.; Eur Urol. 2014 Sep 29. pii: S0302-2838(14)00959-2)

BACKGROUND

The Glass model developed in 2003 uses prognostic factors for noncastrate metastatic prostate cancer (NCMPC) to define subgroups with good, intermediate, and poor prognosis.

OBJECTIVE

To validate NCMPC risk groups in a more recently diagnosed population and to develop a more sensitive prognostic model.

DESIGN, SETTING, AND PARTICIPANTS:

NCMPC patients were randomized to receive continuous androgen deprivation therapy (ADT) with or without docetaxel in the GETUG-15 phase 3 trial. Potential prognostic factors were recorded: age, performance status, Gleason score, hemoglobin (Hb), prostate-specific antigen, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), metastatic localization, body mass index, and pain.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS

These factors were used to develop a new prognostic model using a recursive partitioning method. Before analysis, the data were split into learning and validation sets. The outcome was overall survival (OS).

RESULTS AND LIMITATIONS

For the 385 patients included, those with good (49%), intermediate (29%), and poor (22%) prognosis had median OS of 69.0, 46.5 and 36.6 mo (p=0.001), and 5-yr survival estimates of 60.7%, 39.4%, and 32.1%, respectively (p=0.001). The most discriminatory variables in univariate analysis were ALP, pain intensity, Hb, LDH, and bone metastases. ALP was the strongest prognostic factor in discriminating patients with good or poor prognosis. In the learning set, median OS in patients with normal and abnormal ALP was 69.1 and 33.6 mo, and 5-yr survival estimates were 62.1% and 23.2%, respectively. The hazard ratio for ALP was 3.11 and 3.13 in the learning and validation sets, respectively. The discriminatory ability of ALP (concordance [C] index 0.64, 95% confidence interval [CI] 0.58-0.71) was superior to that of the Glass risk model (C-index 0.59, 95% CI 0.52-0.66). The study limitations include the limited number of patients and low values for the C-index.

CONCLUSION

A new and simple prognostic model was developed for patients with NCMPC, underlying the role of normal or abnormal ALP.

PATIENT SUMMARY

We analyzed clinical and biological factors that could affect overall survival in noncastrate metastatic prostate cancer. We showed that normal or abnormal alkaline phosphatase at baseline might be useful in predicting survival.

Patients' self-assessment *versus* investigators' evaluation in a phase III trial in non-castrate metastatic prostate cancer (GETUG-AFU 15). (Gravis G *et al*.; Eur J Cancer. 2014 Mar;50(5):953-62)

BACKGROUND

Toxicity, which is a key parameter in the evaluation of cancer treatments, can be underestimated by clinicians. We investigated differences between patients and physicians in reporting adverse events of androgen deprivation therapy (ADT) with or without docetaxel in a multicentre phase III trial in non-castrate metastatic prostate cancer.

METHODS

The 385 patients included were invited to complete a 26-symptom questionnaire 3 and 6 months after the start of treatment, among which eighteen symptoms were also assessed by physicians, reported in medical records and graded using the Common Toxicity Criteria of the National Cancer Institute. Positive and negative agreements as well as Kappa concordance coefficients were computed.

FINDINGS

Data were available for 220 and 165 patients at 3 and 6 months respectively. Physicians systematically under-reported patients' symptoms. Positive agreement rates (at respectively 3 and 6 months) for the five most commonly reported symptoms were: 61.0% and 64.3% hot flushes, 50.0% and 43.6% fatigue, 29.4% and 31.1% sexual dysfunction, 24.4% and 14.4% weigh gain/loss, 16.7% and 19.3% for joint/muscle pain. For symptoms most frequently reported as disturbing or very disturbing by patients, the clinicians' failure to report them ranged from 50.8% (hot flushes) to 89.5% (joint/muscle pain) at 3 months, and from 48.2% (hot flushes) to 88.4% (joint/muscle pain) at 6 months.

