NUT Midline Carcinoma

Madam — NUT midline carcinoma (NMC) is a rare, recently discovered, genetically defined, highly aggressive cancer [1]. Because of its rarity, few data are available regarding incidence, risk factors, indication, outcomes and sequencing of treatment modalities. Hence, we decided to audit data of individual patients diagnosed as NMC (defined on the basis of NUT-1 antibody positivity status on immunohistochemistry) in our institute between 2015 and 2018.

We identified 11 patients, with a median age of 22 years (range 9–61 years). The Eastern Cooperative Oncology Group performance status was 0–1 in 81.8% (eight) of the patients and performance status 2 or above in three patients (18.2%). The location was sinonasal in six patients (54.5%) and thoracic in five patients (45.5%). All patients had a midline location except for one (9.1%), in whom the epicentre was the left lower lobe. One-third of our patients (four, 36.7%) had metastatic disease at presentation, with bone being the most common site (three patients, 27.3%); the rest all had locally advanced disease (seven, 63.3%). The treatment intent was curative in one patient (9.1%) and palliative in 10 patients (90.9%). The curative patient received chemoradiation followed by adjuvant chemotherapy with paclitaxel and carboplatin. Among the palliatively treated patients, chemotherapy was received by seven patients (63.3%), one patient received local radiation (9.1%) and two (18.2%) refused treatment. Paclitaxel with carboplatin combination chemotherapy was received by four patients (36.7%), paclitaxel, cisplatin and ifosfamide chemotherapy was received by one patient (9.1%); the remaining two patients received the Vincristine, Adriamycin, Cyclophosphamide-Vincristine, Cyclophosphamide, Dactinomycin regimen (18.2%). Only two patients had a response to chemotherapy (28.6%, $n = 7$) and both had received paclitaxel with carboplatin. The median progression-free survival of our cohort of patients was 2.33 months (95% confidence interval 0.43–5.33) and overall survival was 6.43 months (95% confidence interval 1.27–12.00).

On the basis of our results and multiple case reports [2–5], it can be concluded that NMC is an aggressive malignancy and has dismal outcomes with currently used therapies.

Conflict of Interest

V. Noronha received grants from Dr. Reddy's Laboratories, Amgen and Sanofi Aventis, outside the submitted work. K. Prabhash received grants from Biocon, Dr. Reddy's Laboratories, Fresenius Kabi India, Alkem Laboratories, Natco Pharma, BDR Pharmaceutics and Roche, outside the submitted work.

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DPYD Mutation in Indian Patients

Madam — A pharmacogenomics-based drug modification of 5-fluorouracil (a 25–50% dose reduction) was recommended by the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. However, this was never studied in a prospective systematic manner [1]. A recent study by Henricks *et al.* [2] suggested that the incidence of dihydropyrimidine dehydrogenase gene mutation was 8%, which is higher than the incidence reported among Caucasians in most of the studies. We want to highlight that the incidence of DPYD mutation might have ethnic differences.

We started routine DPYD mutation testing in our hospital in March 2015. DPYD mutation testing was carried out on an ABI 3500 platform using Sanger sequencing. Uptill 31 August 2018 we analysed 1064 consecutive Indian patients who underwent DPYD mutation analysis in our laboratory. The incidence of heterozygous and homozygous DPYD mutation was 25.7% ($n = 273$) and 1.5% ($n = 16$), respectively, which seems much higher than reported in Caucasians. The most common mutations found were heterozygous mutations in exon 13 (c1627A>G) - 12.8% (136); exon 18 (c2194G>A) - 11.4% (121); both exon 18 (c2194G>A) and exon 13 (c1627A>G) - 1.5% (16). Homozygous mutations were found in exon 18 (c2194G>A) - 0.8% (8) and exon 13 (c1627A>G) - 0.8% (8). The incidence of DYPD mutation in the three most common cancers was: head and neck carcinoma 24.4% (142, $n = 583$); gastrointestinal carcinoma 31.8% (125, $n = 393$); oesophageal carcinoma 26.4% (19, $n = 72$).

Furthermore, in the study by Henricks *et al.* [2], the dose modification of 25% was adequate in all except c.1236G>A and c.2846A>T carriers. In our own pilot study, which inspired us to carry out routine DPYD analysis, we saw that with modified doses (a 50% dose reduction) the adverse events with 5-fluorouracil, especially myelosuppression and mucositis, decrease after dose reduction in DPYD-mutated patients [3]. This highlights the importance of carrying out routine DYPD genotyping and modifying the doses according to the CPIC guidelines.

Conflicts of Interest

V. Noronha received grants from Dr. Reddy's Laboratories, Amgen and Sanofi Aventis, outside the submitted work. K. Prabhash received grants from Biocon, Dr. Reddy's Laboratories, Fresenius Kabi India, Alkem Laboratories, Natco Pharma, BDR Pharmaceutics and Roche, outside the submitted work.

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When Can We Discharge Differentiated Thyroid Cancer Patients Who Present With High-Risk Disease and Subsequently Have an Excellent Response to Treatment?

Madam — Further to the publication on low-risk differentiated thyroid cancer (DTC) follow-up [1], the authors wanted to quantify the recurrence rate in DTC patients who present with American Thyroid Association (ATA) high-risk disease and subsequently have an excellent response to treatment (ERST) after dynamic risk stratification (DRS). The only published series include 10 [2] and five patients [3], with no recurrences reported.

We retrospectively analysed DTC patients treated in Leeds between 2001 and 2013, as previously detailed [1]. Of 756 patients stratified into the ERST group, 34 had 'initial ATA high-risk - subsequent DRS low-risk' disease [4,5]. The median follow-up duration was 9.9 (range: 5–17) years. Fifty-nine per cent (20/34) had ERST after total thyroidectomy followed by radioiodine remnant ablation after DRS carried out 6–12 months from treatment completion, whereas 76% (26/34) required additional intervention. Four patients presented with distant metastases – none of whom developed recurrence.

Radiological recurrence occurred in 2/34 (5.9%) patients - one (pT4aN1bM0 papillary thyroid cancer [PTC]) developing biochemical recurrence at 5 years from presentation followed by lung metastases 77 months from diagnosis; the second (pT3N1bM0 PTC) having biochemical recurrence at 3 years followed by regional nodes 38 months from diagnosis. The recurrence rate of ATA low-risk and intermediate-risk disease patients having ERST was 11/722 (1.5%).

This is the largest series of 'initial ATA high-risk - subsequent DRS low-risk' DTC with the longest follow-up duration. The recurrence rate in our group was 5.9% and even if incorrect by a two-fold factor, would remain relatively low. Both recurrences were heralded by biochemical recurrence

* Both have contributed equally.