ARNm

Actualités Recherche – Nouveautés médicales

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Édito

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Communications R&D UNICANCER en 2015

Une année 2015 riche en nouveauté et une année 2016 prometteuse ! 🇫🇷

Carole Desseaux Directrice des Opérations cliniques, R&D UNICANCER

L'année écoulée a été marquée par la consolidation des nouveaux axes de recherche, avec en premier lieu, le lancement en janvier d'un groupe de recherche en radiothérapie oncologique UNITRAD (UNICANCER group of translational research and development in radiation oncology) dont l'objectif est de développer une recherche innovante sur les rayons ionisants. Les ambitions d'UNITRAD sont largement partagées par la communauté scientifique et médicale avec pour preuve trois projets retenus par l'INCa lors de la campagne des PHRC-K 2015. La radiothérapie s'invite également au sein des autres groupes de recherche R&D UNICANCER (ex. GETUG, UCBG…) avec de nombreux projets en discussion.

La médecine personnalisée, discipline phare d'UNICANCER, a eu par ailleurs une très belle tribune cette année avec l'organisation par UNICANCER de la première édition du congrès MAP (Molecular Analysis for Personalised therapy). Ce congrès annuel et international est né de la volonté commune d'UNICANCER, du Cancer Research UK et de l'ESMO d'offrir aux cliniciens et aux chercheurs un lieu d'échange autour des dernières découvertes en médecine de précision afin d'y concevoir la prochaine génération d'essais cliniques. L'édition 2016 se tiendra en septembre à Londres. *Carry on* !

Enfin, et comme nous l'avions annoncé, l'immuno-onco continue son développement dans tous les groupes. L'essai SAFIR 02 permet dorénavant le traitement par le durvalumab de patients qui ne peuvent bénéficier de thérapies ciblées. Bientôt, le démarrage de l'essai ULTIMATE (UCBG), des programmes AcSé tumeurs rares (MedPerso) ou bien encore de l'étude de NIVOREN (GETUG) vont véritablement marquer le déploiement de cette stratégie thérapeutique.

Ces axes forts sont placés sous le signe de la transversalité, ce qui ne peut qu'enrichir encore les réflexions menées au sein de nos groupes. Maintenant, « une idée sans exécution ne reste qu'un songe » ; seul un travail sur nos ressources, nos outils et nos méthodes pourra permettre à R&D UNICANCER de déployer avec un plein succès, la technicité, la flexibilité et la réactivité requises par ces nouvelles approches. Un travail à mener avec les Centres…

2015, a year rich in innovations and 2016, a year full of promise! 🇬🇧

Carole Desseaux, Director of Clinical Operations, R&D UNICANCER.

The past year was marked by the consolidation of new lines of research, with the launching in January of a research group in radiation oncology, UNITRAD (UNICANCER group of translational research and development in radiation oncology), whose goal is to develop innovative research in the field of ionizing radiation. UNITRAD's ambitions are largely shared by the scientific and medical community as evidenced by three projects selected by the INCa during the PHRC-K 2015 campaign. Radiation therapy has also become a topic of interest in other R&D UNICANCER research groups (e.g. GETUG, UCBG …) and many projects are under discussion.

Personalized medicine, UNICANCER's flagship discipline, also had a prominent place on the podium this year with the organization by UNICANCER of the first edition of the MAP (Molecular Analysis for Personalised therapy) Congress. This annual international Congress was born from the common desire of UNICANCER, Cancer Research UK and ESMO to provide clinicians and researchers with a forum where they could discuss the latest discoveries in precision medicine and thus design the next generation of clinical trials. The 2016 edition will be held in September in London. Carry on!

Finally, as announced, immuno-oncology continues to be developed in all groups. Thanks to the SAFIR 02 trial, patients unable to benefit from targeted therapies can now be treated with durvalumab. The initiation of the ULTIMATE trial (UCBG), the AcSé rare tumour programs (MedPerso) and the NIVOREN trial (GETUG) expected soon will truly mark the deployment of this therapeutic strategy.

These key lines are marked by their multi-disciplinarity, which will only enrich the reflections carried out within our groups. However, "an idea that is not put into action remains a dream". Only by working on our resources, tools and methods will R&D UNICANCER be able to deploy with total success the technical skills, flexibility and responsiveness required by these new approaches. A task to be undertaken with the Centres…

French breast cancer Intergroup UNICANCER

French breast cancer intergroup UNICANCER

UCBG

Scientific articles

UNICANCER-PEGASE 07 study: a randomized phase III trial evaluating postoperative docetaxel-5FU regimen after neoadjuvant dose-intense chemotherapy for treatment of inflammatory breast cancer.

BACKGROUND

Inflammatory breast cancer (IBC) is a rare and aggressive disease requiring a multimodal treatment. We evaluated the benefit of adding docetaxel-5-fluorouracil (D-5FU) regimen after preoperative dose-intense (DI) epirubicin-cyclophosphamide (EC) and locoregional treatment in IBC patients.

PATIENTS AND METHODS

PEGASE 07 was a national randomized phase III open-label study involving 14 hospitals in France. Women with nonmetastatic IBC were eligible and randomly assigned to receive either four cycles of DI EC (E 150 mg/m(2) and C 4000 mg/m(2) every 3 weeks with repeated hematopoietic stem cell support), then mastectomy with axillary lymph node dissection, and radiotherapy (arm A) or the same treatment followed by four cycles of D-5FU (D 85 mg/m(2), day 1 and 5FU 750 mg/m(2)/day continuous infusion, days 1-5 every 3 weeks) administered postradiotherapy (arm B). Patients with hormone receptor-positive tumors received hormonal therapy. Disease-free survival (DFS) was the primary end point. Secondary end points included tolerance, pathological complete response (pCR) rate, and overall survival (OS).

RESULTS

Between January 2001 and May 2005, 174 patients were enrolled and treated (87 in each arm). Median follow-up was similar in both arms: 59.6 months [95% confidence interval (CI) 58.4-60.3] in arm A and 60.5 months (95% CI 58.3-61.4) in arm B. The estimated 5-year DFS rates were not different: 55% (95% CI 43.9-64.7) in arm A and 55.5% (95% CI 44.3-65.3) in arm B [hazard ratio (HR) = 0.94 (0.61-1.48); P = 0.81]. Identical results were observed for 5-year OS: 70.2% (95% CI 59.1-78.8) in arm A and 70% (95% CI 58.8-78.7) in arm B [HR = 0.93 (0.55-1.60); P = 0.814]. Following DI EC induction, in-breast and global (breast plus nodes) pCR were 28.9% and 20.1%, respectively. Estrogen receptor and pCR status were independently associated with survival.

CONCLUSION

The addition of D-5FU after preoperative DI EC and standard local therapy did not improve DFS in IBC.

Coexpression of androgen receptor and FOXA1 in nonmetastatic triple-negative breast cancer: ancillary study from PACS08 trial. (Guiu S *et al.,* Future Oncol. 2015;11(16):2283-97. doi: 10.2217/fon.15.102.)

AIM

Microarray studies identified a subgroup of molecular apocrine tumors (estrogen receptor [ER] negative/androgen receptor [AR] positive) that express luminal genes including FOXA1. FOXA1 may direct AR to sites normally occupied by ER in luminal tumors, inducing an estrogen-like gene program that stimulated proliferation.

MATERIALS & METHODS

Expression of AR and FOXA1 was evaluated by immunohistochemistry in 592 patients with nonmetastatic triple-negative breast cancer (TNBC).

RESULTS

Coexpression of AR and FOXA1 was found in 15.2% of patients. These tumors were more frequently lobular, found in older patients and exhibited a lower nuclear grade and a greater degree of node involvement. They less often exhibited lymphocytic infiltrate, pushing margins, syncytial architecture, central fibrosis or necrosis.

CONCLUSION

TNBC with coexpression of AR and FOXA1 seems to behave like luminal tumors with a morphological profile distinct from other TNBC. These biomarkers could be useful to identify a subgroup of TNBC and could have future therapeutic implications.

Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. (Forbes JF,. Lancet. 2015 Dec 11. pii: S0140-6736(15)01129-0. doi: 10.1016/S0140-6736(15)01129-0.)

BACKGROUND

Third-generation aromatase inhibitors are more effective than tamoxifen for preventing recurrence in postmenopausal women with hormone-receptor-positive invasive breast cancer. However, it is not known whether anastrozole is more effective than tamoxifen for women with hormone-receptor-positive ductal carcinoma in situ (DCIS). Here, we compare the efficacy of anastrozole with that of tamoxifen in postmenopausal women with hormone-receptor-positive DCIS.

PATIENTS AND METHODS

In a double-blind, multicentre, randomised placebo-controlled trial, we recruited women who had been diagnosed with locally excised, hormone-receptor-positive DCIS. Eligible women were randomly assigned in a 1:1 ratio by central computer allocation to receive 1 mg oral anastrozole or 20 mg oral tamoxifen every day for 5 years. Randomisation was stratified by major centre or hub and was done in blocks (six, eight, or ten). All trial personnel, participants, and clinicians were masked to treatment allocation and only the trial statistician had access to treatment allocation. The primary endpoint was all recurrence, including recurrent DCIS and new contralateral tumours. All analyses were done on a modified intention-to-treat basis (in all women who were randomised and did not revoke consent for their data to be included) and proportional hazard models were used to compute hazard ratios and corresponding confidence intervals. This trial is registered at the ISRCTN registry, number ISRCTN37546358.

RESULTS

Between March 3, 2003, and Feb 8, 2012, we enrolled 2980 postmenopausal women from 236 centres in 14 countries and randomly assigned them to receive anastrozole (1449 analysed) or tamoxifen (1489 analysed). Median follow-up was 7·2 years (IQR 5·6-8·9), and 144 breast cancer recurrences were recorded. We noted no statistically significant difference in overall recurrence (67 recurrences for anastrozole vs 77 for tamoxifen; HR 0·89 [95% CI 0·64-1·23]). The non-inferiority of anastrozole was established (upper 95% CI <1·25), but its superiority to tamoxifen was not (p=0·49). A total of 69 deaths were recorded (33 for anastrozole vs 36 for tamoxifen; HR 0·93 [95% CI 0·58-1·50], p=0·78), and no specific cause was more common in one group than the other. The number of women reporting any adverse event was similar between anastrozole (1323 women, 91%) and tamoxifen (1379 women, 93%); the side-effect profiles of the two drugs differed, with more fractures, musculoskeletal events, hypercholesterolaemia, and strokes with anastrozole and more muscle spasm, gynaecological cancers and symptoms, vasomotor symptoms, and deep vein thromboses with tamoxifen.