INTERPRETATION

Physicians often failed to report treatment-related symptoms, even the most common and disturbing ones. Patients' self-evaluation of toxicity should be used in clinical trials to improve the process of drug assessment in oncology.

Immediate *versus* deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial (Sternberg CN *et al*., Lancet Oncol, Vol. 16, Issue 1, 76-86)

BACKGROUND

Patients with muscle-invasive urothelial carcinoma of the bladder have poor survival after cystectomy. The EORTC 30994 trial aimed to compare immediate *versus* deferred cisplatin-based combination chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder.

METHODS

This intergroup, open-label, randomised, phase 3 trial recruited patients from hospitals across Europe and Canada. Eligible patients had histologically proven urothelial carcinoma of the bladder, pT3-pT4 disease or node positive (pN1-3) M0 disease after radical cystectomy and bilateral lymphadenectomy, with no evidence of any microscopic residual disease. Within 90 days of cystectomy, patients were centrally randomly assigned (1:1) by minimisation to either immediate adjuvant chemotherapy (four cycles of gemcitabine plus cisplatin, high-dose methotrexate, vinblastine, doxorubicin, and cisplatin [high-dose MVAC], or MVAC) or six cycles of deferred chemotherapy at relapse, with stratification for institution, pT category, and lymph node status according to the number of nodes dissected. Neither patients nor investigators were masked. Overall survival was the primary endpoint; all analyses were by intention to treat. The trial was closed after recruitment of 284 of the planned 660 patients. This trial is registered with ClinicalTrials.gov, number NCT00028756.

FINDINGS

From April 29, 2002, to Aug 14, 2008, 284 patients were randomly assigned (141 to immediate treatment and 143 to deferred treatment), and followed up until the data cutoff of Aug 21, 2013. After a median follow-up of 7.0 years (IQR 5.2-8.7), 66 (47%) of 141 patients in the immediate treatment group had died compared with 82 (57%) of 143 in the deferred treatment group. No significant improvement in overall survival was noted with immediate treatment when compared with deferred treatment (adjusted HR 0.78, 95% CI 0.56-1.08; p=0.13). Immediate treatment significantly prolonged progression-free survival compared with deferred treatment (HR 0.54, 95% CI 0.4-0.73, p<0.0001), with 5-year progression-free survival of 47.6% (95% CI 38.8-55.9) in the immediate treatment group and 31.8% (24.2-39.6) in the deferred treatment group. Grade 3-4 myelosuppression was reported in 33 (26%) of 128 patients who received treatment in the immediate chemotherapy group *versus* 24 (35%) of 68 patients who received treatment in the deferred chemotherapy group, neutropenia occurred in 49 (38%) *versus* 36 (53%) patients, respectively, and thrombocytopenia in 36 (28%) *versus* 26 (38%). Two patients died due to toxicity, one in each group.

INTERPRETATION

Our data did not show a significant improvement in overall survival with immediate *versus* deferred chemotherapy after radical cystectomy and bilateral lymphadenectomy for patients with muscle-invasive urothelial carcinoma. However, the trial is limited in power, and it is possible that some subgroups of patients might still benefit from immediate chemotherapy. An updated individual patient data meta-analysis and biomarker research are needed to further elucidate the potential for survival benefit in subgroups of patients.

Communications orales

ASCO

Docetaxel-estramustine in localized high-risk prostate cancer: Results of the French genito-urinary tumor group GETUG 12 phase III trial. (Karim Fizazi *et al.*; Abstract #127478)

BACKGROUND

Docetaxel-estramustine improves survival in patients (pts) with castrate-resistant prostate cancer (CaP). This phase III trial assessed docetaxel-estramustine in pts with high-risk localized CaP.

