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Patient-reported symptoms possibly related to treatment with osimertinib or chemotherapy for advanced non-small cell lung cancer

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ABSTRACT

Objectives: In the AURA3 trial, individuals received osimertinib 80 mg once daily or chemotherapy for advanced non-small cell lung cancer. Here, we explore patient-reported symptoms possibly related to treatment.

Materials and methods: AURA3 was an open-label, randomized phase III trial involving 419 patients. As part of the trial's exploratory objectives, individuals were asked to complete the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) electronically, first weekly for 18 weeks and then every 3 weeks for up to 57 weeks, subject to the availability of validated local-language versions (English, German, Japanese and Spanish versions were available).

Results: In total, 161 patients (38%; 102 receiving osimertinib, 59 receiving chemotherapy) provided data for PRO-CTCAE analyses (mean age: 64 years; 63% women). Diarrhea was reported more commonly with osimertinib than with chemotherapy, and was mostly graded as occurring rarely or occasionally. Decreased appetite was reported less commonly with osimertinib than with chemotherapy. The proportion of patients reporting nausea changed little from baseline with osimertinib and increased with chemotherapy. Few patients reported vomiting. Both nausea and vomiting were generally graded as mild in severity. Fatigue was reported less commonly with osimertinib than with chemotherapy, and was mostly graded as mild or moderate. Of patients reporting fatigue, the proportion grading it as interfering at least 'somewhat' with their usual or daily activities was lower with osimertinib than with chemotherapy.

Conclusion: Symptoms were generally mild and not frequent, with some differences in symptom patterns between the two treatment groups. The results support and complement the AURA3 trial data and give insight into patients' experience with treatment.

1. Introduction

Symptom reporting directly by patients using specific patient-reported outcome (PRO) instruments is a well-established means of measuring treatment effects in clinical trials and forms part of product development to support regulatory approvals [1]. Laboratory abnormalities and clinical observations that are potentially treatment-related are traditionally captured by the clinical investigators. For symptoms possibly related to treatment, the patient perspective captures information that may not be captured by clinicians, and provides details about frequency, intensity and impact on daily life [2,3]. Reports directly from patients tend to include more symptoms and to indicate a higher degree of symptom intensity than reports originating from the treating clinician [3,4].

The Common Terminology Criteria for Adverse Events (CTCAE) is a lexicon maintained by the US National Cancer Institute (NCI) for use in oncology trials to report adverse events. The CTCAE lexicon is organized by nied by descriptions of severity (grade) [5]. Approximately 10% of items listed in the CTCAE lexicon are symptoms, which, in clinical trials, are reported by the investigators [6]. Recently, the US NCI developed and validated a Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE) to complement the standard CTCAE-based adverse event reporting in oncology trials [7,8]. A multidisciplinary group of

Abbreviations: CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; TKI, tyrosine kinase inhibitor

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investigators and patient representatives reviewed all CTCAE terms and identified 78 as being appropriate for self-reporting by adults with cancer in oncology clinical trials and thus for inclusion in the PRO-CTCAE [3]. In a multi-step process with patient input included at each step, plain-language terminology was developed for each symptom, and appropriate symptom attributes (frequency, severity, interference) were incorporated in the PRO-CTCAE to reflect those used in the corresponding CTCAE item. Translation of the PRO-CTCAE into various non-English language versions and validation of these versions are ongoing, and it is anticipated that the item library will continue to be refined as new possible treatment-related symptoms are identified and researchers gain experience in how these are best analyzed and interpreted [7]. Use of the PRO-CTCAE is supported by the US Food and Drug Administration, together with the Critical Path Institute, for the systematic assessment of possibly treatment-related patient-reported symptoms and their burden to patients, to complement existing clinical safety assessments [9].

PRO-CTCAE data were used in some of the exploratory analyses in the recently completed AURA3 trial, which assessed the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) osimertinib versus platinum-based chemotherapy as standard of care for patients with *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC) [10]. The PRO-CTCAE was included in AURA3 to increase understanding of patients' experience of symptoms potentially related to treatment. The CTCAE was the means to capture and report adverse events. To be included in AURA3, patients needed to have advanced NSCLC with confirmed presence of a p.Thr790Met point mutation (T790 M) in the gene encoding EGFR and to have acquired resistance to first-line EGFR-TKI therapy. Osimertinib is an oral, central nervous system (CNS)-active, third-generation EGFR-TKI selective for both EGFR-TKI sensitizing mutations and T790 M *EGFR* resistance mutations [11–13]. AURA3 met its primary endpoint of significantly improved progression-free survival with osimertinib relative to chemotherapy, and demonstrated improved patient-reported symptoms and health status with osimertinib compared with chemotherapy [10,14]. The most commonly reported adverse events in the early clinical development of osimertinib, captured using the CTCAE, were diarrhea, decreased appetite, nausea and rash [15]. In an interview sub-study that captured feedback on the treatment experience directly from patients, diarrhea, poor appetite, acne, rash, itching and fatigue/tiredness were identified as common symptoms/side effects in these patients [16].