CONCLUSIONS

No clear efficacy differences were seen between the two treatments. Anastrozole offers another treatment option for postmenopausal women with hormone-receptor-positive DCIS, which may be more appropriate for some women with contraindications for tamoxifen. Longer follow-up will be necessary to fully evaluate treatment differences.

Combined evaluation of LC3B puncta and HMGB1 expression predicts residual risk of relapse after adjuvant chemotherapy in breast cancer.

ABSTRACT

In spite of adjuvant chemotherapy, a significant fraction of patients with localized breast cancer (BC) relapse after optimal treatment. We determined the occurrence of cytoplasmic MAP1LC3B/LC3B (microtubule-associated protein 1 light chain 3B)-positive puncta, as well as the presence of nuclear HMGB1 (high mobility group box 1) in cancer cells within surgical BC specimens by immunohistochemistry, first in a test cohort (152 patients) and then in a validation cohort of localized BC patients who all received adjuvant anthracycline-based chemotherapy (1646 patients). Cytoplasmic LC3B(+) puncta inversely correlated with the intensity of SQSTM1 staining, suggesting that a high percentage cells of LC3B(+) puncta reflects increased autophagic flux. After setting optimal thresholds in the test cohort, cytoplasmic LC3B(+) puncta and nuclear HMGB1 were scored as positive in 27.2% and 28.6% of the tumors, respectively, in the validation cohort, while 8.7% were considered as double positive. LC3B(+) puncta or HMGB1 expression alone did not constitute independent prognostic factors for metastasis-free survival (MFS) in multivariate analyses. However, the combined positivity for LC3B(+) puncta and nuclear HMGB1 constituted an independent prognostic factor significantly associated with prolonged MFS (hazard ratio: 0.49 95% confidence interval [0.26-0.89]; P = 0.02), and improved breast cancer specific survival (hazard ratio: 0.21 95% confidence interval [0.05-0.85]; P = 0.029). Subgroup analyses revealed that within patients with poor-prognosis BC, HMGB1(+) LC3B(+) double-positive tumors had a better prognosis than BC that lacked one or both of these markers. Altogether, these results suggest that the combined positivity for LC3B(+) puncta and nuclear HMGB1 is a positive predictor for longer BC survival.

ASCO

Circulating tumor cells (CTC) and pathological complete response (pCR) as independent prognostic factors in inflammatory breast cancer (IBC) in a pooled analysis of two multicentre phase II trials (BEVERLY 1 & 2) of neoadjuvant chemotherapy combined with bevacizumab. (Pierga JY *et al.*)

BACKGROUND

We have reported that CTC detection is an independent prognostic factor in 52 primary HER2+ IBC (Pierga, CCR 2014). We present a pooled analysis of two prospective trials including 152 patients (pts). Predictive and prognostic value of Circulating Endothelial Cells (CEC) for response to bevacizumab was also analyzed.

METHODS

CTC and CEC were detected in 7.5 ml and 4 ml of blood respectively in the neoadjuvant setting in IBC (T4d) pts enrolled in two phase II multicentre trials, evaluating bevacizumab (15mg/kg q3w) in combination with sequential neoadjuvant chemotherapy (CT) of 4 cycles of FEC followed by 4 cycles of docetaxel in HER2 - tumor (BEVERLY 1) or docetaxel, trastuzumab in HER2 + (BEVERLY 2). The CellSearch System, combining EpCAM immunomagnetic selection followed by anti-cytokeratin (A45B/B3) and anti-HER2 staining for CTC and CD146 IMS and CD105 staining for CEC.

RESULTS

From 10/08 to 09/10, 152 pts were included and 137 were evaluable for CTC and CEC. Median follow-up was 43 months. At baseline, 55 pts had ≥ 1 detectable CTC (39%). After 4 cycles of CT, a dramatic drop in CTC to a rate of 9% was observed. pCR rate was 40% and was associated with absence of hormonal receptor and HER2 + status. No correlation was found between CTC and CEC levels or pCR rate. CTC detection at baseline independently predicted 3-year disease-free survival (DFS): (70% vs. 39% for pts with < 1 vs. ≥ 1 CTC/7.5 mL [p < 0.001, HR 2.80 (1.65-4.76)]) and 3-year overall survival (OS) (92% vs 56% HR 4.28 p < 0.001). At multivariate analysis, independent prognostic parameters for DFS were absence of hormonal receptors, no pCR, and CTC detection at base-line. CEC level at baseline or variations during treatment had no prognostic value.

CONCLUSIONS

This is the largest prospectives trial in non-metastatic IBC evaluating CTC detection. We observed a high CTC detection rate of 39%, with a strong and independent prognostic value for DFS and OS. Combination of pCR after neoadjuvant treatment, with CTC at baseline, isolates a subgroup of IBCwith excellent survival. CTC count should be part of IBC stratification in prospective trials.

SABCS

Anastrozole versus tamoxifen for the prevention of loco-regional and contralateral breast cancer in postmenopausal women with locally excised Ductal Carcinoma In-Situ (IBIS-II DCIS). (Cuzick J *et al*.)

BACKGROUND

Background: Third-generation aromatase inhibitors are more effective than tamoxifen for preventing recurrence in postmenopausal women with hormone-receptor-positive invasive breast cancer. However, it is not known whether anastrozole is more effective than tamoxifen for women with hormone-receptor-positive ductal carcinoma in situ (DCIS). Here, we compare the efficacy of anastrozole with that of tamoxifen in postmenopausal women with hormone-receptor-positive DCIS.

METHODS

In a double-blind, multicentre, randomised placebo-controlled trial, we recruited women who had been diagnosed with locally excised, hormone-receptor-positive DCIS. Eligible women were randomly assigned in a 1:1 ratio by central computer allocation to receive 1 mg oral anastrozole or 20 mg oral tamoxifen every day for 5 years. Randomisation was stratified by major centre or hub and was done in blocks (six, eight, or ten). All trial personnel, participants, and clinicians were masked to treatment allocation and only the trial statistician had access to treatment allocation. The primary endpoint was all recurrence, including recurrent DCIS and new contralateral tumours. All analyses were done on a modified intention-to-treat basis (in all women who were randomised and did not revoke consent for their data to be included) and proportional hazard models were used to compute hazard ratios and corresponding confidence intervals. This trial is registered at the ISRCTN registry, number ISRCTN37546358.

RESULTS

Between March 3, 2003, and Feb 8, 2012, we enrolled 2980 postmenopausal women from 236 centres in 14 countries and randomly assigned them to receive anastrozole (1449 analysed) or tamoxifen (1489 analysed). Median follow-up was 7•2 years (IQR 5•6–8•9), and 144 breast cancer recurrences were recorded. We noted no statistically significant difference in overall recurrence (67 recurrences for anastrozole vs 77 for tamoxifen; HR 0•89 [95% CI 0•64–1•23]). The non-inferiority of anastrozole was established (upper 95% CI <1•25), but its superiority to tamoxifen was not (p=0•49). A total of 69 deaths were recorded (33 for anastrozole vs 36 for tamoxifen; HR 0•93 [95% CI 0•58–1•50], p=0•78), and no specific cause was more common in one group than the other. The number of women reporting any adverse event was similar between anastrozole (1323 women, 91%) and tamoxifen (1379 women, 93%); the side-effect profiles of the two drugs differed, with more fractures, musculoskeletal events, hypercholesterolaemia, and strokes with anastrozole and more muscle spasm, gynaecological cancers and symptoms, vasomotor symptoms, and deep vein thromboses with tamoxifen.

CONCLUSIONS

No clear efficacy differences were seen between the two treatments. Anastrozole offers another treatment option for postmenopausal women with hormone-receptor-positive DCIS, which may be be more appropriate for some women with contraindications for tamoxifen. Longer follow-up will be necessary to fully evaluate treatment differences.

SNMMI Annual meeting

Early metabolic response assessment to neoadjuvant endocrine treatment in ER+, HER2- breast cancer: comparison to the morphological and pathological response. (Sarah Boughdad *et al*.)

AACR

Circulating tumor cells (CTC) but not circulating endothelial cells (CEC) are independent prognostic factors in neoadjuvant chemotherapy combined with bevacizumab in HER2 negative inflammatory breast cancer (IBC) in multicentre phase II trial BEVERLY1. (Jean-Yves Pierga *et al*.)

SABCS

UCBG intergroup: 3-years efficacy results of the Unicancer-PACS08 trial including poor prognosis patients treated with docetaxel or ixabepilone in adjuvant setting. (Campone M *et al*.)

EBCC

Results of a phase II trial of abiraterone acetate plus prednisone in patients with a molecular apocrine HER2-negative locally advanced or metastatic breast cancer (UCBG 2012-1). (T. Grellety *et al*.)

GETUG

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Scientific articles

Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. (Gravis G *et al.*, Eur Urol. 2015 Nov 21. pii: S0302-2838(15)01103-3. doi: 10.1016/j.eururo.2015.11.005.)

BACKGROUND

Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. (Gravis G *et al.*, Eur Urol. 2015 Nov 21. pii: S0302-2838(15)01103-3. doi: 10.1016/j.eururo.2015.11.005.)

BACKGROUND: The role of chemotherapy in metastatic non castrate prostate cancer (mNCPC) is debated. Survival benefits of docetaxel (D) added to androgen-deprivation therapy (ADT) were shown in the CHAARTED trial in patients with metastatic high-volume disease (HVD).

OBJECTIVE

To assess the impact of metastatic burden and to update overall survival (OS) data of the GETUG-AFU15 study.

DESIGN, SETTING, AND PARTICIPANTS

Randomized phase 3 trial of ADT plus D versus ADT alone in 385 mNCPC patients; median follow-up of 7 yr.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS

Primary end point was OS. Secondary end points were biochemical progression-free survival (bPFS) and radiographic progression-free survival (rPFS). Retrospective analysis was by tumor volume.