METHODS

Eligibility included non-pretreated high-risk localized CaP, defined as ≥1 of the following criteria: T3-T4, Gleason score (GS)≥8, PSA≥ 20 ng/mL, pN+ (stratification factors). All pts had a staging pelvic lymph node dissection. Pts were randomly assigned to either goserelin 10.8 mg every 3 months for 3 years and 4 cycles of docetaxel 70 mg/m^2 q3w+estramustine 10 mg/kg/d d1-5 (ADT+DE arm) or goserelin alone (ADT arm). Local therapy was administered at 3 months. The primary endpoint is progression-free survival (PFS); events=PSA relapse, radiographic relapse, death. The planned number of pts was 400, to detect a 12% difference at 4 years with a power of 80% and a type I error of 0.05 (two-sided Logrank test). Preliminary results indicated a better PSA response rate (PSA≤0.2 ng/mL: 34% in the ADT+DE arm *vs* 15% in the ADT arm [p<0.0001]), neutropenic fever in 2%, and no negative impact on QoL at 1 year in the ADT+DE arm (Fizazi, Eur J Cancer 2012; 48:209-17). Here we report PFS results.

RESULTS

413 pts were accrued. With a median follow-up of 7.6 years, PFS was marginally improved in the ADT+DE arm: 8-year PFS rate: 62% [55-69] in the ADT+DE arm *vs* 53% [45-60] in the ADT arm (adjusted HR: 0.75 [0.55-1.01], p=0.06). In pts with a GS<8, the 8-year PFS rate was 69% [60-78] (ADT+DE) and 51% [41–61] (ADT) (HR: 0.55 [0.36-0.84], interaction test=0.06 for GS). A non-significant trend favoring ADT+DE was found for clinical PFS (HR: 0.79 [0.55-1.13]). No long-term toxicity signal was detected, with no toxic death. The 8-year cumulative incidence of second cancers (11% *vs* 10%) was similar in the two arms. The 8-year OS rate is 83% [77-89] with no difference between treatment arms (HR: 0.94 [0.60-1.49]). In pts with a GS<8, the 8-year OS rate was 94% [89-98] (ADT+DE) and 85% [78-92] (A DT) (HR: 0.40 [0.17-0.91], interaction test: p=0.02).

CONCLUSIONS

Docetaxel-estramustine is associated with a borderline significant reduction in the risk of relapse or death in high-risk prostate cancer.

ASCO GU

Pattern of relapse in poor-prognosis germ-cell tumors in the GETUG 13 trial: Implications for assessment of brain progression (Y Loriot *et al.*; Abstract #365)

BACKGROUND

GETUG 13 investigated personalized chemotherapy based on tumor marker decline in patients with poor-prognosis GCT and demonstrated that a dose-dense regimen improves progression-free survival in patients with an unfavorable decline (Fizazi K, ASCO 2013). We investigated the pattern of relapse for patients included in GETUG 13.

METHODS

We conducted an analysis of relapse events in patients from GETUG 13 and an unfavorable decline of tumor markers (n=203). Baseline procedures before inclusion in the trial comprised a thoraco-abdomino-pelvic CT scan and an MRI of the brain: 22 patients (10%) had evidence of brain metastases at presentation.

RESULTS

With a median follow-up of 4.1 years (0.3; 8.8 years) when the analysis was performed, a progression event was observed in 94/203 patients (46%). First event consisted in a marker progression only in 41 patients (43%), a radiographic progression only in 29 patients (31%), a mix progression on both markers and imaging in 11 patients (12%), and death in 13 patients (14%). In patients with radiographic progression only, brain was the predominant site (n=16/29, 55%). Among all patients who experienced a radiographic progression (as first and subsequent progression event, n=58), brain only was the site of progression in 26 patients (45%): 12/30 (40%) in patients treated with BEP and 14/28 (50%) in those treated with dose-dense chemotherapy.

CONCLUSIONS

Brain metastases develop often, early, and frequently as the only site of relapse in the course of poor-prognosis GCT. This raises the question of early detection and treatment of brain metastases in these patients, for example by integrating a systematic brain MRI after 2-3 months of chemotherapy.

