in the subsequent 30 to 40 years, progress in myeloma treatment remained stagnant. In fact, the major innovation was the use of high-dose therapy, which was again mainly based on melphalan, followed by autologous stem cell support. The situation has significantly changed in the last decade with the approval of 2 immunomodulatory drugs (IMIDs) (thalidomide and lenalidomide) and 1 proteasome inhibitor (PI) (bortezomib).

Carfilzomib is a second-generation PI that belongs to the epoxiketone family and irreversibly binds the chymotrypsin-like activity of the proteasome. It has shown marked activity, as simple agent, in phase 1 and 2 clinical trials, with 40% to 52% of responses in bortezomib-naïve patients and 17% to 19% in bortezomib-refractory cases and a very low incidence of peripheral neuropathy (PN).[3-5] The possibility of combining PI with IMIDs is very attractive, and the positive results of the bortezomib-lenalidomide-dexamethasone (VRD) combination[6] were the basis for the study reported in this issue of *Blood* by Wang et al.[1] In a previous phase 1b dose-escalation study,[7] the same authors identified the maximum planned dose (MPD) for CRd as 20/27 mg/m^2 for carfilzomib, 25 mg for lenalidomide, and 40 mg for dexamethasone. Here, they show the efficacy and safety of CRd at the MPD in a total of 52 patients; the response rate (RR) was 76.9%, with a median progression-free survival (PFS) of 15.4 months. The benefit of adding carfilzomib to lenalidomide-dexamethasone will be determined in the ASPIRE randomized trial that compares CRd vs Lenalidomide plus low-dose dexamethasone, but the present data already suggest that in lenalidomide-naïve patients, the RR (85%) and median PFS (not reached) is superior to that previously reported for lenalidomide-dexamethasone.[8,9] Moreover, 68% of patients refractory to lenalidomide responded to CRd with a median PFS of 9.9 months. Whether or not the results with CRd combination are superior to previously reported data with VRD is difficult to determine, because the patient populations were rather heterogeneous and small in size. Perhaps the clearest advantage of CRd is the lower incidence of PN (27% vs 64% for any grade PN); however, in the Richardson trial, the more friendly bortezomib schedule (weekly and subcutaneous) was not used. Accordingly, the answer to this question will only come from a randomized trial.

The second relevant question, in the relapse setting, is whether it is preferable to use a combination of the 2 new drugs (PI plus IMID) or to combine one of them with an alkylator (ie, cyclophosphamide) and to reserve the other one for subsequent relapses. In this comparison, costs should also be taken into consideration. How many countries will pay for this expensive triple combination unless there is a study design showing that the triplet at relapse is superior in terms of overall survival (not in terms of RR or PFS) to a sequential treatment approach? If this proves to be positive, then CRd will be cost-effective and will become a new standard for relapse/refractory patients.

A different scenario at relapse is that of young patients who are candidates to receive a transplant as part of the rescue therapy, particularly if this is an allotransplant, because in this setting we want to obtain the best possible response as soon as possible, and therefore the combination of a PI with IMIDs is clearly justified.

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Comment on Albanesi et al, page 3160

Neutrophils: "neu players" in antibody therapy?

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In this issue of *Blood*, Albanesi et al have added weight to the contention that neutrophils are an important effector population in monoclonal antibody (mAb)-mediated tumor cell clearance. Their data, obtained using subcutaneous tumor models and an extensive panel of genetically modified mice, demonstrate that neutrophils are required for mAb efficacy and that they do so through a Syk-dependent Fcγ receptor (FcγR)–mediated mechanism.[1]

Antibody therapeutics which target tumor cells, directly recruiting natural effectors, have become a mainstay for managing hematologic malignancies, with the anti-CD20 mAb rituximab heralding a new era in lymphoma treatment. In contrast, the usefulness of mAbs against solid tumors has been limited and largely confined to reagents, such as anti-her2/neu, anti–epidermal growth factor receptor, and

anti–vascular endothelial growth factor, which at least in part work by blocking the oncogenic or angiogenic properties of their target molecules. Such mAbs may also provide cytotoxic activity via natural effectors, but the relative importance of this to therapeutic activity is still unclear. Indeed, the mechanisms of action of all of these drugs and the identity of the effector cell populations involved remain hotly debated topics, with evidence from both preclinical and clinical studies frequently contradictory. However, through this debate, it is generally accepted that in humans and mice, whatever the effectors used, activatory FcγR are required,[2] and until now there has been little evidence for an important role for complement or neutrophils.