RESULTS AND LIMITATIONS

After a median follow-up of 83.9 mo, median OS in the overall population was 62.1 mo (95% confidence interval [CI], 49.5-73.7) and 48.6 mo (95% CI, 40.9-60.6) for ADT plus D and ADT arms, respectively (hazard ratio [HR]: 0.88 [95% CI, 0.68-1.14]; p=0.3). Median OS in ADT plus D and ADT arms, respectively, was for HVD patients: 39.8 mo (95% CI, 28.0-53.4) versus 35.1 mo (95% CI, 29.9-43.6) (HR: 0.78 [95% CI, 0.56-1.09]; p=0.14), for low-volume disease (LVD) patients; median was not reached (NR; 95% CI, 69.5-NR) and 83.4 mo (95% CI, 61.8-NR) (HR: 1.02 [95% CI, 0.67-1.55]; p=0.9). For upfront metastatic patients, OS was 52.6 mo (95% CI, 43.3-66.8) and 41.5 mo (95% CI, 36.3-54.5), respectively (HR: 0.93 [95% CI, 0.69-1.25]; p=0.6). The bPFS (HR: 0.73 [95% CI, 0.56-0.94]; p=0.014) and rPFS (HR: 0.75 [95% CI, 0.58-0.97]; p=0.030) were significantly longer in the ADT plus D arm. Limitations included the retrospective analysis of metastatic extent and the lack of statistical power to detect a significant difference in subgroups.

CONCLUSIONS

The post hoc analyses of the GETUG-AFU15 study demonstrated a nonsignificant 20% reduction in the risk of death in the HVD subgroup. Patients with LVD had no survival improvement with early D.

Outcome According to Elective Pelvic Radiation Therapy in Patients With High-Risk Localized Prostate Cancer: A Secondary Analysis of the GETUG 12 Phase 3 Randomized Trial. (Blanchard P, *et al.*, Int J Radiat Oncol Biol Phys. 2016 Jan 1;94(1):85-92. doi: 10.1016/j.ijrobp.2015.09.020. Epub 2015 Sep 25.)

PURPOSE

The role of pelvic elective nodal irradiation (ENI) in the management of prostate cancer is controversial. This study analyzed the role of pelvic radiation therapy (RT) on the outcome in high-risk localized prostate cancer patients included in the Groupe d'Etude des Tumeurs Uro-Genitales (GETUG) 12 trial.

METHODS AND MATERIALS

Patients with a nonpretreated high-risk localized prostate cancer and a staging lymphadenectomy were randomly assigned to receive either goserelin every 3 months for 3 years and 4 cycles of docetaxel plus estramustine or goserelin alone. Local therapy was administered 3 months after the start of systemic treatment. Performance of pelvic ENI was left to the treating physician. Only patients treated with primary RT were included in this analysis. The primary endpoint was biochemical progression-free survival (bPFS).

RESULTS

A total of 413 patients treated from 2002 to 2006 were included, of whom 358 were treated using primary RT. A total of 208 patients received pelvic RT and 150 prostate-only RT. Prostate-specific antigen (PSA) concentration, Gleason score, or T stage did not differ according to performance of pelvic RT; pN+ patients more frequently received pelvic RT than pN0 patients (P<.0001). Median follow-up was 8.8 years. In multivariate analysis, bPFS was negatively impacted by pN stage (hazard ratio [HR]: 2.52 [95% confidence interval [CI]: 1.78-3.54], P<.0001), Gleason score 8 or higher (HR: 1.41 [95% CI: 1.03-1.93], P=.033) and PSA higher than 20 ng/mL (HR: 1.41 [95% CI: 1.02-1.96], P=.038), and positively impacted by the use of chemotherapy (HR: 0.66 [95% CI: 0.48-0.9], P=.009). There was no association between bPFS and use of pelvic ENI in multivariate analysis (HR: 1.10 [95% CI: 0.78-1.55], P=.60), even when analysis was restricted to pN0 patients (HR: 0.88 [95% CI: 0.59-1.31], P=.53). Pelvic ENI was not associated with increased acute or late patient reported toxicity.

CONCLUSIONS

This unplanned analysis of a randomized trial failed to demonstrate a benefit of pelvic ENI on bPFS in high-risk localized prostate cancer patients.

Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. (Gravis G *et al.*, Lancet Oncol. 2013 Feb;14(2):149-58. doi: 10.1016/S1470-2045(12)70560-0. Epub 2013 Jan 8.)

BACKGROUND

Early chemotherapy might improve the overall outcomes of patients with metastatic non-castrate (ie, hormone-sensitive) prostate cancer. We investigated the effects of the addition of docetaxel to androgen-deprivation therapy (ADT) for patients with metastatic non-castrate prostate cancer.

METHODS

In this randomised, open-label, phase 3 study, we enrolled patients in 29 centres in France and one in Belgium. Eligible patients were older than 18 years and had histologically confirmed adenocarcinoma of the prostate and radiologically proven metastatic disease; a Karnofsky score of at least 70%; a life expectancy of at least 3 months; and adequate hepatic, haematological, and renal function. They were randomly assigned to receive to ADT (orchiectomy or luteinising hormone-releasing hormone agonists, alone or combined with non-steroidal antiandrogens) alone or in combination with docetaxel (75 mg/m(2) intravenously on the first day of each 21-day cycle; up to nine cycles). Patients were randomised in a 1:1 ratio, with dynamic minimisation to minimise imbalances in previous systemic treatment with ADT, chemotherapy for local disease or isolated rising concentration of serum prostate-specific antigen, and Glass risk groups. Patients, physicians, and data analysts were not masked to treatment allocation. The primary endpoint was overall survival. Efficacy analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00104715.

FINDINGS

Between Oct 18, 2004, and Dec 31, 2008, 192 patients were randomly allocated to receive ADT plus docetaxel and 193 to receive ADT alone. Median follow-up was 50 months (IQR 39-63). Median overall survival was 58•9 months (95% CI 50•8-69•1) in the group given ADT plus docetaxel and 54•2 months (42•2-not reached) in that given ADT alone (hazard ratio 1•01, 95% CI 0•75-1•36). 72 serious adverse events were reported in the group given ADT plus docetaxel, of which the most frequent were neutropenia (40 [21%]), febrile neutropenia (six [3%]), abnormal liver function tests (three [2%]), and neutropenia with infection (two [1%]). Four treatment-related deaths occurred in the ADT plus docetaxel group (two of which were neutropenia-related), after which the data monitoring committee recommended treatment with granulocyte colony-stimulating factor. After this recommendation, no further treatment-related deaths occurred. No serious adverse events were reported in the ADT alone group.

INTERPRETATION

Docetaxel should not be used as part of first-line treatment for patients with non-castrate metastatic prostate cancer.

Definition of lymph node areas for radiotherapy of prostate cancer: A critical literature review by the French Genito-Urinary Group and the French Association of Urology (GETUG-AFU). (Sargos P *et al.*, Cancer Treat Rev. 2015 Dec;41(10):814-20. doi: 10.1016/j.ctrv.2015.10.005. Epub 2015 Oct 23.)

PURPOSE

Recommendations for pelvic lymph node (LN) contouring rely on relatively dated studies that defined the Clinical Target Volume (CTV) of interest proposed for radiotherapy. The aim of this article was to review these recommendations with a critical analysis of published data on prostate cancer drainage.

METHODS

We performed a review of data on LN drainage in prostate cancer, based on anatomy texts and studies on lymphography, pelvic LN dissections, sentinel LN techniques, magnetic resonance imaging, computed tomography and functional imaging. We also present the GETUG experts' opinion, based on a survey on nodal CTV definition.

RESULTS

For lymphatic drainage of prostate cancers, pelvic LN areas classically considered are: distal common iliac, external iliac, internal iliac and obturator regions. Recently published data allow a mapping of sites at risk of pathological LN invasion. In 10-70% of cases, these sites are not included in the pelvic LN CTVs defined in consensuses. In accordance with other cooperative groups, the GETUG experts' survey showed that proximal common iliac, para-aortic, para-rectal and pre-sacral regions could include sites at risk of invasion in extended LN CTV, but were not considered in CTV contouring common practice. New recommendations are needed for nodal CTV in radiotherapy of prostate cancer.

CONCLUSIONS

The assessment of the efficacy and safety of LN radiotherapy is still the subject of several randomised studies. Whether or not meaningful results are obtained depends directly on the quality and homogeneity of the data analysed. A new consensus for delineation of LN regions appears necessary.

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. 2015 Aug;68(2):196-204. doi: 10.1016/j.eururo.2014.09.022. Epub 2014 Sep 30.)

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.

ASCO Genitourinary Cancers Symposium

Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. (Gravis G *et al.*)

BACKGROUND

ADT is standard treatment for metastatic PCa. Recently, the E3805 trial reported a survival benefit for (ADT+D) in high volume disease (HVD) patients, whereas the GETUG-15 trial did not demonstrate a survival improvement among a less selected group of patients (pts) with hormone-naïve metastatic PCa. We report an updated analysis of overall survival (OS) of the GETUG 15 trial and aligned the definition of HVD and low volume disease (LVD) subgroups.

Methods: Long-termOS was analyzed in the intention-to-treat population (n=385 pts). Additionally, we retrospectively assessed the tumor volume as defined per E3805criteria in all patients enrolled in GETUG 15.

RESULTS

With a median follow-up of 82.9 months (95%CI [80.5-84.3]) (vs 50 months (95%CI [80.5-84.3] in the original analysis), 212 patients (55%) have died. The median OS is 46.5 [39.1-60.6] and 60.9 months [46.1-71.4] in the ADT and in the ADT + D arms, respectively (HR: 0.9 [95%CI: 0.7-1.2]). In HVD patients (n=183, 47.5%), median OS rates were 35.1 months [29.9-44.2] in the ADT alone arm and 39 months [28-52.6] in the ADT+D arm (HR: 0.8 [0.6-1.2]).

CONCLUSIONS

With longer follow-up, the addition of docetaxel to ADT did not significantly improve OS in patients with hormone-naïve metastatic prostate cancer. In the retrospective analysis using aligned definition of volume of metastasis as E3805, the HVD outcomes were similar to E3805 for ADT alone and there was a non-significant 4 months increase in OS with ADT+D, in this underpowered subset.

ASCO

Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for biological relapse (BR) after radical prostatectomy (RP): Results of the GETUG-AFU 16 phase III randomized trial. (Carrie C. *et al.*)

BACKGROUND

RT is the standard as salvage treatment after RP. The role of HT is not demonstrated to date. This trial assessed the efficacy of RT alone vs RT+HT on progression-free survival (PFS) (biological or/and clinical relapse) for patients with BR after RP. Secondary objectives were overall survival (OS), toxicity and quality of life.