ASCO

A study of ERG, PTEN, and ki-67 in a phase III trial assessing docetaxel and estramustine in high-risk localized prostate cancer (GETUG 12) (S Rajpar *et al.*)

ASTRO

An unplanned analysis of outcome according to pelvic radiotherapy in the GETUG 12 phase III trial for high-risk localized prostate cancer (P Blanchard *et al.*)

GERICO

Communications orales

SFSPM

Traitement adjuvant systémique du cancer du sein avec récepteurs aux œstrogènes (RO) et HER2 négatif de la femme de plus de 70 ans en fonction du grade génomique (GG). Essai multicentrique des groupes UNICANCER GERICO et UCBG (C Dubot *et al.*)

l'utilité de la chimiothérapie adjuvante (CTA) ajoutée à une hormonothérapie après 70 ans y reste très débattue : son indication devrait tenir compte de son impact sur différents domaines clefs « gériatriques » (fragilité et autonomie) dont l'altération peut compromettre tout bénéfice recherché. Parallèlement les nouveaux outils pronostiques génomiques visent à mieux cerner le groupe de patientes à risque réellement élevé relevant d'une telle CTA en en limitant les indications chez les autres.

Nous proposons d'évaluer le bénéfice en survie apportée par une CTA dans une étude incluant 2000 patientes de plus de 70 ans présentant une tumeur mammaire RO+ HER2-(incluant rechute locale) opérée de manière curative.

Après chirurgie, une évaluation centralisée du grade génomique (GG) est réalisée en RT-PCR sur une coupe paraffinée de la pièce opératoire (Qiagen).

- Les patientes GG élevé ou équivoque sont randomisées : hormonothérapie seule *versus* hormonothérapie précédée d'une chimiothérapie.
- Les patientes non randomisées (GG bas ou autre raison) sont suivies dans une cohorte parallèle.

L'objectif principal est L'objectif principal est la survie globale. Les objectifs secondaires comprennent une analyse des risques compétitifs et des variables gériatriques (dont cormorbidités, autonomie, statut nutritionnel), des volets médico-économique (dont Q-TWiST), éthique (acceptabilité) et qualité de vie (échelle spécifique EORTC ELD15). La recherche translationnelle comprend interactions entre traitements et vieillissement, biomarqueurs pronostiques et pharmacogénétique.

L'effectif de l'étude est basé sur la survie globale à 4 ans en faveur de la CTA (87.5 *vs* 80%; HR 0.60, α=0.05, β=0.20) : 129 événements sont attendus, nécessitant la randomisation de 700 patientes au total.

Entre avril 2012 et juil. 2014, 67 centres en France et en Belgique ont inclus 1093 patientes âgées de 70 à 92 ans. Seules 32 patientes n'ont pas été évaluées pour le GG : pas de bloc tumoral disponibles(15), retrait de consentement (7), statut tumoral non confirmé (7), choix du traitement (3).

Dans le principal centre recruteur, 66% des patientes à qui l'étude a été présentée ont accepté de participer. Le délai médian pour obtenir le résultat du GG est de 17 jours (11–25) après l'envoi du bloc tumoral.

Sur les 1061 évaluations GG effectuées, 420 (40%), 215 (20%) and 416 (39%) ont montré un score bas, équivoque et de haut grade respectivement. Seules 10 (1%) évaluations ont échoué pour des raisons techniques. La proportion des tumeurs à risque élevé (grade haut ou équivoque) est similaire à celle observée dans la population générale atteinte de cancer du sein (40 à 60%). Parmi les patientes à risque élevé, seules 33 patientes n'ont pas été randomisées : retrait de consentement (8), choix du traitement (11), respect des critères d'inclusion (6), statut tumoral non confirmé (3), découverte de métastases (5).