Here, we report results from exploratory analyses conducted in a subset of patients as part of the AURA3 trial to capture patient-reported symptoms possibly related to treatment, using the PRO-CTCAE.

2. Materials and methods

2.1. Study design and patients

AURA3 (NCT02151981) was a multinational, open-label, randomized phase III trial. Patients were screened between August 2014 and September 2015, and 419 eligible patients were enrolled and randomized to treatment. To be eligible for inclusion, patients needed to have evidence both of locally advanced or metastatic NSCLC and of disease progression after first-line EGFR-TKI therapy [10]. An additional requirement was the documented presence of a T790 M *EGFR* mutation.

Patients were randomized in a 2:1 ratio to receive oral osimertinib 80 mg once daily or chemotherapy comprising intravenous pemetrexed 500 mg/m^2 of body surface area plus either carboplatin (at a dose aimed at providing an area under the plasma concentration–time curve of 5 mg/mL/min) or cisplatin 75 mg/m^2 every 3 weeks for up to six cycles, followed by optional pemetrexed maintenance therapy [10]. Treatment continued until disease progression, the development of unacceptable side effects, or a request by either the patient or the treating physician to discontinue treatment. The mean duration of treatment at the data cut-off date was 8.6 months in the osimertinib group and 4.8 months in the chemotherapy group.

Patients for whom validated local-language versions of the PRO-CTCAE were available (English, German, Japanese and Spanish [8]) were asked to complete the instrument electronically at baseline, every week for the first 18 weeks and then every 3 weeks thereafter for up to 57 weeks.

AURA3 was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice Guidelines as defined by the International Conference on Harmonisation, applicable regulatory requirements, and the policy on bioethics and human biologic samples of the trial sponsor, AstraZeneca. All patients provided written informed consent before being screened.

2.2. PRO-CTCAE

PRO-CTCAE is a validated PRO measurement system developed by the US NCI to assess symptoms possibly related to cancer treatments [3,6,8]. The PRO-CTCAE consists of 124 items, which are listed in a publicly available library and cover 78 symptoms [8]. Each item reflects specific symptom attributes included in the corresponding CTCAE. Depending on which PRO-CTCAE symptom is being assessed, up to three of the following item attributes are included: presence (yes; no); frequency (never; rarely; occasionally; frequently; almost constantly); severity (none; mild; moderate; severe; very severe); and/or interference with usual or daily activities (not at all; a little bit; somewhat; quite a bit; very much). Some PRO-CTCAE symptoms comprise just one item (e.g. yes/no for rash, frequency for diarrhea, severity for constipation), whereas others include two items (e.g. frequency and severity for nausea or vomiting, severity and interference with usual or daily activities for decreased appetite) and some include three items (e.g. frequency, severity and interference with usual or daily activities for pain in the abdomen).

The choice of PRO-CTCAE items for use in clinical trials depends on the symptoms anticipated to occur based on previous observations with the treatments that are being assessed. The standard PRO-CTCAE recall period is the past 7 days. For AURA3, 42 items relating to a total of 28 symptoms were selected as relevant from the PRO-CTCAE item bank and included in the trial. Item selection was consistent with that in the AURA2 study, based on documented EGFR-TKI class effects and the comparator effects, identified and potential risks of osimertinib, patient interviews and NCI core cancer symptoms, following NCI guidance [3,8]. Investigator interviews confirmed that the item selection for AURA3 was satisfactory to cover the symptoms that most commonly occurred in AURA3.

2.3. Data analyses

In accordance with the US NCI recommendations [8], PRO-CTCAE data were summarized descriptively as the number (%) of patients reporting each grade for individual items, and all available attribute items were included for each of the reported symptoms. The analyses were exploratory and descriptive, and no statistical comparisons were conducted. Results reported here are for the following 13 items representing eight symptoms, which were identified as common from patient interviews: diarrhea (frequency); fecal incontinence (frequency, interference); decreased appetite (severity, interference); nausea (frequency, severity); vomiting (frequency, severity); rash (presence); acne (severity); and fatigue (severity, interference).

3. Results

3.1. Patients

Data for PRO-CTCAE analyses were available for 161 (38%) of the 419 patients randomized in AURA3 (102 from the osimertinib group and 59 from the chemotherapy group) (Fig. 1). Patient demographics for the two treatment groups are presented in Table 1. The overall mean age of the patients was 64 years, and 63% were women. Most patients