METHODS

Patients (pts) were randomized (1:1; stratification on risk factors at RP and type of planned RT) to RT alone (66Gy on prostate bed +/- pelvic irradiation according to pN status and risk of initial node involvement) or RT+HT (goserelin, for 6 months). Assuming 5-year PFS of 45% for RT arm, the trial required 369 pts per arm to detect an improvement of 12% on PFS in RT+HT arm (90% power and 5% alpha risk). BR was evaluated according to Astro-consensus.

RESULTS

From Oct. 2006 to Mar. 2010, 743 pts (RT: 374; RT+HT: 369) were randomized. Baseline characteristics were well balanced between the arms, median age: 67 y, pT2ac: 54%, pT3ac: 46%, gleason > 6: 76%, positive margins: 51%, seminal vesicles' involvement 13%. PSA doubling time at relapse was > 6 months in 74%. With a median follow-up of 63.1 months, 216 events were notified (138 in RT vs 78 in RT+HT). The intent to treat analysis showed an improved 5-y PFS of 62.1% (CI95%: 57-67) vs 79.6% (IC95%: 75-84) for RT and RT+HT, respectively (log-rank: p < 0.0001). The 5-y OS was 94.8% for RT vs 96.2% for RT+HT (p = 0.18). Cause of death was progressive disease in 2.1% pts on RT arm vs 0.8%. Acute toxicities occured more frequently in RT+HT arm (89% vs 79%). No difference was found in grade ³3 acute toxicities (1.9% vs 2.2%) and late toxicities (18.8% vs 21.9%). No toxic death was observed.

CONCLUSIONS

GETUG-AFU 16 is the first randomized trial comparing RT vs RT+ short HT as salvage treatment for BR after RP with undetectable post-op PSA. RT+HT significantly improve the 5-y PFS without increasing acute or late grade 3 toxicities. A longer follow up is required to quantify the impact on OS but RT+HT could be considered as the standard in this situation.

ASTRO

Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Preliminary Results of GETUG-01.
(Pommier P *et al*.)

PURPOSE

To assess the benefit and toxicity and quality-of-life (QOL) outcomes of pelvic nodes irradiation in nonmetastatic prostate carcinoma patients.

PATIENTS AND METHODS

Between December 1998 and June 2004, 444 patients with T1b-T3, N0 pNx, M0 prostate carcinoma were randomly assigned to either pelvic and prostate radiotherapy or prostate radiotherapy only. Patients were stratified according to the prognostic factor of lymph node involvement (LNI). Short-term 6-month neoadjuvant and concomitant hormonal therapy was allowed only for patients in the high-risk group. The pelvic dose was 46 Gy. The total dose recommended to the prostate was changed during the course of the study from 66 Gy to 70 Gy. Criteria for progression-free survival (PFS) included biologic prostate-specific antigen recurrences or a local or metastatic evolution. Acute and late toxicities were recorded according to the Radiation Therapy Oncology Group and Late Effects in Normal Tissues Subjective, Objective, Management, and Analytic scales, respectively. The QOL outcome was recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, the International Prostatic Symptom Score, and the Sexual Function Index scales.

RESULTS

With a 42.1-month median follow-up time, the 5-year PFS and overall survival were similar in the two treatment arms for the whole series and for each stratified group. On multivariate analysis, low LNI risk and hormonal therapy were statistically associated with increased PFS. However, subgroup analyses based on these factors did not show any benefit for pelvic irradiation. There were no significant differences in acute and late digestive toxicities and in QOL outcomes.

CONCLUSION

Pelvic node irradiation was well tolerated but did not improve PFS.

Randomized Phase 3 Trial of Dose Escalation (80 vs 70 Gy) in High-Risk Prostate Cancers Combined With Long-term Androgen Deprivation: GETUG-AFU 18 Trial, Acute and 1-Year Toxicities. (Hennequin C. *et al.*)

PURPOSE/OBJECTIVE(S)

Results of acute and 1-year toxicities of a Phase 3 randomized trial evaluating the impact of dose escalation (10 Gy) in combination with 3-year androgen deprivation treatment on 5-year biochemical or clinical control in high-risk prostate cancer patients.

MATERIALS/METHODS

Inclusion criteria: cT3 or T4 or a PSA of ≥20 ng/mL or a Gleason score of ≥ 8–10; N0 on CT scan or MRI or pelvic lymph node dissection (PLND). Eligible patients were randomized between 70 Gy or 80 Gy prostate radiation therapy (RT; 3-dimensional conformal RT [3D-CRT] or intensity modulated RT [IMRT]). Pelvic nodal irradiation (46 Gy) was performed for all patients except in the case of negative PLND. LH-RH agonists were given for 3 years in both arms and could be started within 6 months before RT. Randomization (1:1) was stratified on PLND (yes or no) and institution. Primary endpoint is biochemical or clinical control (bPFS; cPFS); secondary endpoints are overall survival, disease-specific survival, acute and late toxicity (CTCAE V3.0), and quality of life (QLQ-C30 and PR25). To improve bPFS or cPFS from 65% to 75% (HR = 0.67), 500 patients were required (a = 5% and 1-b = 80%), with 197 events at 5 years.

RESULTS

A total of 505 patients were included between June 2009 and January 2013, 250 in the 80-Gy arm and 255 in the 70-Gy arm. Main characteristics were well balanced: Mean age: 70.6 years (range, 52–80); Gleason score ≥ 8: 77 (15.3%); median PSA value at diagnosis: 13.8 ng/mL (0.35–109.93); cT3-4: 56.5%; PLND: 16.4%. A transurethral prostate resection (TURP) was performed before RT in 7.5% of the patients. In terms of treatment, 68.4% of patients were treated with IMRT (with 57.3% in the 80-Gy arm, P < .001), and 59.6% were treated by image guided RT (with 55.1% in the 80-Gy arm, P = .004). Acute (during and 1-month post-RT) and 1-year (6 months and 1 year) toxicities were described for Grade ≥3 (G≥3). Acute toxicity was 15.8% and 20.6% in the 80-Gy and 70-Gy arms, respectively (NS). One-year toxicities were 18.1% and 20.5% in the 80-Gy and 70-Gy arms, respectively (NS). No difference in acute or 1-year toxicity was observed between 3D-CRT and IMRT. One-year toxicity was 26.4% and 18.1% (P = .106) for patients with or without pelvic irradiation, respectively; TURP does not increase the incidence of 1-year toxicities (29.4%).

CONCLUSION

No significant difference was observed between acute and 1-year toxicities between the 2 arms. The experimental arm seems well tolerated in the first year, probably due to the RT technique used (IMRT was more frequently used in the 80-Gy arm). The 2-year late toxicity results are planned for 2016, and the primary endpoint analysis is planned for 2017.

Posters

Clinical outcome of newly diagnosed metastatic hormone sensitive prostate cancer (HSPC), in real life, population from a single center: comparison with newly diagnosed metastatic HSPC patients included in the GETUG-AFU 15 trial (Guerin M., *et al.*)

Androgen-deprivation therapy plus docetaxel versus androgen-deprivation therapy alone in metastatic non-castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase III GETUG-AFU 15 trial (Gravis G. *et al.*)

SARCOMA
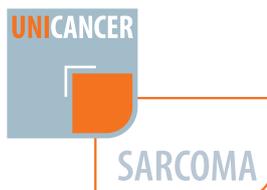
Scientific articles

Impact of gender on efficacy and acute toxicity of alkylating agent - based chemotherapy in Ewing sarcoma: secondary analysis of the Euro-Ewing99-R1 trial. (Van den Berg H, *et al*. Eur J Cancer. 2015 Nov;51(16):2453-64. doi: 10.1016/j.ejca.2015.06.123. Epub 2015 Aug 10.)

BACKGROUND

Based on the randomised Euro-EWING99-R1 trial, vincristine, adriamycin, cyclophosphamide (VAC) may be able to replace vincristine, adriamycin, ifosfamide (VAI) in the treatment of standard-risk Ewing sarcoma. However some heterogeneity of treatment effect by gender was observed. The current exploratory study aimed at investigating the influence of gender on treatment efficacy and acute toxicity.

PATIENTS AND METHODS

Impact of gender on event-free survival (EFS), acute toxicity by course, switches between treatment arms and cumulative dose of alkylating agents was evaluated in multivariable models adjusted for age including terms to test for heterogeneity of treatment effect by gender. The analysis of the EFS was performed on the intention-to-treat population.

RESULTS

EFS did not significantly differ between the 509 males and 347 females (p=0.33), but an interaction in terms of efficacy was suspected between treatment and gender (p=0.058): VAC was associated with poorer EFS than VAI in males, hazard ratio (HR) (VAC/VAI)=1.37 [95% confidence interval (CI), 0.98-1.90], contrasting with HR=0.81 [95%CI, 0.53-1.24] in females. Severe toxicity was more frequent in females, whatever the toxicity type. Thirty patients switched from VAI to VAC (9/251 males, 4%, and 21/174 females, 12%) mostly due to renal toxicity, and three from VAC to VAI (2/258 males, 0.8%, and 1/173 females, 0.6%). A reduction of alkylating agent cumulative dose >20% was more frequent in females (15% versus 9%, p=0.005), with no major difference between VAC and VAI (10% versus 13%, p=0.15).

CONCLUSION

Differences of acute toxicity rate and cumulative doses of alkylating agents could not explain the marginal interaction observed in the Euro-EWING99-R1 trial data. Effects of gender-dependent polymorphism/activity of metabolic enzymes (e.g. known for CYP2B6) of ifosfamide versus cyclophosphamide should be explored. External data are required to further evaluate whether there is heterogeneity of alkylating agent effect by gender.

UCGI - FEDEGYN

UNICANCER

GASTRO INTESTINAL

Scientific articles

Low response rate after cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: long-term results of the UNICANCER ACCORD 16 phase II trial. (Levy A, *et al.*, Radiother Oncol. 2015 Mar;114(3):415-6. doi: 10.1016/j.radonc.2015.02.008. Epub 2015 Mar 11.)