Avec 85% du recrutement attendu réalisé en 28 mois, nous confirmons la faisabilité et la bonne acceptabilité d'un tel programme multicentrique, dans une population habituellement exclue des essais cliniques. Cette étude devrait permettre de progresser sur la sélection de la meilleure stratégie adjuvante pour la population âgée présentant un cancer du sein de phénotype très fréquent, évitant de compromettre l'avantage théorique adjuvant d'une telle chimiothérapie par effets secondaires immédiats et différés significatifs.

SABCS

ASTER 70s UNICANCER phase III trial: can a genomic prognosticator help tailoring adjuvant systemic treatment for luminal breast carcinoma in elderly women? (C Dubot *et al*.)

ESMO

ASTER 70s UNICANCER phase III trial: Adjuvant treatment for women over 70 with luminal breast cancer (C. Dubot *et al*.)

SIOG

Aster 70s UNICANCER phase III trial: Can a genomic prognosticator help tailoring adjuvant systemic treatment for luminal breast carcinoma in elderly women? (C Dubot *et al*.)

ASCO-GU

Feasibility of docetaxel-prednisone (DP) in frail elderly (age 75 and older) patients with castration resistant metastatic prostate cancer (CRMPC): GERICO10-GETUG P03 trial led by Unicancer. (L Mourey *et al*.)

UICC

How to improve health cares in elderly cancer patients? A call for more specific clinical research in geriatric oncology based on the experience of the french unicancer gerico group (18173) (C Mertens *et al*.)

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ICHNO

PACSA: Phase II study of pazopanib in patients with progressive recurrent or metastatic salivary gland carcinoma (D. Cupissol *et al.*)

Médecine personnalisée et Essais précoces

UNICANCER PERSONALIZED MEDICINE

Communications écrites

Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). (André F *et al.*; Lancet Oncol. 2014 Mar;15(3):267-74)

BACKGROUND

Breast cancer is characterised by genomic alterations. We did a multicentre molecular screening study to identify abnormalities in individual patients with the aim of providing targeted therapy matched to individuals' genomic alterations.

METHODS

From June 16, 2011, to July 30, 2012, we recruited patients who had breast cancer with a metastasis accessible for biopsy in 18 centres in France. Comparative genomic hybridisation (CGH) array and Sanger sequencing on PIK3CA (exon 10 and 21) and AKT1 (exon 4) were used to assess metastatic biopsy samples in five centres. Therapeutic targets were decided on the basis of identified genomic alterations. The primary objective was to include 30% of patients in clinical trials testing a targeted therapy and, therefore, the primary outcome was the proportion of patients to whom a targeted therapy could be offered. For the primary endpoint, the analyses were done on the overall population registered for the trial. This trial is registered with ClinicalTrials.gov, number NCT01414933.

423 patients were included, and biopsy samples were obtained from 407 (metastatic breast cancer was not found in four). CGH array and Sanger sequencing were feasible in 283 (67%) and 297 (70%) patients, respectively. A targetable genomic alteration was identified in 195 (46%) patients, most frequently in PIK3CA (74 [25%] of 297 identified genomic alterations), CCND1 (53 [19%]), and FGFR1 (36 [13%]). 117 (39%) of 297 patients with genomic tests available presented with rare genomic alterations (defined as occurring in less than 5% of the general population), including AKT1 mutations, and EGFR, MDM2, FGFR2, AKT2, IGF1R, and MET high-level amplifications. Therapy could be personalised in 55 (13%) of 423 patients. Of the 43 patients who were assessable and received targeted therapy, four (9%) had an objective response, and nine others (21%) had stable disease for more than 16 weeks. Serious (grade 3 or higher) adverse events related to biopsy were reported in four (1%) of enrolled patients, including pneumothorax (grade 3, one patient), pain (grade 3, one patient), haematoma (grade 3, one patient), and haemorrhagic shock (grade 3, one patient).

