EUR. J. ONCOL., vol. 19, Suppl n. 1, pp. 52-54, 2014

Update on *nab*-Paclitaxel in the treatment of pancreatic cancer

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Pancreatic cancer ranks as the fourth leading cause of cancer-related death in the US and, with mortality closely approaching incidence (approximately 39000 deaths and 46,000 new cases expected in 2014) and a dismal 5-year survival rate of 6%, it remains one of the most aggressive and difficult to treat solid tumors (1). Moreover, pancreatic adenocarcinoma (PDAC) patients are usually affected, since the diagnosis, by a complex symptomatology that profoundly impacts on patient's performance status and requires prompt and frequent palliative measures, in order to achieve an improvement in patients' quality of life, regardless of the specific oncologic treatment.

Fluoropyrimidines and gemcitabine (Gem) have been the cornerstone(s) of PDAC treatment in the past 30 years. However, attempts at improving outcomes using Gem-based chemotherapy doublets have not met with success in individual studies and have provided clinically negligible survival advantages, when analyzed together in a pooled fashion (2): indeed, a pooled analysis of 7 randomized trials, including 2422 patients, that compared Gem-monotherapy with three different combination treatments (Gem-cisplatin, Gem-capecitabine and Gem-oxaliplatin) showed a clinically negligible, although statistically significant, absolute survival benefit, ruling out the possibility that Gem-based schedules could improve 1-year survival by more than 5% (3).

More recently, polychemotherapy regimens, including or not Gem, have shown promise. Using the PEFG regimen, consisting of cisplatin, epirubicin, Gem and 5-fluorouracil, Reni et al demonstrated a significant PFS and OS advantage, as compared with Gem alone (4). The PRODIGE 4/ACCORD 11 study also showed a statistically and clinically significant prolongation of both PFS and OS and an increased ORR with the FOLFIRINOX regimen, as compared with Gem monotherapy (5). In light of their toxicity, however, such regimens require a careful selection of young and fit patients, an occurrence that is rather the exception than the rule in advanced PDAC, and are, thus, not suitable for a significant proportion of patients.

Nanoparticle albumin-bound (*nab*)-paclitaxel is a paclitaxel formulation consisting of nanoparticle colloidal suspension, with an average size of 130 nm, prepared with human serum albumin. This formulation without solvents confers a more favorable pharmacologic characteristic that allows the delivery of a higher dose of paclitaxel than Cremaphor-paclitaxel, with significantly lower risk of infusion hypersensitivity reactions and neutropenia, and faster recovery of peripheral neuropathy on stopping the treatment (6). Moreover *nab*-paclitaxel uptake into the cells is at least in part dependent on the expression of secreted protein acidic and rich in cysteine (SPARC), an albumin-binding protein that interacts with the extracellular matrix, influencing cell migration, proliferation, angiogenesis (especially during wound healing), matrix cell adhesion, and tissue remodeling. SPARC expression is often lost in PDAC cells, but is usually upregulated in juxtatumoral fibroblasts (7), where its expression is a strong marker of poor prognosis (8). Thus, SPARC represents an interesting stromal target for PDAC, in which the binding between SPARC and albumin within the desmoplastic pancreatic tumor stroma

may facilitate delivery of albumin-bound therapeutic agents (9). A phase I/II study conducted in metastatic PDAC patients showed that a combination of Gem (1000 mg/m^2) and *nab*-paclitaxel (at the MTD of 125 mg/m^2) on days 1, 8, and 15 of 28-day cycle achieves an impressive 48% ORR and median PFS and OS of 7.9 and 12.2 months, respectively (10). These promising results, along with the favorable safety profile prompted the starting of a phase III study (MPACT), which randomized 861 metastatic PDAC patients to receive a combination of *nab*-paclitaxel plus Gem or single-agent Gem. Overall survival (the primary study endpoint) was significantly improved with *nab*-paclitaxel plus Gem (8.5 months vs 6.7 months; HR 0.72; 95% CI, 0.62-0.83; P<0.001), as were the 1- (35% vs 22%) and 2-year (9% vs. 4%) survival rates. A significant improvement in PFS was also reported (5.5 vs 3.7 months; HR 0.69; 95% CI, 0.58-0.82; P<0.001) and ORR was significantly higher with the combination (23% vs 7%; P<0.001) (11). Treatment benefit for the combination of *nab*-paclitaxel and Gem was uniformly distributed in essentially all patient subgroups of interest. Treatment was well tolerated: the most common adverse events related to the *nab*-paclitaxel/Gem combination were fatigue (in 54% of patients), alopecia (in 50%), and nausea (in 49%). Grade 3 or higher adverse events were neutropenia (38% in the combination group vs 27% in the Gem group), fatigue (17% vs. 7%), and peripheral neuropathy (17% vs. 1%). Febrile neutropenia was reported in 3% versus 1% of the patients in the *nab*-paclitaxel and Gem groups, respectively, and the proportion of patients with serious adverse events was similar in the two treatment arms (50% with *nab*-paclitaxel plus Gem and 43% with Gem) (11). On the bases of these results, *nab*-paclitaxel was recently approved by FDA and EMA for the treatment of advanced PDAC.

Clinical success with the combination of *nab*-paclitaxel and Gem in metastatic disease, paves now the way for further studies of *nab*-paclitaxel in PDAC: neo-adjuvant studies in resectable, borderline resectable, and/or locally advanced patients and adjuvant studies in completely resected patients are now being conducted or planned, with promising preliminary results (12); incorporation of *nab*-paclitaxel into polychemotherapy regimens, in sequential treatment approaches with regimens such as FOLFIRINOX, and/or in combination with promising targeted agents (such as Hedgehog or PI3K/AKT pathway inhibitors) is being pursued; finally, preclinical studies are shedding further light on the peculiar mechanism of action of *nab*-paclitaxel based therapeutic strategies (13, 14), allowing for the continued refinement and optimization of its use in PDAC.

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