ABSTRACT

In the ACCORD 16 phase II trial, immunocompetent patients with histologically confirmed locally advanced anal canal carcinoma (LAACC) received conventional chemoradiotherapy (45 Gy in 25 fractions over 5 weeks, fluorouracil and cisplatin during weeks 1 and 5), in combination with weekly dose cetuximab (250 mg/m^2 with a loading dose of 400 mg/m^2 one week before irradiation), and a standard-dose boost (20 Gy). While the trial was originally designed to include 81 patients, the study was prematurely stopped.

Clinical complete response (cCR) after neoadjuvant chemoradiotherapy and conservative treatment in rectal cancer. Findings from the ACCORD 12/PRODIGE 2 randomized trial. (Gérard JP, *et al.*, Radiother Oncol. 2015 May;115(2):246-52. doi: 10.1016/j.radonc.2015.04.003. Epub 2015 Apr 24.)

BACKGROUND

During the ACCORD 12 randomized trial, an evaluation of the clinical tumor response was prospectively performed after neoadjuvant chemoradiotherapy. The correlations between clinical complete response and patient characteristics and treatment outcomes are reported.

MATERIAL AND METHODS

Between 2005 and 2008 the Accord 12 trial accrued 598 patients with locally advanced rectal cancer and compared two different neoadjuvant chemoradiotherapies (Capox 50: capecitabine+oxaliplatin+50Gy vs Cap 45: capecitabine+45Gy). An evaluation of the clinical tumor response with rectoscopy and digital rectal examination was planned before surgery. A score to classify tumor response was used adapted from the RECIST definition: complete response: no visible or palpable tumor; partial response, stable and progressive disease.

RESULTS

The clinical tumor response was evaluable in 201 patients. Score was: complete response: 8% (16 patients); partial response: 68% (137 patients); stable: 21%; progression: 3%. There was a trend toward more complete response in the Capox 50 group (9.3% vs 6.7% with Cap 45). In the whole cohort of 201 pts complete response was significantly more frequent in T2 tumors (28%; p=0.025); tumors <4cm in diameter (14%; p=0.017), less than half rectal circumference and with a normal CEA level. Clinical complete response observed in 16 patients was associated with more conservative treatment (p=0.008): 2 patients required an abdomino-perineal resection, 11 an anterior resection and 3 patients benefited from organ preservation (2 local excision, 1 "watch and wait". A complete response was associated with more ypT0 (73%; p<0.001); ypNO (92%); R0 circumferential margin (100%).

CONCLUSION

These data support the hypothesis that a clinical complete response assessed using rectoscopy and digital rectal examination after neoadjuvant therapy may increase the chance of a sphincter or organ preservation in selected rectal cancers.

Applying the Longitudinal Model from Item Response Theory to Assess the Health-Related Quality of Life in the PRODIGE 4/ACCORD 11 Randomized Trial. (Barbieri A *et al.*, Med Decis Making. 2015 Dec 18. pii: 0272989X15621883)

INTRODUCTION

A new longitudinal statistical approach was compared to the classical methods currently used to analyze health-related quality-of-life (HRQoL) data. The comparison was made using data in patients with metastatic pancreatic cancer.

METHODS

Three hundred forty-two patients from the PRODIGE4/ACCORD 11 study were randomly assigned to FOLFIRINOX versus gemcitabine regimens. HRQoL was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30. The classical analysis uses a linear mixed model (LMM), considering an HRQoL score as a good representation of the true value of the HRQoL, following EORTC recommendations. In contrast, built on the item response theory (IRT), our approach considered HRQoL as a latent variable directly estimated from the raw data. For polytomous items, we extended the partial credit model to a longitudinal analysis (longitudinal partial credit model [LPCM]), thereby modeling the latent trait as a function of time and other covariates.

RESULTS

Both models gave the same conclusions on 11 of 15 HRQoL dimensions. HRQoL evolution was similar between the 2 treatment arms, except for the symptoms of pain. Indeed, regarding the LPCM, pain perception was significantly less important in the FOLFIRINOX arm than in the gemcitabine arm. For most of the scales, HRQoL changes over time, and no difference was found between treatments in terms of HRQoL.

DISCUSSION

The use of LMM to study the HRQoL score does not seem appropriate. It is an easy-to-use model, but the basic statistical assumptions do not check. Our IRT model may be more complex but shows the same qualities and gives similar results. It has the additional advantage of being more precise and suitable because of its direct use of raw data.

Posters

ESGO

Hyperthermic intraperitoneal chemotherapy (hipec) a promising treatment for relapsed intraperitoneal ovarian cancer. Chipor an ongoing phase III, european multicentric randomized trial. Unicancer – fedegyn 02. (Classe JM *et al.*)

ASCO

Folfox alone or combined to rilotumumab or panitumumab as first-line treatment in patients (pts) with advanced gastroesophageal adenocarcinoma (agea): an open-label, randomized phase II trial (prodige 17 accord 20 mega). (Malka D *et al.*)

Médecine personnalisée et Essais précoces

UNI**CANCER**

GEP

UNI**CANCER**

PERSONALIZED MEDICINE

Scientific articles

Impact of centralization on aCGH-based genomic profiles for precision medicine in oncology. (Commo F *et al.*, Ann Oncol. 2015 Mar;26(3):582-8. doi: 10.1093/annonc/mdu582. Epub 2014 Dec 23.)

BACKGROUND

Comparative genomic hybridization (CGH) arrays are increasingly used in personalized medicine programs to identify gene copy number aberrations (CNAs) that may be used to guide clinical decisions made during molecular tumor boards. However, analytical processes such as the centralization step may profoundly affect CGH array results and therefore may adversely affect outcomes in the precision medicine context.

PATIENTS AND METHODS

The effect of three different centralization methods: median, maximum peak, alternative peak, were evaluated on three datasets: (i) the NCI60 cell lines panel, (ii) the Cancer Cell Line Encyclopedia (CCLE) panel, and (iii) the patients enrolled in prospective molecular screening trials (SAFIR-01 n = 283, MOSCATO-01 n = 309), and compared with karyotyping, drug sensitivity, and patient-drug matching, respectively.

RESULTS

Using the NCI60 cell lines panel, the profiles generated by the alternative peak method were significantly closer to the cell karyotypes than those generated by the other centralization strategies (P < 0.05). Using the CCLE dataset, selected genes (ERBB2, EGFR) were better or equally correlated to the IC50 of their companion drug (lapatinib, erlotinib), when applying the alternative centralization. Finally, focusing on 24 actionable genes, we observed as many as 7.1% (SAFIR-01) and 6.8% (MOSCATO-01) of patients originally not oriented to a specific treatment, but who could have been proposed a treatment based on the alternative peak centralization method.

CONCLUSION

The centralization method substantially affects the call detection of CGH profiles and may thus impact precision medicine approaches. Among the three methods described, the alternative peak method addresses limitations associated with existing approaches.

Influence of tumour burden on trastuzumab pharmacokinetics in HER2 positive non-metastatic breast cancer. (Bernadou G *et al.*, Br J Clin Pharmacol. 2015 Dec 29. doi: 10.1111/bcp.12875)

AIMS

Trastuzumab, an antibody binding to epidermal growth factor receptor-2 (HER2), has been approved to treat HER2-positive breast cancer in different settings. This study aimed at evaluating the influence of tumour size on trastuzumab pharmacokinetics (PK) in non-metastatic breast cancer patients treated with short-term preoperative trastuzumab.

METHODS

Trastuzumab PK data were obtained from a multi-center, randomized and comparative study. This antibody was administered preoperatively to patients with localized HER2-positive breast cancer as a single 4 mg/kg loading dose followed by 5 weekly 2 mg/kg doses. Trastuzumab concentrations were measured repeatedly using an ELISA technique. Tumour size was evaluated at baseline using breast echography. Trastuzumab pharmacokinetics was studied using a population approach and a two-compartment model. The influence of tumour burden on trastuzumab pharmacokinetics was quantified as a covariate.

RESULTS

A total of 784 trastuzumab concentrations were available in the 79 eligible patients. Estimated parameters (interindiviual standard deviation) were: central volume of distribution = 2.1 L (23%), peripheral volume of distribution = 1.3 L (38%) intercompartment clearance = 0.36 L/day, with an elimination half-life of 11.8 days. Typical clearance was 0.22 L/day (19%) and its value was increased with tumour size: in patient with the highest tumour size, trastuzumab clearance was 50% [18%-92%] higher than in patients with the lowest tumour size.

CONCLUSIONS

In non-metastatic breast cancer patients, trastuzumab clearance increases with tumour size. The elimination half-life of trastuzumab was shorter in the present population of patients than in metastatic breast cancer patients previously studied.

First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG). (A.Ravaud *et al.*, Ann Oncol. 2015 Jun;26(6):1123-8)

BACKGROUND

Papillary renal cell carcinoma (PRCC), type 1 and type 2, represents 10%-15% of renal cell carcinomas (RCC). There is no standard first-line treatment of metastatic PRCC (mPRCC). Anti-angiogenics have shown activity in retrospective studies but no prospective studies in pure papillary histology have been reported, but one with foretinib.

PATIENTS AND METHODS

A prospective phase II study evaluated sunitinib in first-line treatment of mPRCC. The primary end point was overall response rate (ORR). Secondary end points were progression-free survival (PFS) and overall survival (OS).

RESULTS

Fifteen and 46 patients, respectively, with type 1 and type 2 mPRCC were enrolled. Using the MSKCC scoring system: 12 (20%), 33 (55%) and 9 (15%) patients were, respectively, in the favourable, intermediate or poor risk group and 7 undetermined. Median follow-up is 51.4 months. In type 1, 2 patients 13% [95% confidence interval (CI) 0.1-30.5] had a partial response (PR), 10 had stable disease (SD) with 5 (33%) ≥12 weeks. In type 2, 5 patients 11% (95% CI 1.9-20.3) had a PR, 25 had SD with 10(22%) ≥12 weeks. Median PFS was 6.6 months (95% CI 2.8-14.8) in type 1 and 5.5 months (95% CI 3.8-7.1) in type 2. Median OS was 17.8 (95% CI 5.7-26.1) and 12.4 (95% CI 8.2-14.3) months, respectively, in type 1 and 2. Safety was as expected with sunitinib for metastatic RCC.

CONCLUSION

Sunitinib showed activity in treatment of type 1 and 2 mPRCC but lower than in clear-cell mRCC. Both PFS and OS are longer in type I PRCC. Sunitinib represents an acceptable option in first-line treatment of mPRCC.