Communications orales

ESMO

Genomic and immune characterization of metastatic breast cancer (mBC): An ancillary study of the SAFIR01 & MOSCATO trials (M Arnedos *et al.*; Abstract #3510)

AIM

So far, little is known about immune and genomic landscape in metastatic breast cancer (mBC).

METHODS

Patients were retrospectively identified from SAFIR01 and MOSCATO studies that performed molecular screening from a biopsy of a metastatic lesion. Whole exome sequencing (WES) was performed using Hi-Seq technology. Coverage was 50x and 100x for normal and tumoral tissue respectively. Bioinformatic analyses reported mutations and copy number alterations. Immune characterisation was determined by the presence of intratumoral and stromal TILs with PD1 and PDL1 expression assessed by IHC (internal protocol, Medimmune). We correlated tumor characteristics and immune and genomics data.

RESULTS

280 samples were stained for immune analyses. Using a 50% cut-off, few tumors presented intratumoral (n=3/244, 1%) and stromal (n=11/244, 5%) TILs. This rate was significantly higher in HER2+ tumors (stromal TIL, 16%; p=0.0002). Positivity for PD1 (n=14/252, 5%) and PDL1 (n=7/255, 3%) were rare, compared to reported in other tumor types. A trend towards higher PDL1 was observed in HER2+ mBC (8.3%; p=0.0653). Ninety-three samples were analysed for WES with 17 genes found mutated in >3 samples ($p < 0.05$). Except for PIK3CA, p53 and AKT1, these genes were mutated in <2% of samples in TCGA analyses of primary tumors and include NAV3 (n=5), FRAS1 (n=7), PI4KA (n=5), PALB2 (n=4), SCAPER (n=4), PRKCB (n=4), CACNA1S (n=4), TSC1 (n=4), GALC (n=4), NPAP1 (n=4), PHACTR3 (n=4). When analysing genes specifically mutated in metastases, an enrichment in pathways involved in MAPK (FDR=0.0035), ER signalling (0.0004), lipids metabolism (0.0001) and GNRH signalling (FDR=0.00018) was observed

CONCLUSIONS

This is the first study that assesses both immune and genomic landscapes in mBC. We observed that mBC dramatically differs from primary tumors, and is enriched in genes potentially involved in resistance mechanisms (ESR1, TSC1) or migration process (FRAS1, SCAPER). TILs, PD1, PDL1 are at very low frequency in metastatic lesions, except for Her2 + ++ mBC. Our results suggest that other immune suppressor networks are involved in mBC. Therefore, CD73, CD39 and FoxP3 are being analysed and will be presented.

SABC

Biomarker-driven access to crizotinib in ALK, MET or ROS1 positive malignancies in adults and children: feasibility of the French National AcSé Program (G Vassal *et al*.)

Pazopanib (P) and cisplatin (CDDP) in patients with advanced solid tumors: a Unicancer phase I study. (V Diéras *et al*.)

Predictor: Randomized phase II study of pre-operative afatinib in untreated non-metastatic head and neck squamous cell carcinoma patients (HNSCC) aiming at identifying predictive and pharmacodynamic biomarkers of efficacy. (C Le Tourneau *et al*.)

SABCS

Alterations of intratumoral signalling in breast cancer patients receiving pre-operative trastuzumab alone or combined with everolimus (Merlin J-L *et al*.)

SARCOME

Communications orales

ESMO

Zoledronate does not reduce the risk of treatment failure in osteosarcoma: results of the French multicentre OS2006 randomised trial (S Piperno-Neumann *et al.*; Abstract #14130)

AIM

Based on anti-tumour effect of zoledronate in vitro and in experimental models of rat osteosarcoma, we assessed whether zoledronate (Z) in combination with chemotherapy and surgery improved Event-Free Survival (EFS) in children and adult patients (pts) with osteosarcoma.

