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Commentary

Nab-paclitaxel - Third-line chemotherapy in advanced gallbladder cancer

Gall bladder cancer (GBC) is a common cancer for north and north-eastern part of India with incidence ranging from 11.8 to 17.1/100,000 population[1]. Majority of patients present in advanced stages and are eligible only for palliative chemotherapy which has not made a significant difference in improving outcomes[2,3]. The practice changing studies for the first- and the second-line palliative chemotherapy have included both cholangiocarcinoma and GBC under the umbrella of biliary tract cancers[4].

Talwar *et al*[5] in their study on Nab-paclitaxel (Nab-P) in advanced GBC made a significant contribution in the management of GBC. The median overall survival (OS) of advanced GBC has been reported to be 4.5 months without treatment[6]. In the subset analysis of ABC0 2 trial[4], no benefit was observed from gemcitabine-cisplatin (Gem-Cis) combination as compared to single-agent gemcitabine, highlighting its importance as a different subset that needs to be looked at separately[3]. Furthermore, given the young median age of patients with GBC at presentation (ranging from 45 to 55 yr) in most studies, it is likely that we will find physically fit patients who will be eligible for second- and third-line treatments[7-9]. Sharma *et al*[7] conducted the first randomized controlled trial in GBC wherein Gem-Cis was compared with modified gemcitabine-oxaliplatin (mGemOx) as the first-line treatment. The median progression-free survival (PFS) was five months [95% confidence interval (CI) 3.2-6] with a median OS of 8.5 months for entire study population, highlighting the aggressive clinical course and biology of GBC[7]. The current study[5] had a similar median PFS of 5.5 months (95% CI 3.7-7.4) in first-line setting when gemcitabine-platinum combination was used[5]. Gem-Cis had a median PFS of 7.4 months as compared to 4.4 months in gemcitabine-carboplatin (Gem-Carbo) group. For patients (n=12) who received second-line FOLFOX4, the median PFS was 5.4 months. Only seven patients received single-agent Nab-P, with a response rate of 52.4 per cent. The median PFS in these patients was 2.9 months (95% CI 2-7.8).

There is retrospective as well as prospective evidence to show that FOLFOX is the new standard of care for the treatment of biliary tract cancers in second-line setting but we still do not have a standard for third-line treatment[9,10]. Results on another second-line chemotherapy regimen CAP-IRI (capecitabine & irinotecan) or FOLFIRI (folinic acid, 5-fluorouracil & irinotecan) also need to be evaluated in a randomized setting[11,12].

It is commendable that the authors discuss a chemotherapy regimen which is easily accessible in third-line setting for a cancer which is not attractive for studies in the Western world[5]. Less than half of the patients with advanced GBC are eligible for second-line therapy and we assume that even a lesser proportion (likely 20-25%) would be eligible for third-line therapy[7]. Data are emerging on the use of basket trials and immunotherapy[13] but this is out of reach for most patients living in a low- and middle-income group countries.

Nab-P has been studied in advanced biliary tract cancer in phase 2 clinical trial in combination of Gem-Cis in the first-line setting[14]. Of the 60 patients, 13 (22%) had GBC. The median PFS was 11.8 months (95% CI 6-15.6) and the median OS was 19.2 months (95% CI 13.2) - not reached which is unprecedented in biliary tract cancers. Nab-P has also been studied in second- and third-line settings in advanced cholangiocarcinoma[15]. Of the 12 patients, five received Nab-P second-line and seven received third-line. This study showed that the median time to progression was six months (range, 2.1-19.2)[15].

A phase 1 third-line study from Japan on the use of paclitaxel in patients who have failed Gem-Cis and

fluoropyrimidine, has shown that this is feasible and effective[16]. The disease control rate in six patients was 83 per cent with a median OS of nine months[16]. Nab-P has been approved in breast cancer, pancreatic cancer and lung cancer in various settings. In view of the rarity of GBC in the Western world, recommendations are not formulated and propagated in international guidelines. National Comprehensive Cancer Network (NCCN) guidelines do not consider any form of therapy in second- or third-line setting[17].

This study[5] had major limitations in view of small number of patients, retrospective design and highly selected group of patients. With such limitations, it is difficult to derive conclusions or make recommendations. However, this study highlighted the proof of concept of activity of Nab-P in selected cases of GBC in Indian patients. Nab-P is an active drug in GBC and must be studied in prospectively designed trials, preferably in the first-line setting in future studies.

***Conflicts of Interest*:** None.

Amol Patel[1] & Bhawna Sirohi[2,*]
[1]Department of Medical Oncology, Army Hospital, Research & Referral, New Delhi 110 010 &
[2]Department of Medical Oncology, Apollo Proton Cancer Centre, Chennai 600 028, Tamil Nadu, India
[*]*For correspondence*: bhawna.sirohi13@gmail.com

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