WCLC

Activity of crizotinib in MET amplified NSCLC: Preliminary results of the AcSé trial. (Moro-Sibilot D., *et al.*)

BACKGROUND

Crizotinib (crz) is registered only for the treatment of patients (pts) with ALK-translocated lung cancer. Crz is also a MET inhibitor. MET is amplified in several malignancies. Activity of crz in MET amplified (+) tumors was explored as part of the French National Cancer Institute (INCa) AcSé program, including both access to tumor molecular diagnosis and an exploratory multi-tumor 2-stage design phase II trial. We report here results in pts with MET + NSCLC.

METHODS

MET analysis on formalin-fixed, paraffin-embedded tumor samples was proposed in 170 investigating centers and performed in 28 regional INCa molecular genetic centers. MET+ was explored by FISH in tumor samples showing an IHC score of ≥2+. Pts with a tumor showing > 6 MET copies, whatever the MET/CEN7 ratio, were eligible, providing they were not eligible for any other academic or industry trial evaluating another MET inhibitor. Study treatment consisted in crz 250 mg BID. The objective response rate (ORR) and disease control rate (DCR) were assessed every 8 weeks, using RECIST v1.1.

RESULTS

From Aug. 5, 2013 to Mar. 1, 2015, 25 pts with MET+ NSCLC were enrolled and received crz. Median age was 59 years (range 30–92). Forty-four percent were females, 92% had tumors of non-squamous histology, and 96% presented with metastatic disease at study entry. Median number of prior treatments was 2 (range 0 – 11). Eight pts were still on treatment at the cut-off date, 17 have stopped crz (15 progressive diseases (PD), 1 adverse event (AE), 1 patient's choice). Among the 18 pts evaluable for response after 8 weeks, we observed 7 partial responses, 6 stable diseases and 5 PD, leading to an ORR of 39% [95% CI:17-64], and a DCR of72% [47-90]. DCR at 6 months was 22% (4 pts out of the 18 evaluable pts). Crz was well tolerated with only 5 grade ≥3 (2 AE + 3 SAEs) and 3 grade 1-2 SAEs. Most common AEs, mainly grade 1 or 2, were nausea (60% of pts), visual disorders (52%), anemia (52%), elevated transaminases (48%) and vomiting (40%).

CONCLUSION

Nationwide biomarker-driven access to crz for pts with MET+ malignancy is feasible. Crz was well tolerated and showed responses in pretreated MET+ lung cancers. Survival data and duration of response will be presented.

Crizotinib in patients with ROS1 NSCLC. Preliminary results of the AcSé trial. (Moro-Sibilot *et al.*)

BACKGROUND

To avoid uncontrolled off-label use and allow for a nationwide safe access to crizotinib (crz) for patients (pts) with an ALK, MET or ROS1 positive (+) tumor, the French National Cancer Institute (INCa) launched the AcSé program, funding both access to tumor molecular diagnosis and an exploratory multi-tumor 2-stage design phase II trial. We report the preliminary results of the ROS1+ NSCLC cohort.

METHODS

ROS1 status was assessed in 28 regional INCa molecular genetic centers by break-apart FISH assays in tumor samples showing an IHC score of ≥1+. Pts with ROS1 rearrangements, progressing after at least one standard treatment (including a platinum-based doublet, unless pts were considered as unfit for chemotherapy) were proposed to receive crz 250 mg BID. Responses were centrally assessed using RECIST v1.1. The objective response rate (ORR) and disease control rate (DCR) were assessed every 8 weeks.

RESULTS

From Aug. 5, 2013 to Mar. 1, 2015, 39 pts with ROS1+ NSCLC were enrolled. 37 pts had received crz, leading to 37 pts with clinical information. Median age: 62 years (range 33–81), 70% females, 95% non-squamous histology, and 94% metastatic disease at study entry. Median number of prior treatments: 2 (range 1 –7). Twenty four pts were still on treatment at the cut-off date, 13 have stopped crz (8 PD, 3 adverse events (AEs), 2 deaths). Among the 27 pts evaluable for response at 8 weeks, we observed 16 PR, 7 SD and 4 PD, leading to ORR=59% [95% CI:39-78], and DCR=85% [66-96]. DCR at 6 months was 57% (disease control was achieved in 12/21 evaluable pts). Crz was well tolerated with only 4 grade ≥3 (1 AE + 3 SAEs) and 9 grade 1-2 SAEs. Most common AEs, mainly grade 1, were visual disorders (54% of pts), peripheral edema (51%), diarrhea (48%), nausea (46%), and elevated transaminases (43%).

CONCLUSION

Crz was well tolerated and achieved a robust treatment response rate in ROS1+ NSCLC. These results underline the interest of integrating ROS1 in biomarkers routine screening. Survival data and duration of response will be presented.

ECCO-ESMO

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

BACKGROUND

Crizotinib (czb) is registered only for the treatment of patients (pts) with ALK+ lung cancer. Czb targets (ALK, MET, ROS1) are also altered (translocation, amplification, mutation) in a wide range of malignancies in adults and children. To avoid off label use and allow for a nationwide safe and controlled access to czb for pts with an ALK, MET or ROS1 positive tumor, the French National Cancer Institute (INCa) launched the AcSé program: access to tumor molecular diagnosis in the 28 INCa molecular genetic centers along with an exploratory phase II trial.

METHODS

Biomarker identification is proposed to pts ≥ 1 year with an advanced disease among more than 15 malignancies (such as colon, gastric, liver, thyroid, renal and breast cancers, cholangiocarcinoma, lymphoma, neuroblastoma, sarcomas, and ROS1 or MET lung cancer) (such as colon, gastric, liver, thyroid, renal and breast cancers, cholangiocarcinoma, lymphoma, neuroblastoma, sarcomas, and ROS1 lung cancer) known from literature to harbor a genomic alteration in a czb target. If not eligible for any other academic or industry trial targeting the same alteration, a patient with an ALK, MET or ROS1 positive tumor may enter one of the 22 specified cohorts defined as a disease and a type of target alteration, and receives czb (adult: 250 mg x 2; child: 280 mg/m^2 x 2). Pts with an altered czb target as evidenced through a pangenomic tumor profiling program are also eligible. Tumor response is evaluated every 2 months using RECIST criteria. Three statistical 2-stage designs are considered for cohorts to anticipate 3 situations in terms of expected response rate and incidence. Accrual stops if 0 response / N1 pts; else N2 additional pts are recruited. 10,000 to 15,000 molecular tests and 490 pts treated in 150 centers are planned over 3 years. From Aug. 2013 to Jan. 2014, 22 pts have been accrued. The AcSé program is currently being expanded to other targeted drugs.

EORTC-PAMM

Tumor signaling alteration in her2-positive breast cancer treated by preoperative trastuzumab - everolimus. (Lion M *et al*.)

BACKGROUND

Deregulation of PI3K/AKT/mTOR and RAS/RAF/MAPK signaling pathways is involved in the development of breast cancer, and in resistance mechanisms to therapy. Our study is a biological, prospective, multicenter, randomized phase 2 study, evaluating the impact of combining everolimus with trastuzumab. The aim of this study was to investigate the clinical significance and theranostic interest of measuring the expression of phosphoproteins from PI3K and MAPK signaling pathways.

MATERIALS AND METHODS

82 eligible patients were randomized to receive trastuzumab (T) alone (loading dose 4mg/kg, then 2mg/kg/week) or combined with everolimus (10 mg/day) (T+E) for a 6 week pre-operative treatment. All patients had needle frozen biopsies taken at baseline before initiation of the treatment, at cycle 4 as an option, and at surgery. All biopsies were validated by a senior pathologist after HE slide examination to ensure a tumor content >50%, prior to protein extraction. The expression of p-P38MAPK, p-AKT, p-GSK3β, p-S6Kinase, p-MEK1 and p-ERK1/2, p-P90RSK, p-IGF1R, was measured using multiplex bead immunoassay. Forty pairs, associating baseline + surgery tumor specimens or baseline + cycle 4 biopsies, were eligible for protein extraction and comparative phosphoprotein expression analysis before and after treatment. Statistical analyses were performed using Student and Wilcoxon tests.

RESULTS AND DISCUSSION

After treatment, in T arm, no significant variation of signaling phosphoproteins expression was observed. The lack of down-regulation of PI3Kinase and MAPKinase pathways in T arm could probably be explained by the implementation of a predominant immunological mechanism of action for T (ADCC). In T+E arm, significant inhibition of PI3Kinase/mTOR pathway was only observed downstream mTOR protein with decreased expression of p-P70S6 kinase. In contrast, a significant increase of p-MEK1, p-ERK1/2, p-P38MAPK was observed as compared to the level of expression measured at baseline. These results could probably be related to the fact that PI3K/AKT/mTOR and RAS/RAF/MAPKinase pathways are interconnected with multiple points of convergence, including a negative feedback loop involving S6K, PI3K and RAS. In the present study, the activation of MAPKinase pathway could be mediated by the suppression of S6K-PI3K-RAS feedback loop induced by everolimus.

CONCLUSION

In the present study, measuring phosphoproteins expression showed that using specific pathway inhibitors may have a rebound effect and cause the activation of compensatory pathways. Combining E with T, altered the regulation of both PI3Kinase and MAPKinase pathways and suggested that using multiple kinase inhibitors to obtain a complete blockade of both signaling pathways could be helpful to prevent activation of compensatory pathways and increase the effectiveness of treatment.

Posters

ASCO

Activity of crizotinib in relapsed MET amplified malignancies: Results of the French AcSé Program. (Vassal G., *et al*.)

Crizotinib in patients with advanced ROS1-rearranged non-small cell lung cancer (NSCLC). Preliminary results of the ACSé phase II trial. (Moro-Sibilot D. *et al*.)

GERICO

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GERICO

Posters

SIOG

Aster 70s or optimal adjuvant treatment for women over 70 with luminal breast cancer: a unicancer phase III trial. (Coussy F *et al*.)

Head & Neck

Communications

ESMO

Cabazitaxel in patients with refractory recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Final results of phase II Trial ORL 03 UNICANCER. (Fayette J. *et al.*)

BACKGROUND

After failure of platinum, anti-EGFR and taxanes R/M SCCHN patients (pts) are considered 'refractory' and methotrexate is the only option as palliative care. Cabatizaxel prolongs survival in hormone - refractory metastatic prostate cancer after failure of docetaxel. Could it be effective for refractory R/M SCCHN pts?

