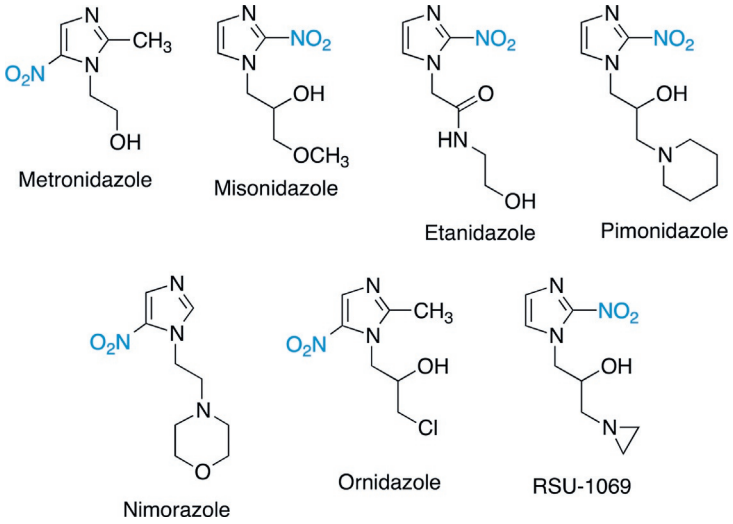
Despite initial promise, these clinical studies were disappointing, and the combination of misonidazole with radiotherapy failed to show significant benefits, with some studies reporting a significant neurotoxicity. In the 1980s, other 2-nitroimidazoles (etanidazole and pimonidazole) were studied as radiosensitizers. Because of their lower lipophilicity compared to that of misonidazole, both compounds showed lower penetration in the nervous system and a more rapid excretion, which result in lower neurotoxicity, but their clinical data did not demonstrate any benefit for radiotherapy. Subsequently, some of the newer 5-nitroimidazoles, such as ornidazole, entered clinical trials, with similarly discouraging results. On the other hand, nimorazole has shown good efficacy in sensitizing tumor cells to radiotherapy in phase III trials,[126] although its use is limited by supply problems.

In the case of RSU-1069, a high efficiency has been observed with certain tumors, such as the KHT sarcoma, but this effect seems to be due to cytotoxicity of the compound itself toward hypoxic cells rather than radiosensitization. Other bioreductive antitumor agents ("hypoxic cytotoxins"), particularly the previously mentioned porfiromycin and tirapazamine, have shown a great efficacy in combination with radiotherapy.[127]



11.2.2 Oxygen Enhancement for Radiosensitization

Because oxygen is probably the most efficient known radiosensitizer, one simple approach to aid radiotherapy is increasing blood oxygen levels. Breathing carbogen, a mixture of oxygen (95–98%) and carbon dioxide (2–5%), before and during irradiation has been shown to enhance tumor radiosensitivity in clinical assays. The role of carbon dioxide is to activate physiological mechanisms against potential suffocation, thereby further decreasing tissue hypoxia. A combination of carbogen with nicotinamide, which increases blood flow, is known as accelerated radiotherapy with carbogen and nicotinamide (ARCON). This therapy is under clinical assays for larynx cancer and has been shown to improve the outcome of radiotherapy in anemic patients.[128]

In another approach, blood levels of oxygen can be increased by decreasing the affinity of hemoglobin for oxygen and thereby displacing oxygen from hemoglobin. One compound that achieves this