Evidence from mouse models has frequently placed monocytes and macrophages as the dominant cell populations for the depletion of normal cells and lymphoid tumors with mAbs.[2-4] In humans, single-nucleotide polymorphisms in FcγRIIa[5] and FcγRIIIa[6] point to the potential role of natural killer (NK) cells, monocytes/macrophages, and perhaps neutrophils in response to mAbs, albeit with only monocytes and macrophages meeting the requirement of expressing both receptors.

The study by Albanesi et al dissects the effector cells required for mAb therapy in two short-term subcutaneous tumor models, B16-F10 melanoma and BT474 breast carcinoma, settings where the mAb appears to prevent the establishment of the malignancy rather than attacking established disease. In agreement with previous studies, they demonstrate FcγR dependence with genetically deficient mice and make the surprising observation that neutrophils are an absolute and sufficient requirement for tumor rejection, ruling out roles for NK cells, monocytes/macrophages, mast cells, basophils, and eosinophils. How much the discrepancy between their findings and those of previous studies relates to differing target cell locations (subcutaneous vs lymphoid) or to the early commencement of mAb administration (on the same day as the tumor) and short duration of their studies (typically around 7 days and a maximum of 20) is yet to be determined. However, it is notable that few studies have used anti-Gr1 reagents to deplete neutrophils in tumor therapies as reported here. Rather, they have inferred the lack of a role for neutrophils from results where mAb activity is lost with the use of clodronate-containing liposomes which seem to selectively target monocytes and macrophages and leave neutrophils "untouched." However, previously none have used such an extensive panel of genetically modified mice. We have no explanation as to why immunoglobulin G (IgG) recruited effectors would be so different with different tumors, and no evidence of any crossover between models. Other questions arising from this work are clear and testable, such as whether these observations can be extended beyond short-term subcutaneous models to treat established or spontaneous disease. Is the acute inflammation associated with local inoculation of tumor required for neutrophil activation or recruitment and could this be lacking in a hematopoietic setting? Can neutrophils be used to overcome immunosuppressive tumor microenvironments and, most importantly, do these observations translate to humans who carry different FcRs?

Given their numbers, cytotoxic machinery, and distribution, neutrophils seem eminently suited to a role as mAb effector cells and yet their potency against malignant targets, unlike microbial pathogens, has usually been unimpressive. Clinical trials using granulocyte–colony-stimulating factor, which induces a rapid release of cytotoxic neutrophils into the circulation, in combination with rituximab have yet to show benefit.[7] Part of this issue might lie in the use of IgG mAbs which, although able to interact with FcγRI, FcγRIIa, and FcγRIIIb on neutrophils, are less potent inducers of neutrophil cytotoxicity than IgA mAb which interact with FcαRI.[8] The potential of IgA in a human FcαRI transgenic murine model of lymphoma was forcefully demonstrated by Pascal et al[9] and it would be useful to compare the efficacy of IgG and IgA in the authors' models with transgenic mice.

Overall, Albanesi et al present clear evidence for the potential of neutrophils to mediate antibody-dependent tumor cell clearance, albeit in short-term tumor establishment models. This role for neutrophils is tested thoroughly in multiple sophisticated systems and difficult adoptive transfer assays. It leads the way for future exploitation of neutrophils, potentially using IgG, or alternatively IgA if issues with preparation of clinical-grade material can be overcome. Neutrophils are clearly more than just the "foot soldiers" needed to scavenge invading microbes and dying cells, and their large armamentarium of cytotoxic molecules, extracellular traps, regulatory cytokines, and effector molecules of humoral immunity underlie their importance in orchestrating immunity, including in tumors.[10] Their findings certainly suggest that the "antibody community" ignores the potential of these cells at their peril, and that neutrophils perhaps deserve to form a greater focus of research aimed at generating new therapeutics to enhance patient outcomes.

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