METHODS

To be included in this multicentre, phase II study, pts required to be progressive after platinum, cetuximab and taxanes (sequential and with various combinations) and to have PS 0-2. Cabazitaxel was given at 25 mg/m² every 3 weeks (wks) for a maximum of 10 cycles. G-CSF support with lenograstim 150 µg/m²/day was delivered after each cycle of chemotherapy. Response was assessed every 6 wks, according to RECIST 1.1 (centralized review). The primary endpoint was non-progression at 6 weeks. A two-stage Simon optimal design was chosen (P0=0.10; P1=0.30) and 29 evaluable pts were required. To accrue the second stage 2/10 non-progressions were needed. A total of 6 non-progressions or more were required in order to make the drug worthy of further study. Planned interim analysis results are provided below.

RESULTS

Thirty one pts have been enrolled, 29 were eligible: 22 males, median age 60 years (30-71), 13 (45%) oropharynx, 2 (7%) metastatic. All received at least 2 previous lines of chemotherapy and cetuximab. Twenty nine pts were evaluable for the primary end point: 21 were progressive and 8 (27.6%; 95%CI 12.7%-47.2%) had Stable Disease. Fifteen pts had severe treatment-related adverse events, with febrile neutropenia in 6 pts /31, 1 death) The main grade 3-4 toxicity was neutropenia with 7 pts (21%) having at least one event.

CONCLUSIONS

Cabazitaxel met its primary endpoint with a 27.6% disease control rate at 6 weeks in heavily pretreated refractory R/M SCCHN pts. Tolerability seems to be acceptable in such a population usually in poor medical condition.

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Scientific articles

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UGT1A1 genotype and irinotecan therapy: general review and implementation in routine practice.

ABSTRACT

Irinotecan is a major drug in the treatment of advanced colorectal cancer. Its active form is the SN38 metabolite, which is cleared by the biliary route after glucuronidation by uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1). UGT1A1 activity exhibits a wide intersubject variability, in part related to UGT1A1 gene polymorphisms. The present review on the impact of the deficient UGT1A1*28 variant on irinotecan efficacy and toxicity was produced by a French joint workgroup comprising the Group of Clinical Onco-pharmacology (GPCO-Unicancer) and the National Pharmacogenetics Network (RNPGx). It clearly emerges that for irinotecan doses at least equal to 180 mg/m(2) , patients homozygous for the UGT1A1*28 allele are at increased risk of developing hematological and/or digestive toxicities. Irinotecan dose reduction is thus recommended in homozygous *28/*28 patients. In addition, this personalized medicine strategy aims to secure high-dose irinotecan administration (≥240 mg/m(2)) that have proven to be safe in homozygous *1/*1 patients only. The clinical relevance of this test is discussed in terms of treatment efficacy improvement, as increasing the irinotecan dose appears to be safe in patients not bearing a deficient allele. Best execution practices, cost-effectiveness, and result interpretation are discussed with the aim of facilitating the implementation of this analysis in clinical practice. The existence of networks of laboratories performing this test in routine hospital treatment, as in France, offers the prospect of widespread screening, thus guaranteeing equal access to safe treatment and optimized therapy for patients receiving irinotecan-based therapy in advanced colorectal cancer.

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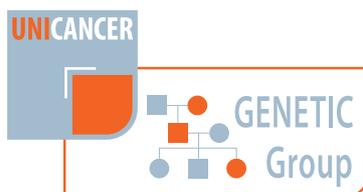
Groupe génétique et cancer

Disclosure of research results: a randomized study on GENEPSO-PS cohort participants. (Mancini J *et al.*, Health Expect. 2015 Jul 23. doi: 10.1111/hex.12390)

BACKGROUND

There exist no recommendations as to how aggregate research results should best be disclosed to long-term cohort participants.

OBJECTIVE

To study the impact of cohort results disclosure documents of various kinds on participants' satisfaction.

DESIGN

Randomized study with a 2x2 factorial design.

Setting and participants: The GENEPSO-PS cohort is used to study the psychosocial characteristics and preventive behaviour of both BRCA1/2 carriers and non-carriers; 235 participants wishing to receive 'information about the survey results' answered a self-administered questionnaire.

INTERVENTIONS

The impact of providing the following items in addition to a leaflet about aggregate psychosocial research results was investigated (i) an up-to-date medical information sheet about BRCA1/2 genetic topics, (ii) a photograph with the names of the researchers.

MAIN OUTCOME MEASURES

Satisfaction profiles drawn up using cluster analysis methods.

RESULTS

Providing additional medical and/or research team information had no significant effect on satisfaction. The patients attributed to the 'poorly satisfied' group (n = 60, 25.5%) differed significantly from those in the 'highly satisfied' group (n = 51, 21.7%): they were younger [odds ratio (OR) = 0.96, 95% confidence interval (0.92-0.99), P = 0.028], less often had a daughter [OR = 4.87 (1.80-13.20), P = 0.002], had reached a higher educational level [OR = 2.94 (1.24-6.95), P = 0.014] and more frequently carried a BRCA1/2 mutation [OR = 2.73 (1.20-6.23), P = 0.017].

CONCLUSIONS

This original approach to disclosing research results to cohort participants was welcomed by most of the participants, but less by the more educated and by BRCA1/2 carriers. Although an easily understandable document is necessary, it might also be worth providing some participants with more in-depth information.

Cigarette smoking in women after BRCA1/2 genetic test disclosure: a 5-year follow-up study of the GENEPSO PS cohort. (Julian-Reynier C, *et al.*, Genet Med. 2015 Feb;17(2):117-24. doi: 10.1038/gim.2014.82. Epub 2014 Jul 10.)

PURPOSE

This study aimed to measure patients' smoking patterns for 5 years after BRCA1/2 test result disclosure.

METHODS

A national cohort consisting of 621 French cancer-free women from families with BRCA1/2 mutations (mean age (SD): 40.5 years (11.5 years)) were included from December 1999 to January 2006, before disclosure of genetic test results, and followed for 5 years. They completed self-administered questionnaires about their cigarette smoking behaviors before receiving their test results (baseline) and 6, 12, 24, and 60 months after disclosure. Multivariate statistical analyses of the changes in participants' smoking behaviors were performed using a zero-inflated Poisson mixed model.

RESULTS

Baseline smoking was found to depend on age, educational level, marital status, alcohol consumption, body mass index, and cancer risk perception. The zero-inflated part of the model showed the occurrence of no significant changes in the percentage of smokers during the 5 years after disclosure of the BRCA1/2 test results; however, daily smoking among BRCA1/2 carriers decreased significantly compared with that of noncarriers (adjusted hazard ratio = 0.83; (95% confidence interval: 0.69-0.99); P = 0.04) after adjusting for baseline smoking behavior.

CONCLUSIONS

It would be worth investigating the possibility of counseling women during the genetic testing process about the multiple risk factors involved in cancer, such as genetic and lifestyle factors.

"Maybe they have found something new" participants' views on returning cohort psychosocial survey results. (Bureau E *et al*, Health Expect. 2015 Dec;18(6):2425-36. doi: 10.1111/hex.12211. Epub 2014 May 30.)

BACKGROUND

Although greater attention is currently being paid to participants in research, no studies have dealt so far with the issue of returning aggregate psychosocial results to cohort participants.

OBJECTIVE

(i) To explore participants' views about disclosure of the aggregate results of a French national psychosocial cohort survey on the epidemiology of preventive behaviour in women from families with a hereditary breast cancer risk. (ii) To assess whether it is worth consulting participants before designing the disclosure process.

DESIGN

A qualitative study using semi-structured face-to-face interviews and a thematic analysis based on Grounded Theory methods.

PARTICIPANTS

Nineteen interviews were conducted with cancer-free female BRCA mutation carriers/non-carriers aged 31-79 who had participated in a cohort survey by answering self-administered questionnaires.

RESULTS

Participants showed considerable interest in the issue of result disclosure. The preferences expressed about disclosure were rarely relevant to the topic investigated, however, as they often focused on medical knowledge about BRCA and not on the psychosocial findings obtained. This confusion may have been due to the participants' experience of the survey procedures, including its longitudinal nature, the occurrence of very few interactions with the investigators and the wide range of topics addressed in the questionnaires.

CONCLUSION

Investigators should ascertain participants' expectations and preferences by consulting them before disclosing the results obtained. Although the disclosure process may not meet participants' expectations completely, consultation is the key to preventing them from having irrealistic expectations about the information they are going to receive.

Breast Cancer Risk Associated with Estrogen Exposure and Truncating Mutation Location in BRCA1/2 Carriers. (Lecarpentier J *et al.*, Cancer Epidemiol Biomarkers Prev. 2015 Apr;24(4):698-707. doi: 10.1158/1055-9965.EPI-14-0884. Epub 2015 Jan 22.)

BACKGROUND

Mutations in BRCA1/2 confer a high risk of breast cancer, but literature values of this risk vary. A genotype-phenotype correlation has been found in both genes, and the effect of reproductive factors differs according to mutation location. Therefore, we hypothesize that such a variation may exist for other factors related to estrogen exposure.

METHODS

We used a weighted Cox regression model to assess variation in breast cancer risk with these factors using location of mutation in homogeneous breast cancer risk region of BRCA1/2 in the GENEPSO study.

RESULTS

We found that late age at menarche reduced breast cancer risk by 31% and that among BRCA1 carriers, a long or a short menstrual cycle increased risk (by 65% and 73%, respectively). Among premenopausal women, overweight was associated with a 45% decrease in risk whereas underweight was associated with an increased risk (HR, 2.40). A natural menopause, mainly after age 50, was associated with a high breast cancer risk (HR, 2.46), and a significant interaction between menopause status and the location of mutations was found leading up to 10% variation in absolute risk according to the age at menopause.

CONCLUSIONS

As observed in the general population, a late menarche, a long or a short menstrual cycle, over- or underweight, and being postmenopausal were associated with breast cancer risk in BRCA1/2 carriers. The association with the menopause was observed only when the mutation was located in the "high-risk" zones.