METHODS

Experimental treatment consisted of 10 Z–injections (4 pre and 6 postoperative), 4 mg/injection in adults, 0.05 mg/kg/injection in younger pts. Chemotherapy included methotrexate-etoposide-ifosfamide +/-adriamycine-cisplatin in children/adolescents, and doxorubicin-ifosfamide/doxorubicin-ifosfamide-cisplatinum in adults. Balanced randomisation between Z+arm and Z-arm was stratified by center, age, chemotherapy type and risk group (localised resectable disease *versus* unresectable primary and/or metastases). The study was planned as an open-label superiority trial, with 3 interim analyses (early stopping for efficacy or harm) disclosed to an independent safety monitoring board (DSMB). 470 pts (170 events) were required to achieve an 80%-power to detect a 13%-improvement of 3-year EFS (H1: 55% *versus* 68%, HR(event)=0.65) with zoledronate (2-sided alpha=0.05).

RESULTS

A second interim analysis was performed after 318 pts (82% with a localised and resectable tumour) have been recruited between April 2007 and February 2014: 158 Z- and 160 Z+. No significant increase in toxicity was found in Z+, except expected hypocalcemia grade 2-4 ($p<0.0001$). With a median follow-up of 3.1 years, 106 events and 58 deaths were reported, including one treatment-related death. The risk of treatment failure was not reduced in Z+ compared to Z-: HR(event)=1.31 [0.79-2.18], p=0.17; HR(death)=1.42 [0.70-2.88], p=0.21. Results were similar after exclusion of eight Z+patients who had received 0 or 1 zoledronate injection, and were homogeneous across the randomisation strata. Futility analysis, performed on DSMB request, showed that the probability of demonstrating a benefit for Z+ was <0.0001. Following DSMB recommendation, the trial steering committee decided to stop accrual in the trial.

CONCLUSIONS

With current follow-up, the addition of zoledronate to chemotherapy did not reduce the risk of failure in osteosarcoma patients.

SIOP

Prognosis impact of remaining lung nodules after metastasectomy in osteosarcoma patients: are they responsible for recurrence? (C Cellier *et al.*; Abstract #0-133)

OBJECTIVES - AIM OF THE STUDY

Survival of patients having a pulmonary metastatic osteosarcoma is improved by the complete removal of all metastases. Due to the dramatic increase of CT–scan quality over the years allowing the detection of millimetric nodules unable to be found at surgery, we aimed to determine if the remaining nodules has an impact on recurrence.

METHODS

We retrospectively compared all lung CT scans performed from diagnosis to first relapse to the surgical and pathological reports in 24 patients treated for an osteosarcoma with a high-dose methotrexate based chemotherapy (OS2006 protocol) and operated on for lung nodules from 2007 to 2012.

MAIN RESULTS

Three patients were excluded, 2 because of countless nodules and one because of tuberous sclerosis a t pathology. Among the 21 patients finally included, 12 were classified as metastatic at diagnosis and 9 had doubtful nodules. With a median follow-up of 35 months from diagnosis [range, 10-61], 5 patients relapsed and 3 experienced a progression. Among 210 nodules (median 6 per patient [1-52]) described at diagnosis, 165 remained after neoadjuvant chemotherapy and 37 new nodules were detected. Among these 202 nodules, 130 (64%) were found at surgery and 111 proved to be lung metastases either viable (n=54) or necrotic (n=57) at pathological analysis. 48 additional nodules were removed (18 viable and 22 necrotic metastases). Among the 72 nodules not found at surgery, 37 were still present at the end of treatment (EOT) of which only 2 (5%) were involved in a relapse (9 nodules described) and 2 (5%) in a progression (13 nodules described).

CONCLUSION

The lung nodules not found at surgery and still remaining on the CT scan at EOT did not seem to be responsible for recurrence in pulmonary metastatic osteosarcoma patients.

