bearing the nitroso group (CNUs) led to much increased activity. These chloroethyl derivatives were lipophilic enough to cross the blood–brain barrier and therefore were useful in the treatment of brain tumors. This property led to the synthesis of a large number of nitrosoureas, including lomustine (CCNU) and its methyl derivative semustine, carmustine (BCNU), nimustine (ACNU), and the water-soluble tauromustine and fotemustine, but toxicity problems have prevented their widespread use. In 1967, streptozotocin (Zanosar®), a hydrophilic natural nitrosourea, was isolated from a strain of *Streptomyces achromogens*. This compound was chosen as a lead because initial SAR studies suggested that hydrophilic nitrosoureas were more potent and less toxic, and a number of analogs, such as chlorozotocin, were prepared.

Currently, the most clinically relevant nitrosoureas are lomustine, BCNU, ACNU, and streptozotocin. Lomustine (CCNU, CeeNU®) is used in brain tumors; breast, pancreatic, and lung cancers; Hodgkin's lymphoma; melanoma; multiple myeloma; and ovarian cancer. Carmustine (BiCNU®) is used in several types of brain cancer (including glioma, glioblastoma multiforme, medulloblastoma, and astrocytoma), multiple myeloma, and lymphoma (Hodgkin's and non-Hodgkin's lymphoma). A new formulation of carmustine with reduced systemic toxicity has been developed for the local treatment of brain tumors. Formulated into a slow-release "wafer" dosage form (Gliadel Wafer®; polifeprosan 20 with carmustine), it is implanted into the resection cavity left after surgical removal of the tumor.[64] It was approved by the FDA in 1997 for use as an adjunct to surgery to prolong survival in patients with recurrent GBM for whom surgical resection is indicated. Nimustine is used in combination with teniposide as a second- or third-line chemotherapy for recurrent glioblastoma.[65]

After the discovery in the mid-1960s that streptozotocin was selectively toxic to the β cell of the pancreatic islets, it was assumed that this drug might be used in pancreatic cancers. Indeed, it was approved by the FDA as a treatment for pancreatic islet cell cancer in 1982 and marketed as Zanosar®, although its use is generally limited to patients whose cancer cannot be removed by surgery. Regarding chlorozotocin, a phase II study showed that it is active against metastatic melanoma to the same degree as other chloroethylnitrosoureas in clinical use,[66] but without causing bone marrow toxicity.