Hereditary diffuse gastric cancer syndrome: improved performances of the 2015 testing criteria for the identification of probands with a CDH1 germline mutation. (Benusiglio PR, *et al.*, J Med Genet. 2015 Aug;52(8):563-5. doi: 10.1136/jmedgenet-2015-103153. Epub 2015 May 29.)

ABSTRACT

The international, consensus testing criteria for CDH1 germline mutations were recently revised in order to increase their performances, particularly their sensitivity. It is paramount to identify a high proportion of actual mutation carriers, as finding a mutation in a proband and subsequently in some of his relatives allows for risk-reducing recommendations regarding diffuse gastric cancer (DGC) and lobular breast cancer (LBC). We collected data on all French probands tested for CDH1 in a retrospective study on the hereditary DGC syndrome (HDGC). Out of 627 probands, 52 were carriers. We compared the new, 2015 version of these criteria to the 2010 version, and showed that both the sensitivity and the Youden index (J), an index that estimates the criteria discriminating power, increased.

Targeted Sequencing of the Mitochondrial Genome of Women at High Risk of Breast Cancer without Detectable Mutations in BRCA1/2. (Blein S *et al.*, PLoS One. 2015 Sep 25;10(9):e0136192. doi: 10.1371/journal.pone.0136192. eCollection 2015)

ABSTRACT

Breast Cancer is a complex multifactorial disease for which high-penetrance mutations have been identified. Approaches used to date have identified genomic features explaining about 50% of breast cancer heritability. A number of low- to medium penetrance alleles (per-allele odds ratio < 1.5 and 4.0, respectively) have been identified, suggesting that the remaining heritability is likely to be explained by the cumulative effect of such alleles and/or by rare high-penetrance alleles. Relatively few studies have specifically explored the mitochondrial genome for variants potentially implicated in breast cancer risk. For these reasons, we propose an exploration of the variability of the mitochondrial genome in individuals diagnosed with breast cancer, having a positive breast cancer family history but testing negative for BRCA1/2 pathogenic mutations. We sequenced the mitochondrial genome of 436 index breast cancer cases from the GENESIS study. As expected, no pathogenic genomic pattern common to the 436 women included in our study was observed. The mitochondrial genes MT-ATP6 and MT-CYB were observed to carry the highest number of variants in the study. The proteins encoded by these genes are involved in the structure of the mitochondrial respiration chain, and variants in these genes may impact reactive oxygen species production contributing to carcinogenesis. More functional and epidemiological studies are needed to further investigate to what extent variants identified may influence familial breast cancer risk.

Mutation analysis of PALB2 gene in French breast cancer families. (Damiola F *et al.*, Breast Cancer Res Treat. 2015 Dec;154(3):463-71. doi: 10.1007/s10549-015-3625-7. Epub 2015 Nov 12.)

ABSTRACT

Several population-based and family-based studies have demonstrated that germline mutations of the PALB2 gene (Partner and Localizer of BRCA2) are associated with an increased risk of breast cancer. Distinct mutation frequencies and spectrums have been described depending on the population studied. Here we describe the first complete PALB2 coding sequence screening in the French population. We screened the complete coding sequence and intron-exon boundaries of PALB2, using the EMMA technique, to assess the contribution of pathogenic mutations in a set of 835 familial breast cancer cases and 662 unrelated controls from the French national study GENESIS and the Paul Strauss Cancer Centre, all previously tested negative for BRCA1 and BRCA2 pathogenic mutations. Our analysis revealed the presence of four novel deleterious mutations: c.1186insT, c.1857delT and c.2850delC in three cases, c.3418dupT in one control. In addition, we identified two in-frame insertion/deletion, 19 missense substitutions (two of them predicted as pathogenic), 9 synonymous variants, 28 variants located in introns and 2 in UTRs, as well as frequent variants. Truncating PALB2 mutations were found in 0.36 % of familial breast cancer cases, a frequency lower than the one detected in comparable studies in other populations (0.73-3.40 %). This suggests a small but significant contribution of PALB2 mutations to the breast cancer susceptibility in the French population.

Short-term risk of colorectal cancer in individuals with lynch syndrome: a meta-analysis. (Jenkins MA *et al.*, J Clin Oncol. 2015 Feb 1;33(4):326-31. doi: 10.1200/JCO.2014.55.8536. Epub 2014 Dec 22.)

PURPOSE

For carriers of germline mutations in DNA mismatch repair genes, the most relevant statistic for cancer prevention is colorectal cancer (Lynch syndrome) risk, particularly in the short term.

Methods: We conducted a meta-analysis of all independent published Lynch syndrome studies reporting age- and sex-dependent colorectal cancer risks. We estimated 5-year colorectal cancer risk over different age groups, separately for male and female mutation carriers, and number needed to screen to prevent one death.

RESULTS

We pooled estimates from analyses of 1,114 Lynch syndrome families (508 with MLH1 mutations and 606 with MSH2 mutations). On average, one in 71 male and one in 102 female MLH1 or MSH2 mutation carriers in their 20s will be diagnosed with colorectal cancer in the next 5 years. These colorectal cancer risks increase with age, peaking in the 50s (one in seven males and one in 12 females), and then decrease with age (one in 13 males and one in 19 females in their 70s). Annual colonoscopy in 16 males or 25 females in their 50s would prevent one death from colorectal cancer over 5 years while resulting in almost no serious complications. In comparison, annual colonoscopy in 155 males or 217 females in their 20s would prevent one death while resulting in approximately one serious complication.

CONCLUSION

For MLH1 or MSH2 mutation carriers, current guidelines recommend colonoscopy every 1 to 2 years starting in their 20s. Our findings support this regimen from age 30 years; however, it might not be justifiable for carriers who are in their 20s.

Familial hematological malignancies: ASXL1 gene investigation. (Hamadou WS *et al.*, Clin Transl Oncol. 2015 Aug 19. [Epub ahead of print])

PURPOSE

Familial aggregation among patients with several hematological malignancies has been revealed. This emphasizes the importance of genetic factors. Only few genes predisposing to familial hematological malignancies have been reported until now due to the low occurrence. We have described in previous study PRF1 and CEBPA variants that might contribute to the background of genetic factors, which encourage us to extend our investigations to other cooperating genes. The aim of this study is to determine whether germline additional sex combs-like 1 (ASXL1) gene mutations may be involved?

METHODS/PATIENTS

In this study, we investigated the candidate gene ASXL1 by direct sequencing in 88 unrelated Tunisian and French families with aggregated hematological malignancies.

RESULTS

We report a new p.Arg402Gln germline missense substitution in two related Tunisian patients which has not been previously described. We identified here this variant for the first time in non-Hodgkin lymphoma. The p.Arg402Gln variant was not found in 200 control chromosomes. In silico analysis has predicted potential deleterious effect on ASXL1 protein.

CONCLUSIONS

From an extended candidate genes analyzed in the field of familial hematological malignancies, ASXL1 might be involved. This variant should be considered since a potential damaging effect was predicted by in silico analysis, with a view to develop functional assay in order to investigate the biological assessment.

Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. (Bougeard G *et al.*, J Clin Oncol. 2015 Jul 20;33(21):2345-52. doi: 10.1200/JCO.2014.59.5728. Epub 2015 May 26.)

PURPOSE

The aim of the study was to update the description of Li-Fraumeni syndrome (LFS), a remarkable cancer predisposition characterized by extensive clinical heterogeneity.

PATIENTS AND METHODS

From 1,730 French patients suggestive of LFS, we identified 415 mutation carriers in 214 families harboring 133 distinct TP53 alterations and updated their clinical presentation.

RESULTS

The 322 affected carriers developed 552 tumors, and 43% had developed multiple malignancies. The mean age of first tumor onset was 24.9 years, 41% having developed a tumor by age 18. In childhood, the LFS tumor spectrum was characterized by osteosarcomas, adrenocortical carcinomas (ACC), CNS tumors, and soft tissue sarcomas (STS) observed in 30%, 27%, 26%, and 23% of the patients, respectively. In adults, the tumor distribution was characterized by the predominance of breast carcinomas observed in 79% of the females, and STS observed in 27% of the patients. The TP53 mutation detection rate in children presenting with ACC or choroid plexus carcinomas, and in females with breast cancer before age 31 years, without additional features indicative of LFS, was 45%, 42% and 6%, respectively. The mean age of tumor onset was statistically different ($P < .05$) between carriers harboring dominant-negative missense mutations (21.3 years) and those with all types of loss of function mutations (28.5 years) or genomic rearrangements (35.8 years). Affected children, except those with ACC, harbored mostly dominant-negative missense mutations.

CONCLUSION

The clinical gradient of the germline TP53 mutations, which should be validated by other studies, suggests that it might be appropriate to stratify the clinical management of LFS according to the class of the mutation.

Mutation screening of MIR146A/B and BRCA1/2 3'-UTRs in the GENESIS study. (Garcia AI *et al.*, Eur J Hum Genet. 2016 Jan 20. doi: 10.1038/ejhg.2015.284.)

ABSTRACT

Although a wide number of breast cancer susceptibility alleles associated with various levels of risk have been identified to date, about 50% of the heritability is still missing. Although the major BRCA1 and BRCA2 genes are being extensively screened for truncating and missense variants in breast and/or ovarian cancer families, potential regulatory variants affecting their expression remain largely unexplored. In an attempt to identify such variants, we focused our attention on gene regulation mediated by microRNAs (miRs). We screened two genes, MIR146A and MIR146B, producing miR-146a and miR-146b-5p, respectively, that regulate BRCA1, and the 3'- untranslated regions (3'-UTRs) of BRCA1 and BRCA2 in the GENESIS French national case/control study (BRCA1- and BRCA2-negative breast cancer cases with at least one sister with breast cancer and matched controls). We identified one rare variant in MIR146A, four in MIR146B, five in BRCA1 3'-UTR and one in BRCA2 3'-UTR in 716 index cases and 619 controls. Among these 11 rare variants, 7 were identified each in 1 index case. None of the three relevant MIR146A/MIR146B variants affected the pre-miR sequences. The potential causality of the four relevant BRCA1/BRCA2 3'-UTRs variants was evaluated with luciferase reporter assays and co-segregation studies, as well as with bioinformatics analyses to predict miRs-binding sites, RNA secondary structures and RNA accessibility. This is the first study to report the screening of miR genes and of BRCA2 3'-UTR in a large series of familial breast cancer cases. None of the variant identified in this study gave convincing evidence of potential pathogenicity.

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