Zoledronate does not reduce the risk of treatment failure in osteosarcoma: results of the French multicentre OS2006 randomised trial. (L Brugières *et al*.; Abstract #O-037)

PURPOSE

Based on anti-tumour effect of zoledronate in vitro and in experimental models of rat osteosarcoma, we assessed whether zoledronate (Z) in combination with chemotherapy and surgery improved Event-Free Survival (EFS) in children and adults with osteosarcoma.

METHODS

Experimental treatment consisted of 10 Z-injections (4 pre and 6 postoperative), 4 mg/injection in adults, 0.05 mg/kg/injection in younger patients. Chemotherapy included methotrexate-etoposide-ifosfamide +/-adriamycine-cisplatin in children/adolescents, and doxorubicin-ifosfamide-cisplatinum in adults. Balanced randomisation between Z+arm and Z-arm was stratified by centre, age, chemotherapy type and risk group (localised resectable disease *versus* unresectable primary and/or metastases). The study was planned as an open-label superiority trial, with three interim analyses (early stopping for efficacy or harm) disclosed to an independent data and safety monitoring board (DSMB). 470 patients (170 events) were required to achieve an 80%-power to detect a 13%-improvement of 3-year EFS (H1: 55% *versus* 68%, HR(event)=0.65) with zoledronate (2-sided alpha=0.05).

RESULTS

A second interim analysis was performed after the inclusion of 318 patients (82% with a localised and resectable tumour) recruited between April–2007 and February–2014: 158 Z- and 160 Z+. No significant increase in toxicity was found in Z+, except expected hypocalcemia grade 2-4 ($p<0.0001$). With a median follow-up of 3.1 years, 106 events and 58 deaths were reported, including one treatment-related death. The risk of failure was not reduced in Z+ compared to Z-: HR(event)=1.31 [0.79-2.18], p=0.17; HR(death)=1.42 [0.70-2.88], p=0.21. Results were similar after exclusion of eight Z+patients who had received <1 zoledronate-injection, and were homogeneous across the randomisation strata. Futility analysis, performed on DSMB request, showed that the probability of demonstrating a benefit was <0.0001. Following DSMB recommendation, the trial steering committee decided to stop accrual in the trial.

CONCLUSION

With current follow-up, the addition of zoledronate to chemotherapy did not reduce the risk of failure in osteosarcoma patients.

CTOS

Zoledronate does not reduce the risk of treatment failure in osteosarcoma: results of the French multicentre OS2006 randomised trial. (L Brugières *et al.*; Paper 036)

PURPOSE

Based on anti-tumour effect of zoledronate in vitro and in experimental models of rat osteosarcoma, we assessed whether zoledronate (Z) in combination with chemotherapy and surgery improved Event Free Survival (EFS) in children and adults with osteosarcoma.

METHODS

Experimental treatment consisted of 10 Z-injections (4 pre and 6 postoperative), 4 mg/injection in adults, 0.05 mg/kg/injection in younger patients (pts) . Chemotherapy included methotrexate-etoposide-ifosfamide +/-adriamycine-cisplatin in children/adolescents, and doxorubicin-ifosfamide-cisplatinum in adults. Balanced randomisation between Z+arm and Z-arm was stratified by centre, age, chemotherapy type and risk group (localised resectable disease *versus* unresectable primary and/or metastases). The study was an open-label superiority trial, with three interim analyses (early stopping for efficacy or harm) disclosed to an independent safety monitoring board (DSMB). 470 pts (170 events) were required to achieve an 80%-power to detect a 13%-improvement of 3-year EFS (H1: 55% *vs* 68%, HR(event)=0.65) with zoledronate (2-sided alpha=0.05).

RESULTS

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CONCLUSION

With current follow-up, the addition of zoledronate to chemotherapy did not reduce the risk of failure in osteosarcoma patients.

GSF-GETO

Is the monitoring of angiogenic factors relevant in patients with osteosarcoma? (M.D. Tabone *et al.*)

CTOS

Impact of zoledronic acid on children growth: results of the OS2006 randomized trial (MC Le Deley *et al.*; Poster#57)

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